Feeding in neonates with antenatal doppler abnormalities- a systematic review and meta-analysis

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Research Article

Keywords: Early feeding, rapid advancement, necrotizing enterocolitis, feeding intolerance, mortality

Posted Date: December 21st, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1163424/v1>

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Abstract

Preterm neonates with antenatal doppler abnormalities are at increased risk of necrotizing enterocolitis (NEC). In these neonates, we did a meta-analysis to compare the impact of early versus late initiation of feeding, and slow versus rapid feed advancement on the important neonatal outcomes. The databases of PubMed, Embase, Cochrane central, CINAHL and google scholar were searched on 6th September 2020. We included all randomized controlled trials addressing the study objective(s). The risk of bias was assessed using the Risk of Bias tool, version 2. Certainty of evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. Early feeding did not increase the incidence of NEC stage 2 or more (odds ratio/OR 1.27, 95% confidence interval/CI 0.83, 1.96; 6 studies, 772 participants) and mortality (OR 0.79, 95% CI 0.4, 1.57; 3 studies, 498 participants). A trend was noted towards an increased incidence of feeding intolerance (OR 1.37, 95% CI 0.98, 1.92). There was a significant reduction in time to reach full feeds, duration of total parental nutrition, duration of hospital stay, and rates of hospital-acquired infections. The time to regain birth weight was not different. Rapid feed advancement decreased the time to reach full feeds, without affecting other outcomes. The overall certainty of the evidence was rated low. Heterogeneity was not significant. *Conclusion:* There is low-certainty evidence to recommend early feed initiation in preterm neonates with antenatal doppler abnormalities. The data is insufficient to make a recommendation on the rapidity of feed advancement.

Introduction

Preterm infants are at increased risk of various adverse outcomes compared to the term population in terms of feed intolerance, necrotizing enterocolitis, infections, respiratory morbidities- bronchopulmonary dysplasia, growth failure in short term and abnormal neurodevelopment in the long term. Neonates with abnormal antenatal Doppler of umbilical artery in the form of absent or reverse end diastolic flow (AREDF), or increased resistance to blood flow in ductus venosus and inferior vena cava, or middle cerebral artery redistribution are a subset of preterms with even further increased risk of morbidities [1]. These neonates are usually delivered preterm and are small for gestation (SGA). In the fetal life, they are exposed to chronic hypoxia leading to preferential shunting of blood to the brain at the expense of circulation to the gut. Postnatally, SGA babies have reduced wall thickness, length, villous weight, and crypt depth [2]. Furthermore, this subset of neonates also has intestinal dysbiosis and an alteration of the proliferation-apoptosis homeostasis of the gut. Hence there are structural, functional, and secretory changes in these neonates and enteral feeding in already compromised gut exacerbates feed intolerance and maybe one of the associated etiologies for the development of NEC and thereby poor outcomes [3].

A systematic review of 14 observational studies has shown an increased risk of NEC in neonates with antenatal doppler abnormalities with odds of 2.13 (95% CI 1.4-3.0) compared to controls without AREDF [4]. In preterms to prevent NEC, several strategies like using mother's own milk (MOM), donor milk, standardized feeding regimen, probiotics avoiding prolonged empirical antibiotics, avoiding proton pump inhibitors are being used [5]. However, in growth-restricted babies with antenatal doppler abnormalities, due to fear of NEC, there are considerable variations in initiation and advancement of feeds. Feeds are often delayed and are advanced at a slower rate, thereby delaying the enteral nutrition, and placing them at increased risk of parenteral nutrition induced liver failure and infections [6]. Hence, a focused systematic review of the available evidence is needed to reduce the variations and improve outcomes in this vulnerable subset of preterms. In neonates with antenatal abnormal dopplers, we compared the impact of early feeding and rapid advancement of feeds with delayed feeding and slow advancement of feeds, respectively result on neonatal outcomes (Primary/Critical: Necrotizing enterocolitis/NEC and mortality; Secondary/Important: feed intolerance, total parenteral nutrition days, duration of hospitalization, healthcare associated infections, cost of care, and neurodevelopment at 18-24 months of corrected age).

