Cochrane Library

Cochrane Database of Systematic Reviews

High versus standard volume enteral feeds to promote growth in preterm or low birth weight infants (Review)

Abiramalatha T, Thomas N, Gupta V, Viswanathan A, McGuire W

Abiramalatha T, Thomas N, Gupta V, Viswanathan A, McGuire W.
High versus standard volume enteral feeds to promote growth in preterm or low birth weight infants.
Cochrane Database of Systematic Reviews 2017, Issue 9. Art. No.: CD012413.
DOI: 10.1002/14651858.CD012413.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

High versus standard volume enteral feeds to promote growth in preterm or low birth weight infants

Thangaraj Abiramalatha[1], Niranjan Thomas[2], Vijay Gupta[2], Anand Viswanathan[3], William McGuire[4]

[1]Neonatology, Sri Ramachandra Medical College and Research Institute, Chennai, India. [2]Neonatology, Christian Medical College, Vellore, India. [3]Cochrane South Asia, Prof. BV Moses Center for Evidence-Informed Health Care and Health Policy, Christian Medical College, Vellore, India. [4]Centre for Reviews and Dissemination, The University of York, York, UK

Contact address: Thangaraj Abiramalatha, Neonatology, Sri Ramachandra Medical College and Research Institute, Chennai, Tamil Nadu, India. abi_paeds@yahoo.com.

Editorial group: Cochrane Neonatal Group.
Publication status and date: New, published in Issue 9, 2017.

Citation: Abiramalatha T, Thomas N, Gupta V, Viswanathan A, McGuire W. High versus standard volume enteral feeds to promote growth in preterm or low birth weight infants. *Cochrane Database of Systematic Reviews* 2017, Issue 9. Art. No.: CD012413. DOI: 10.1002/14651858.CD012413.pub2.

ABSTRACT

Background

Breast milk alone, given at standard recommended volumes (150 to 180 mL/kg/d), is not adequate to meet the protein, energy, and other nutrient requirements of growing preterm or low birth weight infants. One strategy that may be used to address these potential nutrient deficits is to give infants enteral feeds in excess of 200 mL/kg/d ('high-volume' feeds). This approach may increase nutrient uptake and growth rates, but concerns include that high-volume enteral feeds may cause feed intolerance, gastro-oesophageal reflux, aspiration pneumonia, necrotising enterocolitis, or complications related to fluid overload, including patent ductus arteriosus and bronchopulmonary dysplasia.

Objectives

To assess the effect on growth and safety of feeding preterm or low birth weight infants with high (> 200 mL/kg/d) versus standard (≤ 200 mL/kg/d) volume of enteral feeds. Infants in intervention and control groups should have received the same type of milk (breast milk, formula, or both), the same fortification or micronutrient supplements, and the same enteral feeding regimen (bolus, continuous) and rate of feed volume advancement.

To conduct subgroup analyses based on type of milk (breast milk vs formula), gestational age or birth weight category of included infants (very preterm or VLBW vs preterm or LBW), presence of intrauterine growth restriction (using birth weight relative to the reference population as a surrogate), and income level of the country in which the trial was conducted (low or middle income vs high income) (see 'Subgroup analysis and investigation of heterogeneity').

Search methods

We used the Cochrane Neonatal standard search strategy, which included searches of the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 2) in the Cochrane Library; MEDLINE (1946 to November 2016); Embase (1974 to November 2016); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to November 2016), as well as conference proceedings, previous reviews, and trial registries.

Selection criteria

Randomised and quasi-randomised controlled trials that compared high-volume versus standard-volume enteral feeds for preterm or low birth weight infants.

Data collection and analysis

Two review authors assessed trial eligibility and risk of bias and independently extracted data. We analysed treatment effects in individual trials and reported the risk ratio and risk difference for dichotomous data, and the mean difference for continuous data, with respective 95% confidence intervals. . We assessed the quality of evidence at the outcome level via the GRADE approach.

Main results

We found one eligible trial that included 64 infants. This trial was not blinded. Analysis showed a higher rate of weight gain in the high-volume feeds group: mean difference 6.20 g/kg/d (95% confidence interval 2.71 to 9.69). There was no increase in the risk of feed intolerance or necrotising enterocolitis with high-volume feeds, but 95% confidence intervals around these estimates were wide. We assessed the quality of evidence for these outcomes as 'low' or 'very low' because of imprecision of the estimates of effect and concern about risk of bias due to lack of blinding in the included trial. Trial authors provided no data on other outcomes, including gastro-oesophageal reflux, aspiration pneumonia, necrotising enterocolitis, patent ductus arteriosus, bronchopulmonary dysplasia, or long-term growth and neurodevelopment.

Authors' conclusions

We found only very limited data from one small unblinded trial on the effects of high-volume feeds on important outcomes for preterm or low birth weight infants. The quality of evidence is low to very low. Hence, available evidence is insufficient to support or refute high-volume enteral feeds in preterm or low birth weight infants. A large, pragmatic randomised controlled trial is needed to provide data of sufficient quality and precision to inform policy and practice.

PLAIN LANGUAGE SUMMARY

High versus standard volumes of feeds for preterm or low birth weight infants

Review question

Does giving preterm or low birth weight infants more milk than is usually given promote growth without causing feeding problems?

Background

Infants born very early (preterm) or very small (low birth weight) need extra nutrients for growth compared to bigger or more mature infants. One way to deliver extra nutrition is to give infants more milk than usual ("high-volume feeds"), typically more than 200 mL per kilogram per day. Although giving high volumes of milk to preterm or low birth weight infants might increase growth rates, concerns include that infants may not tolerate high-volume feeds and may experience side effects including severe bowel problems. We have looked for evidence from clinical trials that assessed whether high-volume feeds are beneficial or harmful for preterm or low birth weight infants.

Study characteristics

Through literature searches up-to-date until Novebember 2016, we found only one small randomised controlled trial (with 64 very low birth weight infant participants) that addressed this question.

Key results

Very low birth weight infants who receive more milk than standard volumes gain weight more quickly during their hospital stay. We found no evidence suggesting that giving infants high volumes of milk causes feeding or gut problems, but this finding is not certain.

Conclusions

Available evidence is insufficient to support or refute the use of high-volume feeds in preterm or low birth weight infants. High-volume feeds might increase the rate of weight gain, but more trials are needed to confirm this finding and to examine whether high-volume feeds cause any problems for preterm or low birth weight infants.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

High-volume feeds vs standard-volume feeds for preterm or low birth weight infants

Patient or population: preterm or low birth weight infants
Setting: neonatal care facilities
Intervention: high-volume feeds
Comparison: standard-volume feeds

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with standard-volume feeds	Risk with high-volume feeds			
Weight gain (g/kg/d)	Mean weight gain was 18.7 g/kg/d	Mean weight gain was 6.2 g/kg/d higher (2.71 higher to 9.69 higher)	-	61 (1 RCT)	⊕⊕◯◯ LOW[a,b]
Feed intolerance	Study population		RR 1.81 (0.89 to 3.67)	61 (1 RCT)	⊕⊕◯◯ LOW[a,b]
	258 per 1000	467 per 1000 (230 to 947)			
Necrotising enterocolitis	Study population		RR 1.03 (0.07 to 15.78)	61 (1 RCT)	⊕◯◯◯ VERY LOW[a,c]
	32 per 1000	33 per 1000 (2 to 509)			

*__Risk in the intervention group__ (and its 95% CI) is based on assumed risk in the comparison group and __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; RCT: randomised controlled trial; RR: risk ratio

[a]Downgraded for risk of bias (lack of blinding).
[b]Downgraded for imprecision.
[c]Downgraded (by 2) for serious imprecision.

BACKGROUND

Description of the condition

The optimal growth rate of infants born preterm or with low birth weight (LBW) is not known (Higgins 2012). Consensus guidelines suggest that caregivers should aim to achieve a postnatal growth rate similar to the gestation-equivalent foetal intrauterine growth rate (Agostoni 2010). Many preterm or LBW infants, especially those born very preterm or at very low birth weight (VLBW), do not achieve these rates of growth and are growth restricted at the time of hospital discharge (Ehrenkranz 1999; Steward 2002; Clark 2003; Cooke 2004; Sakurai 2008; Shan 2009; Lima 2014; Horbar 2015; Stevens 2016). Growth deficits can persist through childhood and adolescence and into adulthood (Dusick 2003; Hack 2003; Brandt 2005; Euser 2008; Stein 2013). Slow postnatal growth is associated with neurodevelopmental impairment and with poorer cognitive and scholastic outcomes (Brandt 2003; Franz 2009; Neubauer 2013; Leppanen 2014). Furthermore, concerns include that nutritional deficiency and growth restriction during infancy may have adverse effects on long-term metabolic and cardiovascular health (Higgins 2012; Embleton 2013; Lapillonne 2013).

