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Feeding infants below 29 weeks' gestation with abnormal antenatal Doppler: analysis from a randomised trial

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ABSTRACT

Objective To describe feeding and gastrointestinal outcomes in growth-restricted infants <29 weeks' gestation and to determine the rate of feed advancement which they tolerate.

Design Analysis of prospectively collected data from a randomised feeding trial, the Abnormal Doppler Enteral Prescription Trial (ADEPT).

Setting 54 neonatal units in the UK and Ireland.

Participants 404 preterm, growth-restricted infants with abnormal antenatal Doppler studies from ADEPT. 83 infants <29 weeks and 312 infants ≥29 weeks' gestation were included in this analysis.

Interventions In ADEPT, infants were randomised to start milk 'early' on day 2 after birth, or 'late' on day 6. Subsequent feed advancement followed a regimen, which should have achieved full feeds by day 16 in the early and day 20 in the late group.

Main outcome measures Full feeds were achieved later in infants <29 weeks; median age 28 days {IQR 22–40} compared with 19 days {IQR 17–23} in infants ≥29 weeks (HR 0.35, 95% CI 0.3 to 0.5). The incidence of necrotising enterocolitis was also higher in this group; 32/83 (39%) compared to 32/312 (10%) in those ≥29 weeks (RR 3.7, 95% CI 2.4 to 5.7). Infants <29 weeks tolerated very little milk for the first 10 days of life and reached full feeds 9 days later than predicted from the trial regimen.

Conclusions Growth-restricted infants born <29 weeks' gestation with abnormal antenatal Doppler failed to tolerate even the careful feeding regimen of ADEPT. A slower advancement of feeds may be required for these infants.

Trial registration number ISRCTN87351483.

What is known about this topic

- Early introduction of enteral feeds in growth-restricted preterm infants with abnormal Doppler results in them achieving full feeds sooner, with no increase in necrotising enterocolitis.
- Feeding high-risk preterm infants with breast milk reduces necrotising enterocolitis.

What this study adds

- Infants with low gestation <29 weeks and abnormal antenatal Doppler are very slow to tolerate enteral feeding and have a high rate of necrotising enterocolitis (NEC).
- Receiving the majority of feeds as breast milk prior to reaching full enteral feeds was associated with a reduced risk of NEC.
- Increased duration of minimal enteral feeds, slower feed advancement and use of breast milk may be needed to facilitate gut adaptation and decrease feeding intolerance.

INTRODUCTION

Feeding extremely preterm and growth-restricted infants remains a challenge. In the growth-restricted fetus with absent or reversed end diastolic flow (AREDF) in the umbilical artery, blood flow to the head is preserved at the expense of the visceral organs. These infants have impaired gut function after birth, which may result in intestinal disturbances, ranging from intolerance of enteral feeding to necrotising enterocolitis (NEC). Extreme prematurity[1] and abnormal antenatal Doppler[2] are risk factors for NEC.

Our group recently reported the results of the ADEPT multicentre randomised trial[3] comparing early and late enteral feeding in preterm infants with AREDF. The results showed that infants started on milk feeds on the second day of life achieved full milk feeds 3 days sooner than those where feeds were introduced on day 6, with no difference found in NEC incidence. However, in the subgroup under 29 weeks' gestation, the median age to reach full enteral feeds was 9 days later than predicted from the study feeding regimen and the incidence of NEC was over three times higher than in infants over 29 weeks' gestation.

Feeding strategies are often modified when there is evidence of intolerance. Minimal enteral feeds and slow rates of feed advancement are frequently used in preterm neonates to facilitate gastrointestinal adaptation, improve feeding tolerance and reduce the risk of NEC.[4 5] For the high-risk group of babies with AREDF and low gestation, the optimal duration of minimal enteral feeding and rates of feed advancement are uncertain.

The aim of this secondary analysis was to describe feeding and gastrointestinal outcomes in growth-restricted preterm infants under 29 weeks'

gestation with abnormal antenatal Doppler and to determine the rate of feed advancement which they tolerate.