Methods

The protocol was registered in the PROSPERO database (registration number CRD42020195845) and can be accessed from the website <https://www.crd.york.ac.uk/PROSPERO/>. We followed the Cochrane handbook for systematic reviews of interventions [7], the PRISMA (preferred reporting items for systematic reviews and meta-analyses) reporting guidelines [8], and the GRADE handbook [9]. The differences between the protocol and final review are provided in the online supplemental material.

We included all randomized controlled studies comparing early versus delayed feeding, and slow versus rapid feed advancement in neonates with antenatal doppler abnormalities. The population of interest was preterm neonates (<37 weeks) with antenatal doppler abnormalities defined as absent or reverse end diastolic flow (AREDF), or increased resistance to blood flow in ductus venosus and inferior vena cava, or middle cerebral artery redistribution. Early feeding was defined as feed initiation within 48 – 72 hours of birth, and delayed feeding was defined as feed initiation beyond this time point. Slow advancement was defined as <20-30 ml/kg/day advancement per day, and rapid advancement as >20-30 ml/kg/day.

The databases of PubMed, Embase, CINAHL, Cochrane CENTRAL, and Google Scholar were searched on the 6th of September 2020 for studies published between 1990 and 5th of September 2020. The search terminology is provided in the online supplemental material. We also searched for grey literature from various sources like dissertation websites and contacting researchers who have worked on this subject.

We included the studies when they provided data on at least one of the pre-specified outcomes. These outcomes included feeding intolerance (1 or more of the following: >50% prefeed aspirates, abdominal girth increase by >2 cm, vomiting, bilious aspirates, blood in stools), necrotizing enterocolitis stage 2 or more (modified Bell's staging), time to attain full enteral feeds (at least 150 ml/kg/d), duration of total parenteral nutrition (TPN), mortality, health-care associated infections (culture proven sepsis), duration of hospital stay, cost of care, and neurodevelopmental outcomes at 18-24 months corrected age. We excluded conference abstracts and letters to the editor without original data, and studies published in languages other than English. We excluded studies done in growth-restricted babies without data on antenatal doppler findings.

The database search was performed by 2 reviewers (AS and RP). The studies obtained by database search were entered into Rayyan software. After excluding duplicates and non-English studies, the titles and abstracts were assessed for eligibility by 2 reviewers independently (AS and RP), and any discrepancy was

sorted out by mutual discussion, or involvement of the third reviewer (SM). The following data were extracted by RP and AS in a blinded manner: study identification details; study characteristics including the study setting, study design, feeding strategies, definitions used for feed intolerance, NEC, and hospital-acquired infections; population characteristics including the gestational age, birth weight, gender, antenatal steroid use, mode of delivery, chorioamnionitis, and resuscitation details; feeding strategy in the intervention and control arms (timing of initiation, type of milk used, volume at initiation, rapidity of advancement, and volume of feed advancement); and the data on aforementioned outcomes. When the data were missing/ unclear, we contacted the corresponding author through email. Any discrepancy was resolved by discussion, or by consulting the third reviewer (SM).

We assessed the risk of bias (ROB) of included studies using the Cochrane Risk of Bias tool, version 2 for randomised controlled trials [10]. We assessed the methods used for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, selective reporting, and completeness of outcome data. An intention to treat analysis was considered desirable. The assessment was done by 2 reviewers (RP and AS) in a blinded manner from all the eligible studies. Any discrepancy was resolved by discussion, or by consulting the third reviewer (SM).