Description of the intervention

Human breast milk is the recommended form of enteral nutrition for newborn infants for at least the first six months of postnatal life (Johnston 2012). However, breast milk alone, given at volumes that meet the nutritional needs of term infants, may not meet the higher nutritional requirements of growing preterm or LBW infants (Embleton 2007). International consensus guidelines state that 'standard' volumes (about 150 to 180 mL/kg/d) of breast milk do not provide the recommended amount of energy (110 to 135 kCal/kg/d) or protein (3.5 to 4.5 g/kg/d) to meet the metabolic needs of very preterm or VLBW infants (Table 1) (CPS 1995; AAP 2004; Agostoni 2010).

In neonatal care facilities in high-income countries, the strategy most commonly employed to address these potential nutrient deficits is to supplement breast milk with extra nutrients, usually in the form of a commercially available powder or liquid 'multi-nutrient fortifier' extracted from cow's milk (Uhing 2009; Klingenberg 2012; Cormack 2013; Dutta 2015). Multi-nutrient fortification may be especially important for infants who receive donated (donor expressed) breast milk, which typically contains lower levels of energy and protein than breast milk expressed by the mother (Arslanoglu 2013). A Cochrane Review of randomised controlled trials provides evidence that feeding preterm infants with multi-nutrient fortified breast milk rather than unfortified breast milk increases growth rates during the initial hospitalisation period (Brown 2016). However, commercially available fortifiers are expensive, and their use is less feasible in resource-poor settings in low- or middle-income countries (Chawla 2008; Kler 2015).

'High-volume' feeds

An alternative, cheaper way of meeting the recommended daily intakes of energy, protein, and other nutrients for preterm or LBW infants is to increase the total volume of enteral feeds (Klingenberg 2012). Feeding preterm or LBW infants with daily volumes of milk in excess of 200 mL/kg ('high-volume' feeds) has been proposed as a safe and effective growth-enhancement strategy (Valman 1974; Lewis 1984; Doege 2007). Whereas feeding preterm or LBW infants with unfortified maternal breast milk at 150 mL/kg/d typically would provide 100 kCal/kg/d and between 1.8 and 3.0 g/kg/d of protein (depending on the type of expressed breast milk), feeding at 200 mL/kg/d could provide 135 kCal/kg/d and between 2.4 and 4.0 g/kg/d of protein. However, because of concerns about fluid overload and complications such as feed intolerance, necrotising enterocolitis (NEC), patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), and metabolic complications such as hyponatraemia, high-volume enteral feeding has not become an established practice (Chawla 2008; Sankar 2008; Bertino 2009; Klingenberg 2012; Raban 2013).

Formula feeding

Standard 'term' formula, designed to match the composition of mature breast milk, does not provide the recommended nutrient needs for growing preterm infants. Commercially available 'preterm formula', enriched with energy (about 80 kCal/100 mL) and protein (about 2.2 g/100 mL), is commonly used to provide the extra nutrients required without increasing the volume of feeds beyond about 150 mL/kg/d to 180 mL/kg/d (Klingenberg 2012; Tudehope 2013). Nutrient-enriched formula is more expensive, is not widely available, and is used less often in low- and middle-income countries (Chawla 2008). Theoretically, the same strategy as applies to breast milk-fed infants could apply, that is, high-volume feeding with standard formula as a cheaper and more readily available alternative to standard-volume feeding with nutrient-enriched preterm formula.

How the intervention might work

Feeding preterm or LBW infants higher volumes of milk (more than 200 mL/kg/d) may be expected to promote nutrient accretion and faster rates of growth (increase in weight, length, and head circumference). Higher levels of nutrient intake during this critical period may be important for optimising long-term growth and neurodevelopment (Embleton 2013). Potential disadvantages of high-volume enteral feeding also are known. High volumes of milk may add to the physiological and metabolic stress of the immature gastrointestinal tract and its blood supply, thus increasing

risk of NEC. This may result in or worsen gastro-oesophageal reflux, increasing risk of apnoea or aspiration. High-volume feeds may lead to fluid overload and associated complications such as peripheral or pulmonary oedema, PDA, and BPD. Furthermore, enteral feeding that is ceased owing to intolerance may reduce total nutrient intake over time, thus adversely affecting growth.

Why it is important to do this review

Given the potential of high-volume enteral feeding to increase nutrient accretion and growth rates, while improving developmental outcomes in preterm or LBW infants, as well the potential risks of this feeding strategy, we undertook a systematic review that would identify and appraise data from randomised controlled trials, to provide a synthesis of evidence that could inform practice and research. No systematic review has examined this topic.

OBJECTIVES

To assess the effect on growth and safety of feeding preterm or LBW infants with high (> 200 mL/kg/d) versus standard (≤ 200 mL/kg/d) volume of milk. Infants in intervention and control groups should have received the same type of milk (breast milk, formula, or both), the same fortification or micronutrient supplements, and the same enteral feeding regimen (bolus, continuous) and rate of feed volume advancement.

To conduct subgroup analyses based on type of milk (breast milk vs formula), gestational age or birth weight category of included infants (very preterm or VLBW vs preterm or LBW), presence of intrauterine growth restriction (using birth weight relative to the reference population as a surrogate), and income level of the country in which the trial was conducted (low or middle income vs high income) (see Subgroup analysis and investigation of heterogeneity).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials, including cluster-randomised controlled trials.

Types of participants

Preterm (< 37 weeks' gestational age) or LBW (< 2500 grams) infants.

Types of interventions

- Intervention: high-volume enteral feeds: > 200 mL/kg/d
- Control: standard-volume enteral feeds: ≤ 200 mL/kg/d

Infants might have been randomised to the allocated intervention at any stage up to the time of achieving full enteral feeding volumes. The prescribed feeding regimen should have been followed until the infant was able to self-regulate intake.

Types of outcome measures

Primary outcomes

- Rates of weight gain (g/kg/d), linear growth (cm/week), or head growth (cm/week) during hospital stay and z-scores for these parameters; proportion of infants who remain below the 10th percentile for the index population up to discharge from hospital
- Growth measures following discharge from hospital to latest follow-up

Secondary outcomes

- Neurodevelopmental outcomes assessed after 12 months post term: neurological evaluations; developmental scores; and classifications of disability, including auditory and visual disability. We will define neurodevelopmental impairment as the presence of one or more of the following: non-ambulant cerebral palsy; developmental quotient greater than two standard deviations below the population mean; and blindness (visual acuity < 6/60) or deafness (any hearing impairment requiring, or unimproved by, amplification)
- Number of infants with feed intolerance: vomiting, excessive gastric residual volumes (defined by investigators), or abdominal distension that results in reduction or cessation of enteral feeding
- Number of infants with aspiration pneumonia or pneumonitis (clinical or radiological evidence of lower respiratory tract compromise that has been attributed to covert or evident aspiration of gastric contents)
- Number of infants with gastro-oesophageal reflux diagnosed by (i) clinical features; post-feed (if bolus-fed) apnoea, desaturation, irritability, or vomiting; or (ii) oesophageal pH monitoring, multiple intraluminal impedance, or endoscopy
- Frequency of apnoea (no respiratory effort > 20 seconds) or bradycardia (< 100 beats per minute), or apnoea/bradycardia necessitating stimulation, oxygen administration increase, or positive-pressure ventilation (mean number of episodes per day)
- Frequency of episodes of spontaneous fall in oxygen saturation (SpO_2) to 85% or less (mean number of episodes per day)

- Number of infants with NEC (modified Bell stage 2/3; Walsh 1986)
- Number of infants with BPD (oxygen supplementation at 36 weeks' postmenstrual age)
- Number of infants with PDA treated pharmacologically or surgically+++
- All-cause mortality before discharge or up to 44 weeks' postmenstrual age
- Mean duration of hospital stay (days)

Search methods for identification of studies

We used the standard search strategy of Cochrane Neonatal (neonatal.cochrane.org/resources-review-authors).