METHODS

We analysed the prospectively collected trial data from 54 neonatal units that participated in the multicentre randomised controlled Abnormal Doppler Enteral Prescription Trial (ADEPT); the methods and results have been reported elsewhere.[3 6]

The ADEPT trial

Inclusion criteria for recruitment to the main trial were:

1. Gestational age up to and including 34 weeks + 6 days
2. Antenatal ultrasound showing either absent or reversed end diastolic flow velocities on Doppler waveforms from the umbilical artery or cerebral redistribution[7]
3. Small for gestational age (birth weight <10th centile)[8]
4. Postnatal age 20–48 h

Exclusion criteria were major congenital abnormality, twin–twin transfusion, intrauterine transfusion, exchange transfusion, Rhesus isoimmunization, multiorgan failure, inotropic drug support or enteral feeding prior to trial entry.

Four hundred and four infants were recruited and randomly allocated to 'early' or 'late' enteral feeding regimens, with milk feeds started on day 2 and day 6 after birth, respectively. The interventions were based on a pretrial survey of practice and are described in the published protocol.[6] Rates of feed advancement were identical in each group and tailored to birth weight, aiming to reach 150 mL/kg/day over 13 days in the smallest (<600 g) and 9 days in the largest infants (>1250 g). The choice of milk recommended to mothers to feed their baby, in descending order of preference, was: mother's own breast milk, donated breast milk and infant formula.

Data were collected at trial entry, during the infant's stay in the neonatal unit and at discharge by local medical and nursing teams. Collected information included demographic and antenatal Doppler information, a daily log of milk intake and gastrointestinal symptoms, and details of episodes of suspected NEC or other abdominal pathology.

Informed parental consent was obtained for all patients. The study had research ethics committee approval and was registered with Current Controlled Trials ISRCTN87351483.

Subgroup analysis by gestational age group

In the main trial paper,[3] we reported a prespecified subgroup analysis of primary outcomes (age at full feeds and incidence of NEC) stratified by gestation at delivery (<29 or ≥29 weeks). Here, we report an in-depth analysis of feeding and gastrointestinal outcomes by gestational age subgroup, using data recorded on the daily log and the abdominal pathology forms. We also explore risk factors for NEC in the low gestation group (<29 weeks) and examine the volume of feeds tolerated within the first 28 days of life compared to the recommended trial feeding regimen.