Studies (or outcomes) deemed comparable were pooled to include in the meta-analysis. A random-effect model meta-analysis was performed using the Cochrane statistical package, RevMan 5.4 software, for each outcome if two or more studies were available. The comparative effect sizes were calculated as risk ratios (RR) and risk difference (RD) for categorical outcomes and mean differences (MD) for continuous outcomes with their 95% confidence intervals (CIs). The pooled estimates were depicted using forest plots. We used Cochrane handbook recommended formulae for converting median to mean; and range, interquartile range and 95% confidence intervals to standard deviations (online supplemental material). Heterogeneity was assessed using the I^2 statistic [11]. We planned subgroup and sensitivity analysis based on the type of doppler abnormalities (AEDF or REDF), intrauterine growth status (small-for-gestational age and appropriate-for gestational age), and gestational age (< 28 weeks, 29 – 31 weeks, and >32 weeks). We planned to assess heterogeneity by comparing important factors in trial design (bias), intervention (feeding strategy), and co-interventions (probiotics, mothers' own milk use, and antibiotic usage rates). Assessment of publication bias was planned if the number of studies exceeded 10. The Cochrane Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of evidence [9].

Results

Our search strategy yielded 2,830 studies (Figure 1- PRISMA flow diagram). After assessing 9 full-text articles, we included 7 studies in the meta-analysis [12–18]. While 6 studies assessed early versus delayed feeding, 1 study assessed slow versus rapid feed advancement [18]. The characteristics of included studies are provided in Table 1. The characteristics of the participants are provided in Table 2. The characteristics of excluded studies are provided in the online supplemental material.

Table 1
Characteristics of included studies

Author	Study setting	Inclusion criteria	Exclusion criteria	NEC definition	Feeding intolerance definition	Full feeds definition
Abdelmaaboud, 2012	Level 3 NICU, Doha, Qatar	Fulfilling all the 5 criteria: (1) 24-36+6 weeks, (2) <10th centile on Child Growth Foundation Charts, (3) Antenatal ultrasound showing IUGR with AREDF on at least 50% of the Doppler waveforms from the umbilical artery on at least one occasion during pregnancy and an evidence of cerebral redistribution, defined as occurring when both the umbilical artery pulsatility index >95th centile and the middle cerebral artery pulsatility index <5th centile for gestational age; (4) Arterial cord blood pH $\geq$ 7.0, base deficit $\geq$ -12 mmol/L and (5) 5-minute Apgar score > 5.	Major congenital abnormality including known chromosomal abnormality, twin-twin transfusion, intra-uterine transfusion or exchange transfusion, rhesus iso-immunisation, significant multi-organ failure and inotropic drug support prior to trial entry or if they already received any minimal enteral feeding	Modified Bells' staging criteria	Gastric residuals were checked before each feed. (1) Non-bilious residuals: 25-50% + other worrying signs; >50% gastric residuals + AG increase >2 cm. (2) Billious aspirates. (3) Blood in stool, loose stool, metabolic acidosis and other signs of NEC	150-160 ml/kg/day sustained for 72 hours
Amon, 2013	Level 3 NICU, Kafar Saba, Israel	Clinically & hemodynamically stable, birth wt <10th centile as per Israel National registry & gest <37 wks & AREDF	Systemic disease, need for mechanical ventilation, major congenital anomalies including known chromosomal abnormality, enteral feeding before study entry, use of anti-reflux medication or special diet before or during the study period, Apgar score 0 to 3 for > 5 minutes, arterial cord blood pH < 7.0 or base deficit 12 to 16 mmol/L, need for resuscitation, or significant multi-organ failure.	No mention	Clinical signs of abdominal distension/tenderness, visible bowel loops or emesis, gastric residuals>50% of 3hr volume	150 ml/kg
Karagianni, 2009	Level 3 NICU, Greece	27-34 weeks, Birth wt <10th centile, Abnormal Doppler (elevated PI>90th centile), arterial cord pH>7 (base deficit >-12mmol/L) and 5 min APGAR >5	Major congenital anomalies, infections, signs of genetic syndromes and gastrointestinal tract anomalies, exchange transfusion, inotropic support	Bell's criteria 2 & 3	Gastric residuals, bilious vomiting, abdominal distension	Not mentioned
Leaf, 2012	Southampton, Multicentre, UK	Preterm (up to 34+6 weeks of gestation), SGA (birth weight below 10th centile ²³), 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)	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	modified Bell's stage 1, 2, or 3	Not mentioned	150 ml/kg/d sustained-72hrs

NEC- necrotizing enterocolitis, NICU- neonatal intensive care unit, IUGR- intrauterine growth retardation, AG- abdominal girth, AREDF- absent or reversal of end diastolic flow, UA- umbilical artery.