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 2) in the Cochrane Library; MEDLINE (1946 to November 2016); Embase (1974 to November 2016); the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to November 2016); and Maternity and Infant Care (1971 to November 2016). We limited search outputs with relevant search filters for clinical trials, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We did not apply any language restrictions. See Appendix 1 for details of the search terms that we used.

We searched ClinicalTrials.gov, Current Controlled Trials, and the World Health Organization International Trials Registry and Platform (www.whoint/ictrp/search/en/) for completed or ongoing trials.

Searching other resources

We examined reference lists in related reviews, included, and excluded studies. We searched the proceedings of annual meetings of the Pediatric Academic Societies (1993 to 2016), the European Society for Paediatric Research (1995 to 2016), the Royal College of Paediatrics and Child Health (2000 to 2017), and the Perinatal Society of Australia and New Zealand (2000 to 2016). Trials reported only as abstracts were eligible if sufficient information was available from the report, or from contact with trial authors, to fulfil inclusion criteria.

Data collection and analysis

We used standard methods of Cochrane Neonatal.

Selection of studies

We screened the title and abstract of all studies identified by the above search strategy, and two review authors (TA and WM) independently assessed the full articles for all potentially relevant trials. We excluded studies that did not meet all of the inclusion criteria, and we stated the reason for exclusion. We discussed disagreements until we achieved consensus.

Data extraction and management

Two review authors (TA and WM) extracted data independently using a data collection form to aid extraction of information on design, methods, participants, interventions, outcomes, and treatment effects from each included study. We discussed disagreements until we reached consensus. If data from trial reports were insufficient, we contacted trialists to request further information.

Assessment of risk of bias in included studies

We used criteria and standard methods of Cochrane Neonatal to assess the methodological quality of included trials. Two review authors (TA and VA) assessed risk of bias across key domains (Appendix 2) and resolved disagreements in consultation with a third review author (WM). We requested additional information from trial authors to clarify methods and results when necessary.

Measures of treatment effect

We analysed treatment effects in individual trials using Review Manager 5 and reported risk ratios (RRs) and risk differences (RDs) for dichotomous data, and mean differences (MDs) for continuous data, with respective 95% confidence intervals (CIs) (Review Manager 5). We determined the number needed to treat for an additional beneficial outcome (NNTB) or an additional harmful outcome (NNTH) for analyses with a statistically significant difference in RD.

Unit of analysis issues

The unit on analysis was the participating infant in individual randomised controlled trials (RCTs). For cluster-RCTs, we planned to undertake analyses at the level of the individual while accounting for clustering in the data using methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We requested additional data from trialists if information on important outcomes was missing or was reported unclearly. When data were still missing, we planned to examine the impact on effect size estimates in sensitivity analyses using the 'best-worst case scenario' technique.

Assessment of heterogeneity

We planned to examine treatment effects of individual trials and heterogeneity between trial results by inspecting forest plots. We planned to calculate the I^2 statistic for each RR analysis to quantify inconsistency across studies and to describe the percentage of variability in effect estimates that may be due to heterogeneity rather than to sampling error. If we detected moderate or high heterogeneity ($I^2 \geq 50\%$), we planned to explore possible causes (e.g. differences in study design, participants, interventions, or completeness of outcome assessments).

Assessment of reporting biases

If we included more than 10 trials in a meta-analysis, we planned to examine a funnel plot for asymmetry.

Data synthesis

We planned to use a fixed-effect model for meta-analyses.

Quality of evidence

We assessed the quality of evidence for the main comparison at the outcome level using the GRADE approach (Appendix 3). Two review authors (TA and VA) assessed independently the quality of evidence found for outcomes identified as critical or important for clinical decision making. We considered evidence from RCTs as high quality but downgraded evidence one level for serious (or two levels for very serious) limitations on the basis of the following: design (risk of bias), consistency across studies, directness of evidence, precision of estimates, and presence of publication bias. We used GRADEproGDT to create a 'Summary of findings' (SoF) table to report the quality of evidence (GRADEproGDT).

Subgroup analysis and investigation of heterogeneity

We planned to undertake these subgroup analyses, when possible.

- Very preterm (< 32 weeks' gestation) or VLBW (< 1500 grams) infants versus preterm infants born at between 32 and 36 weeks' gestation or with birth weight 1500 to 2499 grams.
- Breast milk-fed versus formula-fed infants.
- Infants with birth weight below the 10th percentile for the reference population ('small for gestational age') versus infants with birth weight 'appropriate for gestational age'.
- Trials conducted in low- or middle-income versus high-income countries (data.worldbank.org/about/country-classifications).

Sensitivity analysis

We planned to undertake sensitivity analyses to determine whether findings were affected when only studies using adequate methods were included (low risk of bias); adequate methods were defined as adequate randomisation and allocation concealment, blinding of intervention and measurement, and less than 10% loss to follow-up.

RESULTS

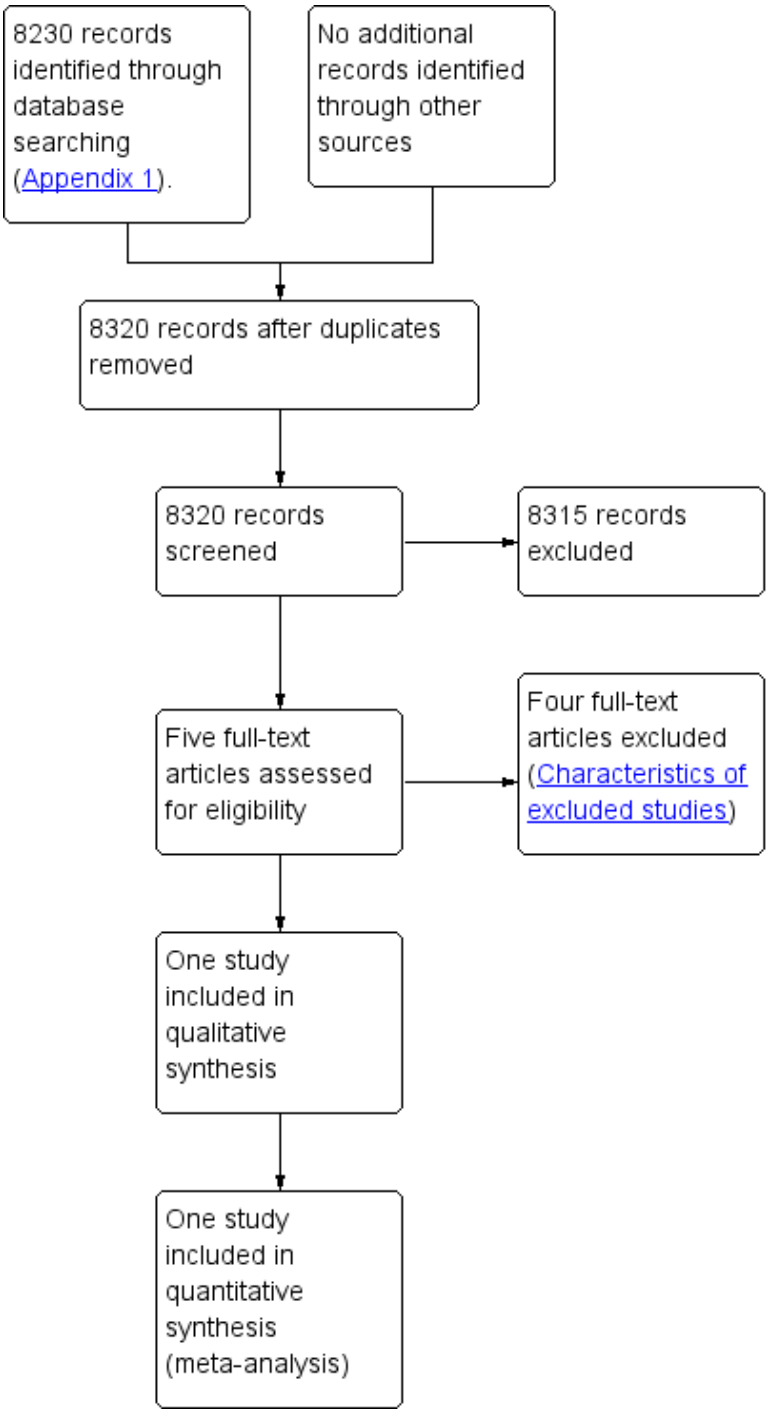
Description of studies

See Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies.