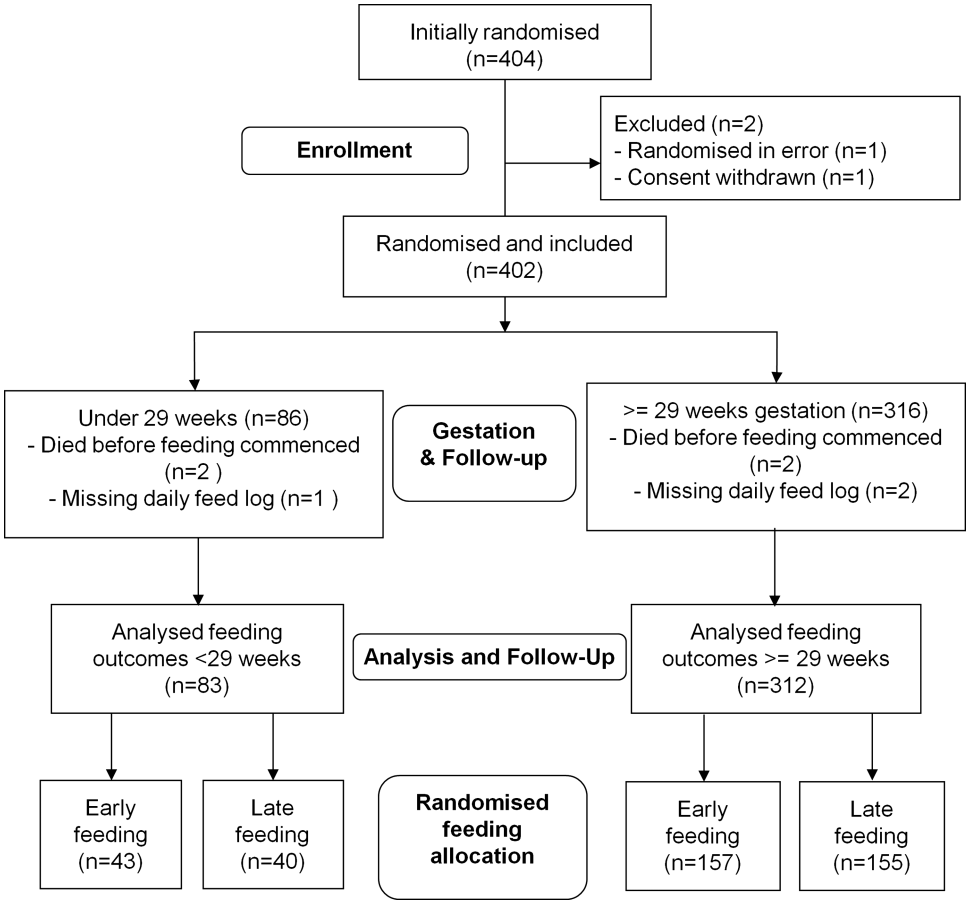

Figure 1 Patient recruitment in the main Abnormal Doppler Enteral Prescription Trial (ADEPT) and in this analysis of feeding outcomes by gestational age.

Definition of feeding intolerance

In ADEPT, predefined guidance on feeding intolerance was given to participating centres and feed volumes could be altered or stopped at the clinician's discretion if there was intolerance. Providing the infant was well with no abnormal abdominal signs, enteral feeds were continued when gastric aspirates were <2–3 mL. The clinician recorded if feeds were omitted, reduced or not increased for these reasons: abdominal distension, vomiting, apnoea, indomethacin/ibuprofen administration, suspected NEC and 'other' reasons. Following any feed deviation, clinicians could either start again from day 1 of the schedule, re-start at the volume previously tolerated or hold for one or more days at a certain volume and then increase as scheduled.

In this analysis, we defined an episode of feeding intolerance as at least 1 day where feeds were omitted, reduced or not increased. To count as a discrete episode, a new episode had to be separated from a previous episode by 3 days without any symptoms of feeding intolerance with feeds reintroduced to at least 20 mL/kg/day. We classified aspirates, distension, vomiting and NEC as gastrointestinal causes, and apnoea, indomethacin and other as non-gastrointestinal causes of feeding intolerance. The point of achieving full feeds was defined as the day on which the infant had tolerated at least 150 mL/kg/day enteral milk for 72 h.

Statistical methods

The analysis was restricted to infants with complete daily feed logs who survived to the randomised age for introduction of enteral feeding with complete data on gastrointestinal outcomes. Gastrointestinal outcomes and symptoms of feeding intolerance were compared between infants <29 and ≥29 weeks' gestation, adjusting for the trial intervention of early and late feeding. Adjusted relative risks (RR) were estimated for dichotomous variables using log binomial regression or log Poisson regression with a robust variance estimator if the binomial model failed to converge.[9] For age to event variables, adjusted hazard ratios (HR) were estimated using Cox regression. Adjusted median differences were calculated for skewed continuous variables using quantile regression. Infants ≥29 weeks' gestation were used as the reference group in all comparisons. We performed an additional comparison of feeding and gastrointestinal outcomes between the early and late feeding groups within infants <29 weeks' gestation.

We examined the association between NEC and the following predefined factors for the group <29 weeks' gestation: gestation at delivery, birth weight, type of milk at first feed, at least 50% breast milk prior to reaching full feeds, ventilation at trial entry, UAC in situ at trial entry, age of passage of first stool, early or late feeding group. We calculated the crude relative risk for each factor separately in a univariate analysis; the number of infants in the <29 weeks group did not permit a reliable multivariate analysis due to the small number of events in each stratum; 95% CIs are presented throughout and two-sided 5% significance level was used to indicate statistical significance. Data were analysed using Stata/SE V.11.2 for Windows.

RESULTS

Clinical characteristics at ADEPT trial entry

Of 404 infants recruited to ADEPT, 86 were <29 weeks' gestation. Eighty-three infants <29 weeks and 312 infants ≥29 weeks remained in the study at commencement feeds and had a daily feed log for analysis of feed tolerance (figure 1). At trial entry, infants <29 weeks were receiving more intensive care interventions, with a higher proportion ventilated, receiving CPAP and with umbilical lines (table 1), compared with those ≥29 weeks. The trial intervention was well adhered to in both gestation groups, with feeds introduced at a median age of day 2 in the early group and day 6 in the late group.