Author	Study setting	Inclusion criteria	Exclusion criteria	NEC definition	Feeding intolerance definition	Full feeds definition
Srinivasan, 2017	Level 3 NICU, Mumbai, India	Preterm (up to 36+6 weeks of gestation), 24 hours postnatal age, and had abnormal antenatal Doppler studies indicative of IUGR. This was defined as the following: (1) AREDF 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)	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	Not mentioned	Not mentioned	Not mentioned
Tewari, 2017	Level 3 NICU, Delhi, India	<32 weeks with AREDF on UA Doppler and birth weight below the 10th centile	Extramural, symmetric IUGR, antenatally suspected intestinal anomaly, lethal congenital anomaly, dysmorphic, needed invasive ventilation, inotropic support or extensive resuscitation and parent unavailable. Intramural preterm IUGR neonates < 27 weeks	Not defined	Abdominal girth >2 cm increase over baseline in 24 h; Pre-feed aspirate volume >50% of feed volume; Pre-feed aspirate color: Billious/ altered or fresh blood; >1 vomitus with yellow or green color and/ or altered blood	150-180ml/kg/d allowing for weight gain consistently 3 days
Jain, 2015	Level 3 NICU, Chandigarh, India	AEDF who were ≥ 1000 g and between 30-36 weeks	Perinatal asphyxia (Apgar score at 5 minutes <6), REDF, shock or inotrope dependency, any gastrointestinal tract or other major congenital malformation	Bell's criteria	Any two of these criteria: gastric residuals >33% of total feeds on 2 consecutive occasions (if total feed volume >8ml) or >50% on a single occasion (if total feed volume was <8ml), abdominal distension (increase in abdominal girth by >2cm from baseline), brown, bilious, or blood stained gastric aspirates, vomiting for which feeds were withheld for ≥ 12 hours and absent bowel sounds on auscultation in two different quadrants for two minutes confirmed by second observer.	150ml/kg/day
NEC- necrotizing enterocolitis, NICU- neonatal intensive care unit, IUGR- intrauterine growth retardation, AG- abdominal girth, AREDF- absent or reversal of end diastolic flow, UA- umbilical artery.						

Table 2: Characteristics of neonates participating in the included studies

Author, year	Gestational age ^a Mean (SD) Median (IQR)		Birth weight ^a		Male gender ^b n(%)		Antenatal steroid use ^b n(%)		PIH ^b n(%)		Cesarean se n(%)
	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control	Experimental	Control	Experimental
Abdelmaaboud, 2012	32.5 ± 3.5	31.8 ± 2.9	740 (620-1270)	810 (630-1945)	30 (45.2)	33 (49.2)	48 (72.7)	52 (77.6)	Preeclampsia: 18 (27.3)	16 (23.9)	57 (86.3)
Arnon, 2013	31 (29-34)	32 (30-34)	1425 (1032-1620)	1542 (963-1683)	Not provided	Not provided	26 (87)	26 (87)	Not provided	Not provided	Not provided
Karagianni, 2009	32 (27-34)	31.3 (27-34)	1080 (680-1440)	1130 (440-1420)	17 (42.5)	16 (39)	33 (82.5)	32 (72)	9 (22.5)	10 (24.4)	39 (97.5)
Leaf, 2012	31 (2.3)	31 (2.3)	1042 (303)	1021 (308)	104 (52)	112 (56)	Not provided	Not provided	83 (41)	76 (38)	189 (94)
Srinivasan, 2017	32.1 (2.07)	32.8 (2.3)	1119 (181.26)	1116 (181.26)	8 (50)	5 (31)	Not provided	Not provided	Not provided	Not provided	15 (93)
Tewari, 2017	<30 wk-28+5 (4), >30wk-31+3 (5)	<30wk-28+3 (5), >30wk-31+2 (5)	<30 833 (121), >30-1212.38 (118.86)	<30-833 (119.70), >30-1232.6 (119.9)	<30- 6 (60), >30-12 (58)	<30- 5 (50), >30-11 (53)	<30-9 (90), >30-16 (76)	<30-8 (80), >30-18 (85)	<30-7, >30-15	<30-8, >30-13	<30-9 (90), >30-15 (72)
Jain, 2015	>1250g-34 (1.4); <1250g-33 (1)	>1250-34(1.2); <1250g-32(1.4)	>1250g-1521 (205); <1250g-1135(67)	>1250g-1563 (391); <1250g-1110 (78)	24 (60)	25 (58)	25 of 34 (73.5)	22 of 38 (58)	26 (65)	29 (67)	31 (77.5)