Results of the search

See Figure 1.

Figure 1. Study flow diagram.



Included studies

We included one trial (Thomas 2012).

The trial enrolled 64 VLBW infants (Thomas 2012). Both appropriate-for-gestational-age and small-for-gestational-age infants were eligible to participate. Infants in the intervention arm received 300 mL/kg/d, and those in the control arm were given 200 mL/kg/d. Participants were fed with expressed breast milk plus individual micronutrient supplementation for iron, calcium, and vitamins. Multi-nutrient fortifiers, which supplement calories and protein, were not used. The primary outcome was daily rate of weight gain from enrolment until the infant reached 1700 grams weight. Secondary outcomes were feed intolerance (two episodes of vomiting or pre-feed gastric aspirates > 50% of previous feed volume), tachypnoea (respiratory rate > 60 breaths per minute), PDA (diagnosed clinically or by echocardiograph), NEC (Bell stage 2a or greater), invasive infection (confirmed by blood culture), and biochemical abnormalities.

Excluded studies

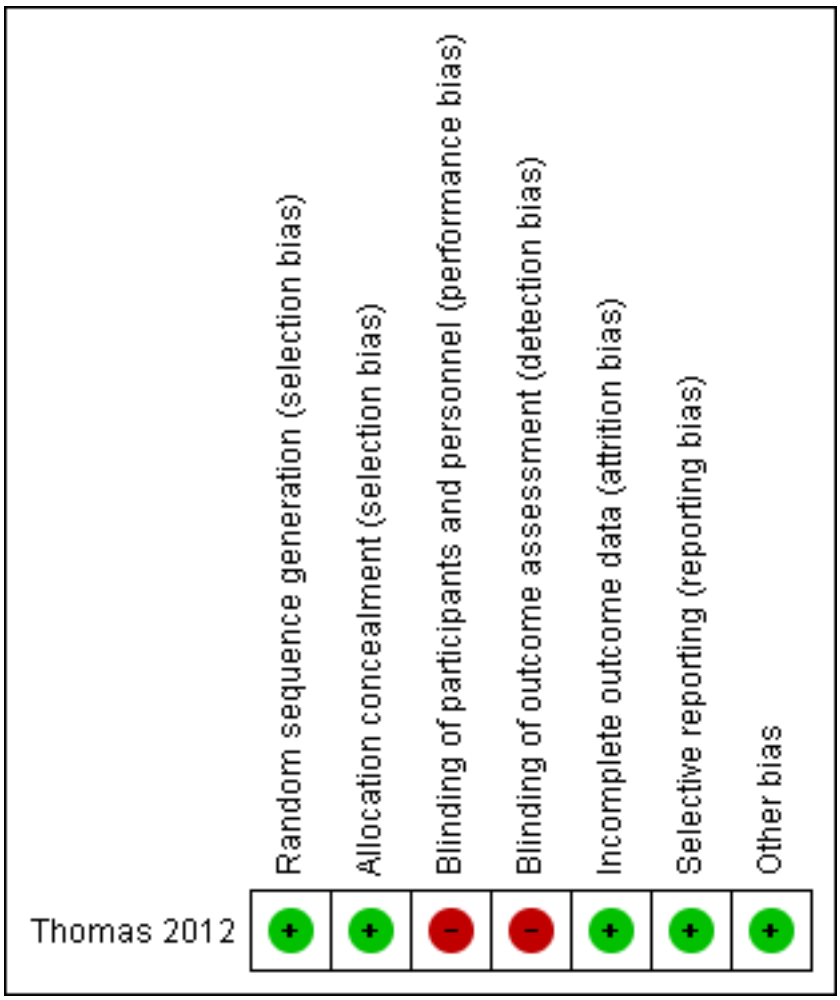
We excluded four studies (Characteristics of excluded studies).

- We excluded two RCTs (Kuschel 2000; Zecca 2014). One of these compared 200 mL/kg/d versus 150 mL/kg/d (Kuschel 2000). This study did not meet our eligibility criteria, which defined any volume up to 200 mL/kg/d as standard-volume feeds, and volumes > 200 mL/kg/d as high-volume feeds. The other trial compared 200 mL/kg/d versus 170 mL/kg/d, and reported rates of feed volume advancement that were different between intervention and control groups (Zecca 2014).
- Two studies were not RCTs (Valman 1974; Lewis 1984). One was an observational study of LBW infants fed 250 mL/kg/d of milk (Lewis 1984). The other was a cohort study comparing two enteral feed volumes; 180 and 230 mL/kg/d (Valman 1974).

Risk of bias in included studies

See Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for the included study.



Allocation

The included trial used computer-generated random numbers for sequence generation and sealed opaque envelopes for allocation concealment (Thomas 2012; personal communication).

Blinding

This trial was unblinded.

Incomplete outcome data

Investigators assessed all participants for primary and secondary outcomes.

Selective reporting

The study protocol was not published. Researchers reported all proposed outcomes (personal communication).

Other potential sources of bias

We identified no other potential source of bias.

Effects of interventions

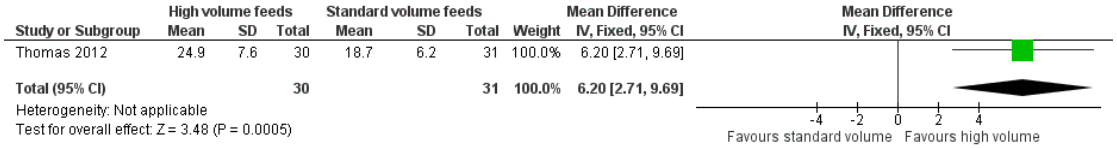
See: **Summary of findings for the main comparison** High-volume feeds vs standard-volume feeds for preterm or low birth weight infants

Primary outcomes

Growth during initial hospital stay (Outcome 1.1)

Trialists reported a higher rate of weight gain in the intervention group (MD 6.2, 95% CI 2.71 to 9.69 g/kg/d; 1 trial, 64 participants) (Analysis 1.1; Figure 3). This trial did not report linear growth and head growth (Thomas 2012).

Figure 3. Forest plot of comparison: 1 High-volume vs standard-volume feeds, outcome: 1.1 Weight gain (g/kg/d).



Post-hospital discharge growth

Trialists did not report growth after hospital discharge (Thomas 2012).

Secondary outcomes

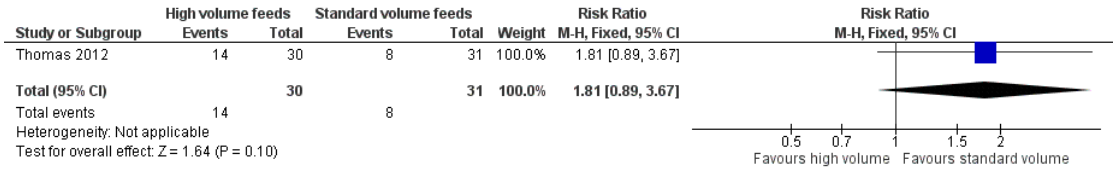
Neurodevelopmental outcomes

Trialists did not report any neurodevelopmental outcomes (Thomas 2012).

Feed intolerance (Outcome 1.2)

Trialists did not show a difference in the incidence of feed intolerance (RR 1.81, 95% CI 0.89 to 3.67; 1 trial, 64 participants) (Analysis 1.2; Figure 4) (Thomas 2012).

Figure 4. Forest plot of comparison: 1 High-volume vs standard-volume feeds, outcome: 1.2 Feed intolerance.



Aspiration pneumonia

Trialists did not report aspiration pneumonia as an outcome (Thomas 2012).

Gastro-oesophageal reflux

Trialists did not report gastro-oesophageal reflux as an outcome (Thomas 2012).

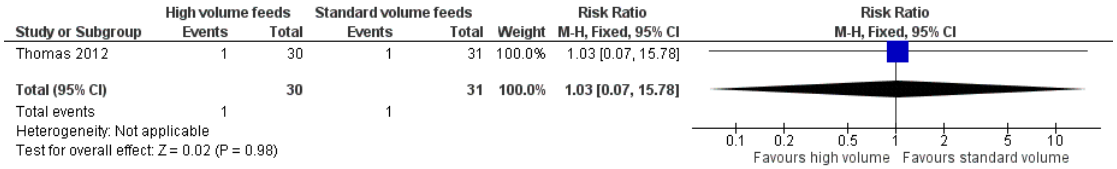
Frequency of apnoea/bradycardia/desaturation

Trialists did not report frequency of apnoea/bradycardia/desaturation as an outcome (Thomas 2012).