Feeding outcomes by gestational age group

Full enteral feeds were reached by 73/83 (88%) infants in the <29 weeks group and 307/312 (98%) in the ≥29 weeks' gestation group; two infants had incomplete daily feed logs and the remaining infants died (table 2). Full feeds were achieved later in infants <29 weeks; median age 28 days {IQR 22–40} compared with 19 days {IQR 17–23} in infants ≥29 weeks (HR 0.35, 95% CI 0.3 to 0.5). This indicates that the relative likelihood of establishing full feeds at any given age was 65% lower in the <29 week compared with the ≥29 week group. Within the <29 week group, median age to achieve full feeds was 25 days {IQR 22–39} in those allocated to early feeds, and 29 days {IQR 24–40} in those allocated to late feeds. This is, on average, 9 days later than predicted from the trial feeding regimen (early 16 days, late 20 days).

At least one episode of intolerance was found in 75/83 (90%) infants <29 weeks compared to 180/312 (58%) infants ≥29 weeks (RR 1.6, 95% CI 1.4 to 1.8). Episodes of feeding intolerance occurred earlier, at lower milk volumes and lasted longer in infants <29 weeks. Similar numbers in this group had feed intolerance due to gastrointestinal or non-gastrointestinal reasons. Infants <29 weeks also had more days of parenteral nutrition and central lines (table 2). There was no evidence of a difference in feeding intolerance between the early and late feeding group among infants <29 weeks (data not shown).

Table 1 Characteristics of mother and baby by gestational age group

Values are numbers (%) unless stated otherwise	<29 weeks' gestation (n=83)	≥29 weeks' gestation (n=312)
Gestation at delivery (weeks)		
Mean [SD]	27.7 [0.9]	31.9 [1.7]
Birth weight (grams)		
Mean [SD]	688 [119]	1126 [272]
Male sex	45 (54)	165 (53)
Doppler studies		
Absent or reversed end diastolic flow	83 (100)	296 (95)
Cerebral redistribution	0 (0)	16 (5)
Pregnancy induced hypertension*	39 (47)	116 (37)
Antenatal steroids	80 (96)	281 (90)
Mode of delivery		
Vaginal	2 (2)	3 (1)
Caesarean	81 (98)	309 (99)
Apgar score at 5 min*		
Median {IQR}	9 {8, 9}	9 {9, 10}
Ventilated at trial entry	30 (36)	16 (5)
CPAP at trial entry	47 (57)	94 (30)
UAC in situ at trial entry	36 (43)	18 (6)
UVC in situ at trial entry*	61 (73)	48 (15)
Day feeding commenced:		
Median [range]	5 [1, 23]	4 [1, 15]

*A small number of infants had unknown/missing data items; for pregnancy induced hypertension and antenatal steroids, 1 case ≥29 weeks; for Apgar at 5 min, 2 cases <29 weeks, 7 cases ≥29 weeks; UVC at trial entry, 1 case ≥29 weeks.