a- mean (SD); b- n (%); c- median (IQR)

SD- standard deviation, IQR- interquartile range, PIH- Pregnancy Induced Hypertension.

In three studies, the neonates were <37 weeks gestational age [12, 13, 16], while 3 other studies included neonates up to 32 weeks [17], 34 weeks [14], and 35 weeks [15]. In five studies, all the neonates included were small for gestational age, while in one study [16], it was not reported. In the five studies that provided data on antenatal steroid use [12–14, 17, 18], no significant differences were noted between the experimental and control arms. None of the studies provided data on the duration of doppler abnormalities, chorioamnionitis and sickness scores at admission to NICU. Jain et al have restricted study population to neonates between 30-36 weeks and weight above 1,000 grams; 60% of neonates in the experimental arm and 63% in the control arm were growth-restricted [18].

While donor human milk was provided as a second option when breast milk was unavailable in the three recent studies [15–17], infant formula was provided in the other four studies [12–14, 18]. The human milk was fortified at feed volumes of 100 – 150 ml/kg in three studies [12, 13, 15], while it was unclear in the others. None of the studies have reported the use of probiotics. The definitions used for NEC (modified Bell's staging) and full feeds (150-180 ml/kg/day sustained for 3 days) were consistent across the studies. Feeding intolerance was variably defined in five studies [12–14, 17, 18], while it was not defined in the other two studies [15, 16]. In all the studies, >50% pre-feed volumes, blood in stool, bilious aspirates and abdominal signs were considered worrisome.

In five studies, early feeding was defined as feeding within 48 hours of birth, while in one study, it was defined as <5 days of birth [14]. The volume at feed initiation varied from 4 – 30 ml/kg/day, duration of trophic feeds from 0 – 6 days, and volume of feed advancement from 12 – 35 ml/kg/day. In 2 studies, the feed initiation and advancement were stratified according to the birth weight [15, 17]. In the study by Jain et al, rapid advancement was defined as 30 ml/kg/day in neonates weighing 1-1.25 kg, and 40 ml/kg/day in those weighing >1.25 kg [18]. Slow advancement was defined as 20 ml/kg/day and 30 ml/kg/day in the above weight ranges, respectively. Further details of feed initiation and advancement in the experimental and control arms are summarized in the online supplemental material.

When compared to delayed feeding, the strategy of early feeding did not increase the incidence of NEC stage 2 or more (odds ratio/OR 1.27, 95% confidence interval/CI 0.83, 1.96) and mortality (OR 0.79, 95% CI 0.4, 1.57). A trend was noted towards an increased incidence of feeding intolerance (OR 1.37, 95% CI 0.98, 1.92). There was a significant reduction in time to reach full feeds (mean difference/MD -3.03 days, 95% CI -3.53, -2.53 days), duration of total parental nutrition (MD -3.14 days, 95% CI -3.98, -2.3 days), and duration of hospital stay (MD -4.98 days, 95% CI -8.31, -1.65 days). There was also a significant reduction in rates of hospital-acquired infections (OR 0.67, 95% CI 0.45, 0.98). The time to regain birth weight was not different. The forest plots are shown in figure 2.