NEC stage 2/3 (Outcome 1.3)

Trialists did not show a difference in risk of NEC stage 2/3 (RR 1.03, 95% CI 0.07 to 15.78) (Analysis 1.3; Figure 5) (Thomas 2012).

Figure 5. Forest plot of comparison: 1 High-volume vs standard-volume feeds, outcome: 1.3 Necrotising enterocolitis.



BPD

Trialists did not report BPD as an outcome (Thomas 2012).

PDA

Trialists did not report PDA as an outcome (Thomas 2012).

All-cause mortality before discharge or at 44 weeks

Trialists reported no death in either of the groups (Thomas 2012).

Duration of hospital stay

Trialists did not report duration of hospital stay as an outcome (Thomas 2012).

Subgroup analyses

- Very preterm or VLBW infants: All participants in the included trial were VLBW
- Breast milk-fed infants: All participants in the included trial were breast milk fed.
- Small-for-gestational-age infants: Trialists did not show a statistically significant effect on rate of weight gain in a subgroup of small-for-gestational-age infants: High volume (n = 10) 22.5 g/kg/d versus standard volume (n = 14) 17.6 g/kg/d. Trialists did not report standard deviations (SDs) and did not report data for appropriate-for-gestational-age infants, so a subgroup comparison was not possible (Thomas 2012).
- Low- or middle-income countries: The only included trial was conducted in a low- or middle-income country (India).

DISCUSSION

Summary of main results

Only one small randomised controlled trial (RCT) met the inclusion criteria for this Cochrane Review (Thomas 2012). This trial was unblinded but otherwise of good methodological quality. Analysis showed a higher rate of weight gain in the high-volume enteral feeds group. An increase in weight gain of 6.2 g/kg/d in the high-volume feeds group would be clinically significant because it amounts to 43 g/kg/week and 186 g/kg/month. However, owing to the small sample size (n = 64), data is insufficient to provide a precise estimate of the effect of high-volume enteral feeds on risk of necrotising enterocolitis (NEC) and feed intolerance. We found no data for other outcomes such as linear and head growth, post-discharge growth, duration of hospital stay, neurodevelopmental outcomes, and risk of complications such as patent ductus arteriosus (PDA), bronchopulmonary dysplasia (BPD), aspiration pneumonia, or gastro-oesophageal reflux.

Overall completeness and applicability of evidence

Although the included trial showed that high-volume enteral feeds increase the rate of weight gain, it is plausible that giving high volumes could have resulted in greater feed intolerance and interruption or cessation of enteral feeding that in turn reduced growth rates. The included trial prespecified definitions of feed intolerance that mandated interrupting or ceasing feed volume advancement - principally two ore more episodes of vomiting - or detecting a pre-feed 'gastric residual volume' that was more than half the volume of the preceding enteral feed. This trial did not show a statistically significant difference in the incidence of feed intolerance, but the 95% confidence interval (CI) was wide (risk ratio (RR) 1.81, 95% CI 0.89 to 3.67), with the upper bound consistent with a greater than three-fold increase in the incidence of feed intolerance. Similarly, the estimate of effect on the risk of NEC is imprecise, with the upper bound of the 95% CI (RR 1.03, 95% CI 0.07 to 15.78) consistent with a greater than 15-fold increase in the incidence of NEC.

Most participants in the included trial were stable very preterm (mean gestational age at birth: 32 weeks) or very low birth weight (VLBW) (mean birth weight: 1200 g) infants. About two-fifths of all participants were small for gestational age. Owing to lack of data, however, subgroup comparisons of appropriate-for-gestational-age versus small-for-gestational-age infants were not possible. The fact that risks of feed intolerance and NEC may differ between these groups of infants may limit the applicability of these data from a low- or middle-income country, where being small for gestational age is a major contributor to VLBW, to high-income countries, where short gestation (with appropriate growth) is the main cause. It is not clear, furthermore, whether study findings are applicable to other subgroups of infants at risk of developing feed intolerance or NEC, including those with intrauterine growth restriction or compromise, as investigators did not assess these risk factors.

All infants recruited to the included trial were fed with expressed maternal breast milk. Human milk feeding reduces the risk of feed intolerance and NEC in preterm infants, and it is unclear whether this finding could be applied to infants fed artificial formulas. Similarly, all participants received bolus intragastric feeds at two- to three-hourly intervals, and it is unclear whether findings can be applied to infants who receive continuous infusion of intragastric feeds, because RCTs have reported conflicting findings about effects of continuous enteral infusion on feed tolerance and NEC in very preterm or VLBW infants (Premji 2011).

Quality of the evidence

The quality of the evidence from the only included trial was low for the primary outcome of weight gain (downgraded for lack of blinding and imprecision of results). The quality of evidence was very low for feed intolerance and NEC (downgraded for lack of blinding and serious imprecision of results).

Although allocation was concealed in the included trial, the intervention was not blinded to caregivers and investigators, and surveillance bias may have influenced assessment of some outcomes, including feed intolerance and NEC. Clinicians' and caregivers' subjective assessments of when to investigate (e.g. examining the infant's abdomen for tenderness or distension) or intervene (e.g. interrupting or ceasing enteral feeds) may have been affected by perceived risks associated with high-volume feeds. The unblinded design may also have influenced care practices. For example, the perception that high-volume feeds may be more likely to cause gastro-oesophageal reflux may influence the attitude of healthcare staff regarding investigation or management of episodes of apnoea, bradycardia, or oxygen desaturation (linked putatively to reflux).

Potential biases in the review process

We found only one small trial for inclusion in this review. Although we conducted a comprehensive search, including a search of conference proceedings, we cannot exclude fully the possibility of publication bias because we do not know whether other published (but not indexed) or unpublished trials have been conducted.

Agreements and disagreements with other studies or reviews

We are not aware of other systematic reviews on the use of high-volume enteral feeds to increase nutrient intake in preterm or low birth weight infants.

Two of the studies excluded from this review were RCTs involving preterm infants in neonatal units in high-income countries (Kuschel 2000; Zecca 2014). Although these trials compared different volumes of enteral feeds, in both the studies the higher volume was 200 mL/kg/d, which is the upper limit for our a priori definition of "standard-volume" feeds.

Consistent with our included trial, both trials showed higher rates of weight gain among infants fed higher volumes of milk than among those given standard volumes of milk: weight gain of 16.2 versus 15.7 g/kg/d until discharge in one study, and discharge weight z-score of -2.04 versus -2.31 in the other study (Kuschel 2000; Thomas 2012; Zecca 2014). However, higher-volume feeds did not result in greater length and head circumference at discharge in both studies. The other benefit of higher-volume feeds was shorter duration of hospital stay (Zecca 2014). Although one study showed higher rates of fluid retention in the form of oedema with or without respiratory deterioration in the higher-volume feeds group (27%) than in the standard-volume feeds group (14%), this difference was not statistically significant (Kuschel 2000).

AUTHORS' CONCLUSIONS

Implications for practice

Although data from one small unblinded trial indicate that high-volume enteral feeds increase the rate of weight gain without increasing risk of feed intolerance or necrotising enterocolitis (NEC), the quality of evidence is low to very low. Hence, available evidence is insufficient to support or refute high-volume enteral feeds in preterm or low birth weight (LBW) infants.

Implications for research

A large randomised controlled trial (RCT) is needed to assess whether high-volume versus standard-volume enteral feeds improve important clinical outcomes for preterm or LBW infants. Such a trial should assess weight and linear and head growth, post-discharge growth, neurodevelopmental outcomes, and risk of potential complications of high-volume enteral feeds. A trial of this intervention may be regarded as a research priority, especially in settings where a multi-nutrient fortifier is less likely to be used to supplement nutrient intake.

ACKNOWLEDGEMENTS

None.