Table 2 Feeding and gastrointestinal outcomes by gestational age group

Values are numbers (%) unless stated otherwise	<29 weeks' gestation (n=83)	≥29 weeks' gestation (n=312)	Effect measure* (95% CI)
Died after feeding commenced and before reaching full enteral feeding	9 (11)	4 (1)	8.3 (2.6 to 26)
Age at which full enteral feeding was established			
Median IQR	28 {22, 40}	19 {17, 23}	0.35 (0.3 to 0.5)
At least one episode of feeding intolerance	75 (90)	180 (58)	1.6 (1.4 to 1.8)
Number of days of feeding intolerance in babies with at least one episode			
Median {IQR}	7 {3, 16}	3 {2, 6}	4 (1.7 to 6.3)
Age to first day of intolerance since birth			
Median IQR	6 {3, 9}	14 {5, –}†	2.6 (2.0 to 3.4)
Feed volume (mL/kg/day) on first day of intolerance:			
Median {IQR}	5.6 {0.6, 12}	13 {4, 33}	−6.9 (−11 to −3)
At least one episode of feeding intolerance due to gastrointestinal causes (aspirates, distension vomiting or NEC)	62 (75)	139 (45)	1.7 (1.4 to 2.0)
At least one episode of feeding intolerance due to non-gastrointestinal causes (apnoea, indomethacin or other)	60 (72)	119 (38)	1.9 (1.6 to 2.3)
Number of days of parenteral nutrition—amino acids			
Median {IQR}	20 {15, 28}	13 {10, 15}	8 (5.5 to 10.5)
Number of days of central lines			
Median {IQR}	17 {12, 25}	12 {8, 14}	6 (3.5 to 8.5)
Necrotising enterocolitis (NEC)	32 (39)	32 (10)	3.7 (2.4 to 5.7)
Bell's Stage 1	17 (20)	13 (4)	
Bell's Stage 2	7 (8)	10 (3)	
Bell's Stage 3	8 (10)	8 (3)	
Gastrointestinal surgery (laparotomy, bowel resection or stoma)	10 (12)	10 (3)	3.8 (1.6 to 8.7)
Gastrointestinal perforation	7 (8)	4 (1)	6.6 (2.0 to 22)
Gastrointestinal necrosis	5 (6)	7 (2)	2.7 (0.9 to 8.3)
Septic ileus	9 (11)	12 (4)	2.8 (1.2 to 6.5)
Dysmotility or meconium milk plug	6 (7)	9 (3)	2.5 (0.9 to 6.7)
Cholestasis‡	28 (35)	40 (13)	2.6 (1.8 to 4.0)
Died of gut pathology	5 (6)	3 (1)	6.3 (1.5 to 26)

*Effect measures are adjusted for the trial intervention; early or late feeding group. Relative risks are presented for binary variables; hazard ratios for age to event variables, and median difference for continuous variables. The reference group are the infants ≥29 weeks' gestation.
†There is no estimate for 75th centile as fewer than 75% of babies ≥29 weeks' gestation had an episode of feed intolerance.
‡Information on cholestasis was unknown for two infants <29 weeks and eight infants ≥29 weeks' gestation.

Gastrointestinal outcomes by gestational age group

Half of the cases of NEC in the study occurred in infants <29 weeks, despite the fact that they accounted for only 22% of the patients (table 2). The number of episodes of all-stage NEC was 32/83 (39%) in the <29 week group and 32/312 (10%) in the ≥29 week group (RR 3.7, 95% CI 2.4 to 5.7). The risk of Stage II/III NEC was also higher in this group (RR 3.1, 95% CI 1.6 to 5.9).

Almost all adverse gastrointestinal outcomes were significantly more likely in infants <29 weeks, abdominal surgery was required by 10 (12%), gastrointestinal perforation found in 7 (8%), septic ileus in 9 (11%) and cholestasis in 28 (35%). There was no evidence of a difference in gastrointestinal outcomes between early and late feeding groups among infants <29 weeks (data not shown).

The only factor significantly associated with NEC risk was breast milk, with a reduced risk of those receiving at least 50% breast milk prior to reaching full enteral feeds (RR 0.46, 95% CI 0.27 to 0.78) (table 3).

Volumes of milk tolerated in infants <29 weeks' gestation

The median volume of milk tolerated by infants <29 weeks' gestation in the first 10 days of life was much lower than the target trial feeding regimen (figure 2). Early and late feeding groups tolerated median volumes of <20 mL/kg/day in the first 10 days of life, with a subsequent rate of advancement which remained slower than the targeted feeding regimen.

DISCUSSION

This study has confirmed that infants with a combination of gestation <29 weeks, intrauterine growth restriction and abnormal antenatal Doppler blood flow have a very high rate of NEC and other gastrointestinal conditions. Low gestation was an additional risk factor for feed intolerance and NEC, over and above abnormal Doppler. Ninety per cent of babies <29 weeks demonstrated feed intolerance and 39% developed NEC. Randomisation to early or late introduction of milk feeds did not modify this risk, but receiving the majority of feeds as breast milk during milk advancement was associated with a reduced risk of NEC. This high-risk group was very slow to tolerate enteral feeds, with a median age of 28 days to reach full feeds, suggesting that feeds may have to be tailored differently from other preterm groups.