On the risk of bias assessment using RoB2 tool, 5 studies were adjudged to have some concerns [12–14, 16, 17], while 1 study had a low risk of bias [15]. For outcomes with subjectivity in assessment (i.e., feeding intolerance), 4 studies were adjudged to be at high risk of bias due to lack of blinding of outcome assessment [12, 15–17]. The assessment is shown in Table 3 and the criteria used in the online supplemental material. Heterogeneity was not noted for the outcomes studied, except the duration of hospital stay ($I^2 = 35\%$). Subgroup analysis, sensitivity analysis and publication bias assessment were not performed because of the small number of eligible studies.

Table 3
Risk of bias in the included studies

Author, year	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias	Overall effect
Abdelmaaboud, 2012	Some concerns ^a	Low	Low	Low ^d	Some concerns ^e	Some concerns ^g	Favours experimental
Arnon, 2013	Some concerns ^b	Low	Low	Low	Some concerns ^f	Some concerns	Favours experimental
Karagianni, 2009	Some concerns ^a	Some concerns ^c	Low	Low	Some concerns ^e	Some concerns	Favours experimental
Leaf, 2012	Low	Low	Low	Low ^d	Low	Low ^g	Unpredictable
Srinivasan, 2017	Low	Low	Low	Low ^d	Some concerns ^e	Some concerns ^g	Unpredictable
Tewari, 2017	Low	Low	Low	Low ^d	Some concerns ^e	Some concerns ^g	Unpredictable
Jain, 2015	Low	Low	Low	Low	Low	Low	NA
a- Methods to generate random sequence and conceal allocation not mentioned.							
b- No information provided on allocation concealment							
c- Post randomization exclusions were done							
d- Outcome assessors were not blinded for the intervention. The prior knowledge can influence assessment of outcomes of feed intolerance. Hence, the assessment for this outcome is high risk of bias. For other outcomes like necrotizing enterocolitis stage 2 or more, mortality, duration of parenteral nutrition, duration of hospital stay, hospital acquired sepsis, time to reach full feeds and time to regain birth weight, prior knowledge is unlikely to influence assessment of outcomes. They were adjudged to be at low risk of bias.							
e- Trail protocol, registration details, and statistical analysis plan not available							
f- The published protocol mentions this as an observational study for electrogastrography (EGG). Hence, in effect, this protocol was not published/ or is planned as the study progressed							
g- high risk for outcomes of feeding intolerance and NEC; some concerns for other outcomes.							

On GRADE assessment, the certainty of evidence was rated high for days on parenteral nutrition; moderate for mortality, and time to reach full feeds; low for NEC 2 or more, hospital-acquired sepsis, duration of hospital stay, and time to regain birth weight; and very low for feeding intolerance (Table 4).

Table 4. GRADE evidence profile

Comparison 1: Early versus delayed initiation of feed in neonates with antenatal doppler abnormalities