REFERENCES

References to studies included in this review

Thomas 2012 *{published data only}*

Thomas N, Cherian A, Santhanam S, Jana AK. A randomized control trial comparing two enteral feeding volumes in very low birth weight babies. *Journal of Tropical Pediatrics* 2012;**58**(1):55–8. PUBMED: 21320855]

References to studies excluded from this review

Kuschel 2000 *{published data only}*

Kuschel CA, Evans N, Askie L, Bredemeyer S, Nash J, Polverino J. A randomized trial of enteral feeding volumes in infants born before 30 weeks' gestation. *Journal of Paediatrics and Child Health* 2000;**36**(6):581–6.

Lewis 1984 *{published data only}*

Lewis MA, Smith BA. High volume milk feeds for preterm infants. *Archives of Disease in Childhood* 1984;**59**(8): 779–81.

Valman 1974 *{published data only}*

Valman HB, Aikens R, David-Reed Z, Garrow JS. Retention of nitrogen, fat, and calories in infants of low birth weight on conventional and high-volume feeds. *British Medical Journal* 1974;**3**(5926):319–20.

Zecca 2014 *{published data only}*

Zecca E, Costa S, Barone G, Giordano L, Zecca C, Maggio L. Proactive enteral nutrition in moderately preterm small for gestational age infants: a randomized clinical trial. *Journal of Pediatrics* 2014;**165**(6):1135–9.e1.

Additional references

AAP 2004

American Academy of Pediatrics Committee on Nutrition. Nutritional needs of preterm infants. In: Kleinman RE editor(s). *Pediatric Nutrition Handbook*. Elk Grove Village, IL: American Academy of Pediatrics, 2004:23-54.

Agostoni 2010

Agostoni C, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, Decsi T, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. *Journal of Pediatric Gastroenterology and Nutrition* 2010;**50**(1):85–91. [PUBMED: 19881390]

Arslanoglu 2013

Arslanoglu S, Corpeleijn W, Moro G, Braegger C, Campoy C, Colomb V, et al. Donor human milk for preterm infants: current evidence and research directions. *Journal of Pediatric Gastroenterology and Nutrition* 2013;**57**(4): 535–42. [PUBMED: 24084373]

Bertino 2009

Bertino E, Giuliani F, Prandi G, Coscia A, Martano C, Fabris C. Necrotizing enterocolitis: risk factor analysis and role of gastric residuals in very low birth weight infants. *Journal of Pediatric Gastroenterology and Nutrition* 2009;**48** (4):437–42. [PUBMED: 19330932]

Brandt 2003

Brandt I, Sticker EJ, Lentze MJ. Catch-up growth of head circumference of very low birth weight, small for gestational age preterm infants and mental development to adulthood. *Journal of Pediatrics* 2003;**142**(5):463–8. [PUBMED: 12756374]

Brandt 2005

Brandt I, Sticker EJ, Gausche R, Lentze MJ. Catch-up growth of supine length/height of very low birth weight, small for gestational age preterm infants to adulthood. *Journal of Pediatrics* 2005;**147**(5):662–8. [PUBMED: 16291360]

Brown 2016

Brown JV, Embleton ND, Harding JE, McGuire W. Multi-nutrient fortification of human milk for preterm infants. *Cochrane Database of Systematic Reviews* 2016, Issue 5. [DOI: 10.1002/14651858.CD000343.pub3]

Chawla 2008
Chawla D, Agarwal R, Deorari AK, Paul VK. Fluid and electrolyte management in term and preterm neonates. *Indian Journal of Pediatrics* 2008;**75**(3):255–9. [PUBMED: 18376094]

Clark 2003
Clark RH, Thomas P, Peabody J. Extrauterine growth restriction remains a serious problem in prematurely born neonates. *Pediatrics* 2003;**111**(5):986–90. [PUBMED: 12728076]

Cooke 2004
Cooke RJ, Ainsworth SB, Fenton AC. Postnatal growth retardation: a universal problem in preterm infants. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2004;**89**(5):F428–30. [PUBMED: 15321963]

Cormack 2013
Cormack B, Sinn J, Lui K, Tudehope D. Australasian neonatal intensive care enteral nutrition survey: implications for practice. *Journal of Paediatrics and Child Health* 2013;**49**(4):E340–7. [PUBMED: 23227901]

CPS 1995
Nutrition Committee, Canadian Paediatric Society. Nutrition needs and feeding of premature infants. *Canadian Medical Association Journal* 1995;**152**(11):1765–85. [PUBMED: 7773894]

Doege 2007
Doege C, Bauer J. Effect of high volume intake of mother's milk with an individualized supplementation of minerals and protein on early growth of preterm infants < 28 weeks of gestation. *Clinical Nutrition* 2007;**26**(5):581–8. [PUBMED: 17655982]

Dusick 2003
Dusick AM, Poindexter BB, Ehrenkranz RA, Lemons JA. Growth failure in the preterm infant: can we catch up?. *Seminars in Perinatology* 2003;**27**(4):302–10. [PUBMED: 14510321]

Dutta 2015
Dutta S, Singh B, Chessell L, Wilson J, Janes M, McDonald K, et al. Guidelines for feeding very low birth weight infants. *Nutrients* 2015;**7**(1):423–42. [PUBMED: 25580815]

Ehrenkranz 1999
Ehrenkranz RA, Younes N, Lemons JA, Fanaroff AA, Donovan EF, Wright LL, et al. Longitudinal growth of hospitalized very low birth weight infants. *Pediatrics* 1999;**104**(2 Pt 1):280–9. [PUBMED: 10429008]

Embleton 2007
Embleton ND. Optimal protein and energy intakes in preterm infants. *Early Human Development* 2007;**83**(12):831–7. [PUBMED: 17980784]

Embleton 2013
Embleton ND. Early nutrition and later outcomes in preterm infants. *World Review of Nutrition and Dietetics* 2013;**106**:26–32. [PUBMED: 23428677]

Euser 2008
Euser AM, de Wit CC, Finken MJ, Rijken M, Wit JM. Growth of preterm born children. *Hormone Research* 2008;**70**(6):319–28. [PUBMED: 18953169]

Franz 2009
Franz AR, Pohlandt F, Bode H, Mihatsch WA, Sander S, Kron M, et al. Intrauterine, early neonatal, and postdischarge growth and neurodevelopmental outcome at 5.4 years in extremely preterm infants after intensive neonatal nutritional support. *Pediatrics* 2009;**123**(1):e101–9. [PUBMED: 19117831]

GRADEproGDT [Computer program]
McMaster University (developed by Evidence Prime). GRADEproGDT [www.gradepro.org]. Version accessed 10 May 2017. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Hack 2003
Hack M, Schluchter M, Cartar L, Rahman M, Cuttler L, Borawski E. Growth of very low birth weight infants to age 20 years. *Pediatrics* 2003;**112**(1 Pt 1):e30–8. [PUBMED: 12837903]

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

Higgins 2012
Higgins RD, Devaskar S, Hay WW Jr, Ehrenkranz RA, Greer FR, Kennedy K, et al. Executive summary of the workshop "Nutritional Challenges in the High Risk Infant". *Journal of Pediatrics* 2012;**160**(3):511–6. [PUBMED: 22240111]

Horbar 2015
Horbar JD, Ehrenkranz RA, Badger GJ, Edwards EM, Morrow KA, Soll RF, et al. Weight growth velocity and postnatal growth failure in infants 501 to 1500 grams: 2000-2013. *Pediatrics* 2015;**136**(1):e84–92. [PUBMED: 26101360]

Johnston 2012
Johnston M, Landers S, Noble L, Szucs K, Viehmann L. Breastfeeding and the use of human milk. *Pediatrics* 2012;**129**(3):e827–41. [PUBMED: 22371471]

Kler 2015
Kler N, Thakur A, Modi M, Kaur A, Garg P, Soni A, et al. Human Milk Fortification in India. *Nestle Nutrition Institute Workshop Series* 2015;**81**:145–51. [PUBMED: 26111571]

Klingenberg 2012
Klingenberg C, Embleton ND, Jacobs SE, O'Connell LA, Kuschel CA. Enteral feeding practices in very preterm infants: an international survey. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2012;**97**(1):F56–61. [PUBMED: 21856644]

Lapillonne 2013
Lapillonne A, Griffin IJ. Feeding preterm infants today for later metabolic and cardiovascular outcomes. *Journal*

of Pediatrics 2013;**162**(3 Suppl):S7–16. [PUBMED: 23445851]

Leppanen 2014
Leppanen M, Lapinleimu H, Lind A, Matomaki J, Lehtonen L, Haataja L, et al. Antenatal and postnatal growth and 5-year cognitive outcome in very preterm infants. *Pediatrics* 2014;**133**(1):63–70. [PUBMED: 24344103]

Lima 2014
Lima PA, Carvalho MD, Costa AC, Moreira ME. Variables associated with extrauterine growth restriction in very low birth weight infants. *Jornal de Pediatria* 2014;**90**(1):22–7. [PUBMED: 24156833]

Neubauer 2013
Neubauer V, Griesmaier E, Pehbock-Walser N, Pupp-Peglow U, Kiechl-Kohlendorfer U. Poor postnatal head growth in very preterm infants is associated with impaired neurodevelopment outcome. *Acta Paediatrica* 2013;**102**(9): 883–8. [PUBMED: 23772884]

Premji 2011
Premji SS, Chessell L. Continuous nasogastric milk feeding versus intermittent bolus milk feeding for premature infants less than 1500 grams. *Cochrane Database of Systematic Reviews* 2011, Issue 11. [DOI: 10.1002/14651858.CD001819.pub2; PUBMED: 22071802]

Raban 2013
Raban MS, Joolay Y, Horn AR, Harrison MC. Enteral feeding practices in preterm infants in South Africa. *South African Journal of Child Health* 2013;**7**:8–12.