Studies have examined the influence of antenatal Doppler findings on serious neonatal complications such as NEC[2] but few have reported the incidence of feed intolerance. Similar findings to our own were documented by Robel-Tillig *et al*,[10] who found a very high incidence of intestinal dysmotility and delayed feed tolerance in babies with abnormal antenatal umbilical artery pulsatility index. However, this was not found by

Table 3 Risk factors for necrotising enterocolitis (NEC) in babies <29 weeks' gestation

	Babies <29 weeks' gestation only	
Risk factor	**NEC/n (%)**	**Effect measure (95% CI)**
Gestation at delivery (weeks)		
25^{+0} to 26^{+6}	6/15 (40)	referent
27^{+0} to 28^{+6}	26/68 (38)	0.96 (0.48 to 1.90)
Birth weight		
<750 g	23/53 (43)	referent
≥750 g	9/30 (30)	0.69 (0.37 to 1.29)
Breast milk (mothers or donated) at first feed		
No	5/11 (45)	referent
Yes	27/71 (38)	0.84 (0.41 to 1.71)
At least 50% breast milk prior to reaching full feeds		
No	4/5 (80)	referent
Yes	28/76 (37)	0.46 (0.27 to 0.78)
Ventilation at trial entry		
No	22/53 (42)	referent
Yes	10/30 (33)	0.80 (0.44 to 1.46)
UAC in situ at trial entry		
No	16/47 (34)	referent
Yes	16/36 (44)	1.31 (0.76 to 2.24)
Passage of first stool		
≤72 h	15/46 (33)	referent
>72 h	17/37 (46)	1.41 (0.82 to 2.42)
Feeding group		
Early	17/43 (40)	referent
Late	15/40 (38)	0.95 (0.55 to 1.64)

Mihatsch *et al*[11] with similar fetal Doppler findings or by Adiotomre *et al*[12] following fetal absent end-diastolic flow in the umbilical artery.

In the absence of a uniform definition for feeding intolerance, feeding strategies are often modified based on factors associated with feed tolerance or NEC, such as prefeed gastric residual volumes[13 14] the colour of aspirates, abdominal distension, emesis, the presence of blood in stool and apnoea.[15] Symptoms which led clinicians to stop or reduce feeds in our babies <29 weeks occurred at low feed volumes of less than 6 mL/kg/day, with clinicians reporting GI and non-GI symptoms as equally important reasons to modify the baby's feeding. In this open trial without blinding of enteral feeding, clinician bias to report intolerance in fed patients cannot be excluded, but this is representative of the practical decisions involved in clinical practice.

Once feeds have been initiated, there is a choice of minimal enteral feeds and progressive feeds, which can be advanced at a slow or fast rate. Although early studies suggested that small volumes of enteral feeds accelerate maturation of gastrointestinal function,[4 16] with slow advancement providing protection against NEC,[5] the most recent systematic reviews do not provide conclusive evidence of the benefits of minimal enteral feeding[17] or slow advancement.[18] These reviews included high-risk infants but did not concentrate exclusively on this patient group with extreme prematurity and abnormal Doppler.

Two smaller randomised trials used minimal enteral nutrition when examining the effect of early or delayed introduction of feeds in growth-restricted infants with abnormal antenatal Doppler. Both used minimal enteral feeding in their early feeding arm, and ages of feed introduction comparable to ADEPT. Overall NEC rates at all gestations were 12% in Karagianni's study[19] and only 2% (one case) in Van Elburg's study,[20] compared with 16% in the full ADEPT trial. It is difficult to know whether this relates to any protective effect of minimal enteral nutrition, given small patient numbers, differences in antenatal Doppler and gestation distribution between the studies. All our infants <29 weeks and 95% of our infants over this gestation had severe Doppler abnormalities with AREDF in the umbilical artery.

Even in our very high-risk group <29 weeks, we found that breast milk was protective against NEC, in keeping with other observational studies and randomised trials.[21 22] Measures to increase the proportion of milk given as breast milk during the introduction of feeds to these patients should be a priority.