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early	delayed feed initiation	Relative (95% CI)	Absolute (95% CI)		
Necrotizing enterocolitis 2A or more												
6	randomised trials	serious ^a	not serious	not serious	serious ^b	none	54/385 (14.0%)	44/387 (11.4%)	OR 1.27 (0.83 to 1.96)	26 more per 1,000 (from 17 fewer to 87 more)	⊕⊕●● Low	CRITICAL
Feeding intolerance												
5	randomised trials	very serious ^c	not serious	not serious	serious ^b	none	112/355 (31.5%)	90/356 (25.3%)	OR 1.37 (0.98 to 1.92)	64 more per 1,000 (from 4 fewer to 141 more)	⊕●●● Very low	IMPORTANT
Time to reach full feeds												
5	randomised trials	serious ^d	not serious	not serious	not serious	none	345	346	-	MD 3.03 lower (3.53 lower to 2.53 lower)	⊕⊕⊕● Moderate	IMPORTANT
Duration of hospital stay												
5	randomised trials	serious ^d	not serious	not serious	serious ^b	none	345	945	-	MD 4.98 lower (8.31 lower to 1.65 lower)	⊕⊕●● Low	IMPORTANT
Mortality												
3	randomised trials	not serious	not serious	not serious	serious ^b	none	16/249 (6.4%)	20/249 (8.0%)	OR 0.79 (0.40 to 1.57)	16 fewer per 1,000 (from 47 fewer to 40 more)	⊕⊕⊕● Moderate	CRITICAL
Hospital acquired sepsis												
4	randomised trials	serious ^e	not serious	not serious	serious ^b	none	63/279 (22.6%)	85/279 (30.5%)	OR 0.67 (0.45 to 0.98)	78 fewer per 1,000 (from 140 fewer to 4 fewer)	⊕⊕●● Low	IMPORTANT
Days on total parenteral nutrition												
3	randomised trials	not serious	not serious	not serious	not serious	none	249	249	-	MD 3.14 lower (3.98 lower to 2.3 lower)	⊕⊕⊕⊕ High	IMPORTANT
Time to regain birth weight												
2	randomised trials	serious ^f	not serious	not serious	serious ^b	none	97	98	-	MD 4.15 higher (9.57 lower to 17.86 higher)	⊕⊕●● Low	IMPORTANT

CI: confidence interval; MD: mean difference; OR: odds ratio

Explanations

- Of the 6 studies, 3 had "some concerns" in the randomization process, 1 due to deviation from intended intervention, and 5 studies in the selection of reported results.
- The confidence intervals are wide
- Of the 5 studies, 4 were adjudged to be at high risk of bias in the measurement of the outcome due to lack of blinding of outcome assessors. 2 studies had some concerns in the randomization process, 1 due to deviation from the intended intervention, and 4 in the selection of the reported result.
- Of the 5 studies, 2 had some concerns in the randomization process and 4 in the selection of the reported result.
- Of the 4 studies, 1 study had some concerns in the randomization process, and 3 studies in the selection of the reported outcome.
- Of the 2 studies, 1 had some concerns in the randomization process and both in the selection of the reported outcome.

Comparison 2: Slow compared to Rapid advancement of feeds for neonates with antenatal doppler abnormalities

Certainty assessment							№ of patients		Effect		Certainty	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Slow	Rapid advancement of feeds	Relative (95% CI)	Absolute (95% CI)		
Necrotizing enterocolitis												
1	randomised trials	not serious	serious ^a	not serious	serious ^b	none	3/40 (7.5%)	4/43 (9.3%)	OR 0.79 (0.17 to 3.77)	18 fewer per 1,000 (from 76 fewer to 186 more)	⊕⊕●● Low	CRITICA ^a
Feeding intolerance												
1	randomised trials	not serious	serious ^a	not serious	serious ^b	none	9/40 (22.5%)	11/43 (25.6%)	OR 0.84 (0.31 to 2.32)	32 fewer per 1,000 (from 160 fewer to 188 more)	⊕⊕●● Low	IMPORTA ^a
Mortality												
1	randomised trials	not serious	serious ^a	not serious	serious ^b	none	0/40 (0.0%)	5/43 (11.6%)	OR 0.09 (0.00 to 1.62)	105 fewer per 1,000 (from -- to 59 more)	⊕⊕●● Low	CRITICA ^a
Hospital acquired sepsis												
1	randomised trials	not serious	serious ^a	not serious	serious ^b	none	3/40 (7.5%)	6/43 (14.0%)	OR 0.50 (0.12 to 2.15)	65 fewer per 1,000 (from 120 fewer to 119 more)	⊕⊕●● Low	IMPORTA ^a
Time to reach full feeds												
1	randomised trials	not serious	serious ^a	not serious	serious ^b	none	40	43	-	MD 0.2 lower (0.39 lower to 0.01 lower)	⊕⊕●● Low	IMPORTA ^a
Duration of parenteral nutrition												
0	randomised trials						0	0	-	see comment	-	IMPORTA ^a
Duration of hospital stay												
1	randomised trials	not serious	serious ^a	not serious	serious ^b	none	40	43	-	MD 3.4 higher (0.45 lower to 7.25 higher)	⊕⊕●● Low	IMPORTA ^a
Time to regain birth weight												
0	randomised trials						0	0	-	see comment	-	IMPORTA ^a