Review Manager 5 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Sakurai 2008
Sakurai M, Itabashi K, Sato Y, Hibino S, Mizuno K. Extrauterine growth restriction in preterm infants of gestational age ≤ 32 weeks. *Pediatrics International* 2008; **50**(1):70–5. [PUBMED: 18279209]

Sankar 2008
Sankar MJ, Agarwal R, Mishra S, Deorari AK, Vinod PK. Feeding of low birth weight infants. *Indian Journal of Paediatrics* 2008;**75**:459–69.

Schünemann 2013
Schünemann H, Broż ek J, Guyatt G, Oxman A, editors. GWG. GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations. www.guidelinedevelopment.org/handbook. Updated October 2013.

Shan 2009
Shan HM, Cai W, Cao Y, Fang BH, Feng Y. Extrauterine growth retardation in premature infants in Shanghai: a multicenter retrospective review. *European Journal of Pediatrics* 2009;**168**(9):1055–9. [PUBMED: 19096875]

Stein 2013
Stein AD, Barros FC, Bhargava SK, Hao W, Horta BL, Lee N, et al. Birth status, child growth, and adult outcomes in low- and middle-income countries. *Journal of Pediatrics* 2013;**163**(6):1740–6.e4. [PUBMED: 24064150]

Stevens 2016
Stevens TP, Shields E, Campbell D, Combs A, Horgan M, La Gamma EF, et al. Variation in enteral feeding practices and growth outcomes among very premature Infants: a report from the New York State Perinatal Quality Collaborative. *American Journal of Perinatology* 2016;**33**(1): 9–19. [PUBMED: 26084749]

Steward 2002
Steward DK, Pridham KF. Growth patterns of extremely low-birth-weight hospitalized preterm infants. *Journal of Obstetric, Gynecologic, and Neonatal Nursing* 2002;**31**(1): 57–65. [PUBMED: 11843020]

Tudehope 2013
Tudehope DI. Human milk and the nutritional needs of preterm infants. *Journal of Pediatrics* 2013;**162**(3 Suppl): S17–25. [PUBMED: 23445843]

Uhing 2009
Uhing MR, Das UG. Optimizing growth in the preterm infant. *Clinics in Perinatology* 2009;**36**(1):165–76. [PUBMED: 19161873]

Walsh 1986
Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatric Clinics of North America* 1986;**33**(1):179–201. [PUBMED: 3081865]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Thomas 2012

Methods	RCT
Participants	64 newborn VLBW infants were enrolled when they achieved 200 mL/kg/d enteral feeds. Both appropriate-for-gestational-age and small-for-gestational-age infants were included. Only birth weight (not gestational age) criteria were used for enrolment
Interventions	Intervention arm (N = 32): *Feeds were graded up by 20 mL/kg/d up to 300 mL/kg/d Control arm (N = 32): *Feeds were continued at 200 mL/kg/d Babies in both intervention and control arms were given expressed breast milk along with individual micronutrient supplements for calcium, iron, and vitamins. Multi-nutrient milk fortifiers, which supplement calories and proteins, were not used. Feeds were given by nasogastric tube at 2- to 3-hourly intervals
Outcomes	Primary outcome: weight gain (g/kg/d) from enrolment until baby reached weight of 1700 grams Secondary outcomes: feed intolerance, tachypnoea, NEC (stage 2a or greater), bacteraemia or fungaemia, biochemical abnormalities
Notes	Setting: Neonatology Unit, Christian Medical College Hospital, Vellore (a tertiary care teaching hospital in South India) *Twelve infants in the high-volume group did not achieve the targeted 300 mL/kg/d (although all achieved feed volumes > 250 mL/kg/d), and 6 infants in the standard-volume group received higher volumes than targeted (up to 215 mL/kg/d), but analyses were done by "intention-to-treat"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Personal communication: 'computer-generated random sequence'
Allocation concealment (selection bias)	Low risk	Personal communication: 'sealed opaque envelopes opened by the principal investigator only at the time of allocation'
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded

Thomas 2012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Three (of 64) randomised infants were removed from the study by parents, did not complete the intervention, and were not included in analyses
Selective reporting (reporting bias)	Low risk	Personal communication: 'all proposed outcomes reported'
Other bias	Low risk	Nil

NEC: necrotising enterocolitis.
RCT: randomised controlled trial.
VLBW: very low birth weight.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Kuschel 2000	This study compared 2 enteral feed volumes: 150 mL/kg/d and 200 mL/kg/d (both "standard" volumes)
Lewis 1984	This is a retrospective study of 87 low birth weight infants fed 250 mL/kg/d; not a randomised controlled trial
Valman 1974	This is a cohort study comparing 2 feed volumes: 180 mL/kg/d and 230 mL/kg/d; not a randomised controlled trial
Zecca 2014	This study compared 2 enteral feed volumes: 170 mL/kg/d and 200 mL/kg/d (both "standard" volumes); rate of advancement of feeds was different between groups (in 170-mL groups, feeds were started at 60 mL/kg/d on day 1 and were advanced to full feeds on day 9; in 200-mL group, feeds were started at 100 mL/kg/d on day 1 and were advanced to full feeds on day 4)

DATA AND ANALYSES

Comparison 1. High-volume vs standard-volume feeds

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Weight gain (g/kg/d)	1	61	Mean Difference (IV, Fixed, 95% CI)	6.20 [2.71, 9.69]
2 Feed intolerance	1	61	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [0.89, 3.67]
3 Necrotising enterocolitis	1	61	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.07, 15.78]

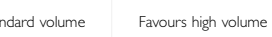
Analysis 1.1. Comparison 1 High-volume vs standard-volume feeds, Outcome 1 Weight gain (g/kg/d).

Review: High versus standard volume enteral feeds to promote growth in preterm or low birth weight infants

Comparison: 1 High-volume vs standard-volume feeds

Outcome: 1 Weight gain (g/kg/d)

Study or subgroup	High volume feeds		Standard volume feeds		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Thomas 2012	30	24.9 (7.6)	31	18.7 (6.2)		100.0 %	6.20 [2.71, 9.69]
Total (95% CI)	**30**		**31**			**100.0 %**	**6.20 [2.71, 9.69]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.48 (P = 0.00049)							
Test for subgroup differences: Not applicable							

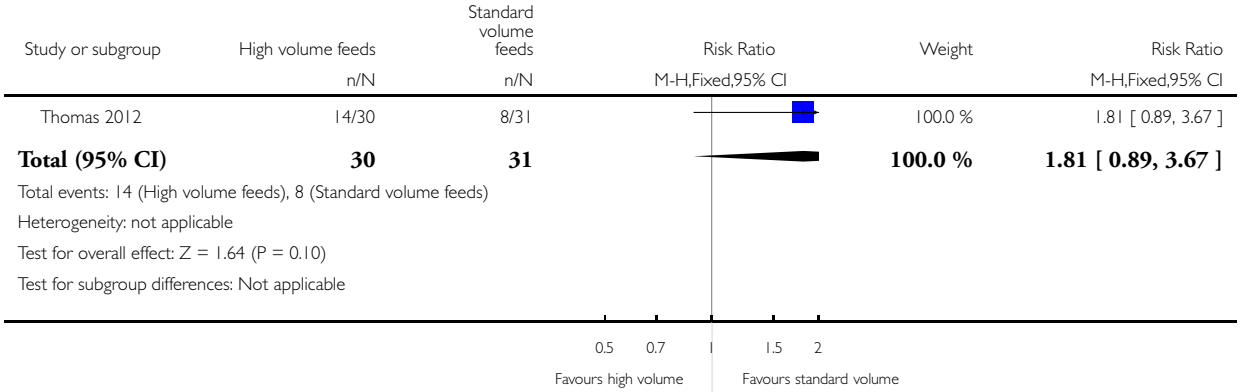


Analysis 1.2. Comparison 1 High-volume vs standard-volume feeds, Outcome 2 Feed intolerance.