The overall results of ADEPT have shown that starting enteral feeds early in preterm growth-restricted infants with abnormal antenatal Doppler is beneficial. However, this subgroup analysis suggests that growth-restricted infants <29 weeks may require

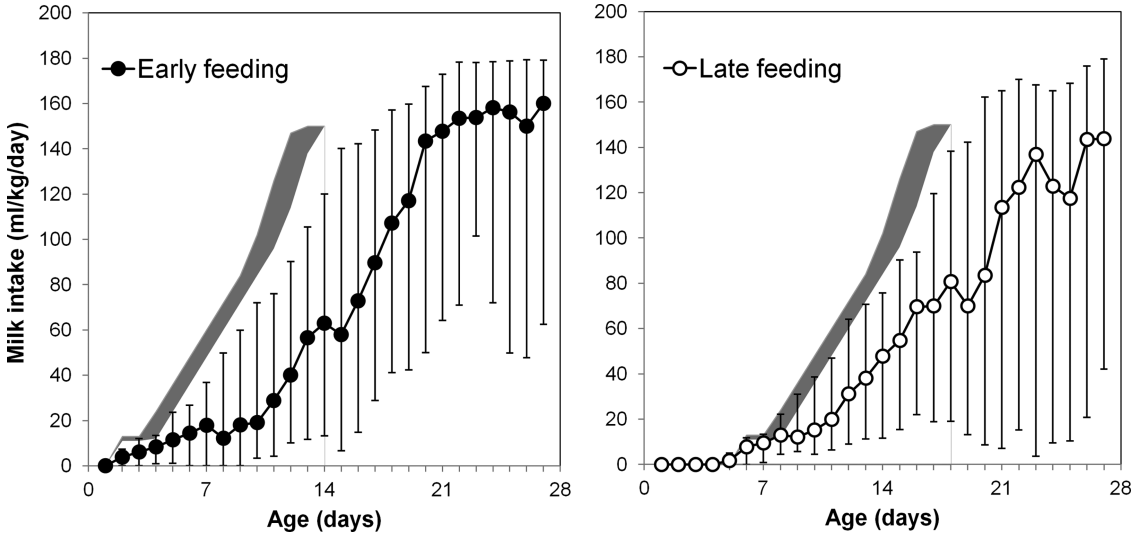

Figure 2 Median volumes of milk (with IQR) tolerated by babies <29 weeks' gestation in the early and late feeding groups. Neither group tolerated the recommended trial feeding regimen (shown by the grey-shaded area).

an increased duration of minimal enteral feeds and a slower rate of feed advancement to facilitate gut adaptation. Clinicians should exercise patience when feeding this group, as the median age to reach full enteral feeds was 28 days, with many infants taking much longer. Their risk of NEC is very high, and further work is required to determine whether different approaches to feeding can modify this risk.

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Contributors The roles of the contributors were as follows: SK: Designed the study, coordinated recruitment and data collection at their site, contributed to data monitoring and analysis, supervised the writing of the manuscript and approved the manuscript as submitted. Guarantor of the paper. NG: Contributed to the subgroup data analysis, drafted the initial manuscript and approved the manuscript as submitted. LL: Performed the data analysis, contributed to data monitoring, contributed to writing the manuscript and approved the manuscript as submitted. JD: Conceptualised and designed the study, coordinated recruitment and data collection at their site, contributed to data monitoring and analysis, supervised the writing of the manuscript and approved the manuscript as submitted. KMcC: Was involved in designing the study, coordinated recruitment and data collection at their site, contributed to data monitoring and analysis, contributed to writing of the manuscript and approved the manuscript as submitted. PM: Was involved in designing the study, coordinated recruitment and data collection at their site, contributed to data monitoring and analysis, contributed to writing of the manuscript and approved the manuscript as submitted. EJ: Was involved in data monitoring and analysis, contributed to writing of the manuscript and approved the manuscript as submitted. PB: Was involved in designing the study, coordinated data monitoring and analysis, contributed to writing of the manuscript and approved the manuscript as submitted. AL: Conceptualised and designed the study, coordinated recruitment and data collection at their site, contributed to data monitoring and analysis, supervised the writing of the manuscript and approved the manuscript as submitted.

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Competing interests None.

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Data sharing statement Data are held by the National Perinatal Epidemiology Unit, Oxford. The data are not routinely available to outside bodies.

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