CI: confidence interval; MD: mean difference; OR: odds ratio

Explanations

- a. Wide confidence interval
- b. Small sample size

When compared to slower feed advancement, rapid feed advancement resulted in decreased time to reach full feeds (MD -0.2 days, 95% CI -0.39, -0.01). There was no difference in other outcomes. The overall risk of bias was adjudged to be low. However, because of the small sample size and wide confidence intervals, the certainty of evidence was rated low.

Discussion

Summary of main results:

We evaluated the benefits and harms of early initiation of feeds in neonates with antenatal doppler abnormalities. Six studies with 772 newborns met the inclusion criteria. Early feeding strategy decreased the time to reach full feeds, duration of parenteral nutrition, duration of hospital stay, and rates of hospital-acquired infection. Although there was a trend towards an increase in rates of feeding intolerance, the incidence of NEC did not increase. There was no effect on mortality and time to regain birth weight.

One study with 83 newborns was eligible for assessment of slow versus rapid advancement of feeds. There was a clinically insignificant reduction in time to reach full feeds. Other outcomes were not affected.

We could not find any review which addressed the same question, and hence are unable to make any comparisons with existing literature.

Overall completeness and applicability of evidence:

The available evidence is sufficient to understand that early feeding in neonates with antenatal doppler abnormalities does not increase rates of NEC or mortality. However, as only one study assessed the rapidity of feed advancement, with a small sample size, more evidence is needed to answer this question.

Quality of evidence:

The overall quality of evidence was low. The main factors limiting the quality of evidence were the risk of bias and imprecision in estimates. The risk of bias was predominantly due to problems with the randomization process and selective reporting of the outcomes. The assessment of outcome was not blinded in 4 of the 7 studies, but this is unlikely to impact outcomes other than feeding intolerance.

The only eligible study comparing slow versus rapid feed advancement excluded neonates with extremely low birth weight and gestational age <30 weeks, limiting the generalizability. Also, the sample size was very small.

Potential biases in the review process:

We are unlikely to miss any published literature with the extensive literature search performed. The process of data screening, data extraction and risk of bias assessment was performed by 2 reviewers in a blinded manner and the discrepancies were resolved on group meetings involving the third reviewer. This would minimize the introduction of additional bias. For two studies, we requested data from the author and received the required information [17, 18].

Conclusions

Implications for practice:

There is low-quality evidence that early feeding does not increase rates of necrotizing enterocolitis and moderate-quality evidence that it does not impact mortality. There is very low-quality evidence on a trend towards an increased incidence of feeding intolerance. There is low- to moderate-quality evidence on shorter time to reach full feeds, duration of parenteral nutrition, duration of hospital stay, and lower hospital-acquired infections. As benefits outweigh the harms, it is recommended to use the early feeding strategy in neonates with antenatal doppler abnormalities.

There is low quality evidence that rapid feed advancement reduces time to reach full feeds in neonates with gestational age >30 weeks, and birth weight >1 kg. The available data is insufficient to recommend one strategy over the other.

Implication for research:

Future trials could be undertaken to assess the benefits and harms of early feeding strategies while other evidence-based practices to reduce necrotizing enterocolitis were followed, namely use of probiotics, mothers' own milk and rational antibiotic use. Further studies are necessary in neonates with antenatal doppler abnormalities, but no intrauterine growth retardation. More studies are needed comparing slow versus rapid advancement of feeds.

Declarations

Acknowledgements: None

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Figures

Figure 1: PRISMA flow diagram

Figure 1

PRISMA flow diagram

Figure 2

Forest plots showing comparison of early versus delayed initiation of feeds in neonates with antenatal doppler abnormalities

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