Review: High versus standard volume enteral feeds to promote growth in preterm or low birth weight infants

Comparison: 1 High-volume vs standard-volume feeds

Outcome: 2 Feed intolerance

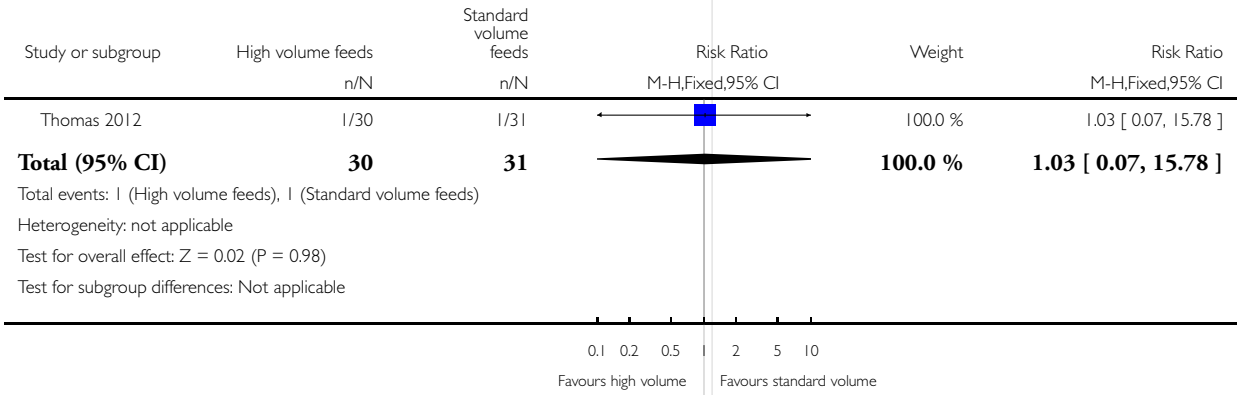


Analysis 1.3. Comparison 1 High-volume vs standard-volume feeds, Outcome 3 Necrotising enterocolitis.

Review: High versus standard volume enteral feeds to promote growth in preterm or low birth weight infants

Comparison: 1 High-volume vs standard-volume feeds

Outcome: 3 Necrotising enterocolitis



ADDITIONAL TABLES

Table 1. Typical energy and protein content of human milk or formula

per 100 mL	Expressed breast milk (EBM)	EBM + Fortifier	Term formula	Preterm formula
Energy (kCal)	67	74 to 80	67	80
Protein (g)	1.2 to 1.7	2.0 to 2.5	1.5	2.4

APPENDICES

Appendix 1. Search strategy

De-duplicated search results from: PubMed, Embase, CINAHL, Cochrane Library (Search date: No limit - November 14, 2016)
Search terms: breast milk OR diet supplementation OR ((fortif* OR supplemented OR supplementation) near ((human OR breast OR expressed) NEAR milk))
Plus the following database-specific terms:
PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))
Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)
CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)
Cochrane Library: (infant or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW)

Appendix 2. Risk of bias

- Random sequence generation: We categorised the method used to generate the allocation sequence as:
    - low risk of bias: Any random process (e.g. random number table; computer random number generator; coin tossing; shuffling of cards or envelopes; throwing of dice; drawing of lots; minimisation) (may be implemented without a random element; this is considered equivalent to being random);
    - high risk of bias: any non-random process (e.g. sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; allocation by preference of the participant; allocation based on results of a laboratory test or series of tests; allocation based on availability of the intervention); or
    - unclear risk of bias: insufficient information about the sequence generation process to permit judgement.
- Allocation concealment: We categorised the method used to conceal the allocation sequence as:
    - low risk of bias: randomisation method described that would not allow investigator/participant to know or influence the intervention group before eligible participants entered the study (i.e. central allocation, including telephone, Web-based, and pharmacy-controlled randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes);

○ high risk of bias: open random allocation schedule (i.e. list of random numbers); assignment envelopes used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque, or were not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure; or

○ unclear risk of bias: randomisation stated but no information provided on method used.

- Blinding of participants and personnel: We assessed blinding of participants, clinicians and caregivers, and outcome assessors separately for different outcomes and categorised the methods used as:

○ low risk of bias: no blinding or incomplete blinding, but review authors judged that the outcome was not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that blinding could have been broken;

○ high risk of bias: no blinding or incomplete blinding, and the outcome was likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that blinding could have been broken, and the outcome was likely to be influenced by lack of blinding; or

○ unclear risk of bias: insufficient information to permit judgement.

- Incomplete outcome data: We described the completeness of data including attrition and exclusions from analysis for each outcome and reasons for attrition or exclusion when reported. We assessed whether missing data were balanced across groups or were related to outcomes. We categorised completeness as:

○ low risk of bias: no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to introduce bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not sufficient to have a clinically relevant impact on observed effect size; missing data imputed by appropriate methods;

○ high risk of bias: reason for missing outcome data likely to be related to true outcome, with imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation; or

○ unclear risk of bias: insufficient information to permit judgement.

- Selective reporting: We assessed reporting bias due to selective outcome reporting as:

○ low risk of bias: study protocol available, and all of the study's prespecified (primary and secondary) outcomes of interest in the review had been reported in the prespecified way; study protocol not available, but it was clear that published reports included all expected outcomes, including those that were prespecified;

○ high risk of bias: not all of the study's prespecified primary outcomes reported; one or more primary outcomes reported by measurements, analysis methods, or subsets of data (i.e. subscales) that had not been prespecified; one or more reported primary outcomes not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review reported incompletely, so they could not be entered into a meta-analysis; study report failed to include results for a key outcome that would be expected to be reported for such a study; or

○ unclear risk of bias: insufficient information to permit judgement.

- Other bias: We analysed bias due to problems not covered elsewhere in the table as:

○ low risk of bias: study appears to be free of other sources of bias;

○ high risk of bias: study had a potential source of bias related to the specific study design used; stopped early because a data-dependent study design was used; stopped early as the result of a data-dependent process (including a formal stopping rule); had extreme baseline imbalance; was claimed to be fraudulent; had some other problem; or

○ unclear risk of bias: insufficient information to assess whether an important risk of bias existed; insufficient rationale or evidence to suggest that an identified problem would introduce bias.

Appendix 3. GRADE assessment of quality of evidence

GRADE considers evidence from randomised controlled trials as high quality that may be downgraded on the basis of consideration of any of five areas.

- Design (risk of bias).
- Consistency across studies.
- Directness of evidence.
- Precision of estimates.
- Presence of publication bias.

The GRADE approach results in assessment of the quality of a body of evidence according to four grades (Schünemann 2013).

- High: We are very confident that the true effect lies close to the estimate of effect.
- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different.
- Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.
- Very low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

CONTRIBUTIONS OF AUTHORS

All review authors developed the protocol. TA and WM screened search outputs, assessed study eligibility, and extracted and synthesised data. TA and VA assessed risk of bias across key domains and undertook GRADE assessment with WM. All review authors revised the final review.

DECLARATIONS OF INTEREST

Dr. Thomas was the principal investigator in the only study included in the review (Thomas 2012).

SOURCES OF SUPPORT

Internal sources

- University of York, UK.
- Christian Medical College, Vellore, India.
- Sri Ramachandra Medical College and Research Institute, Chennai, India.

External sources

- National Institute for Health Research, UK.

This report is independent research funded by a UK National Institute of Health Research Grant (NIHR) Cochrane Programme Grant (13/89/12). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR, or the UK Department of Health.

- Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, USA.

Editorial support of the Cochrane Neonatal Review Group has been funded with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201600005C.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.