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[Intervention Review]

Dilute versus full-strength formula in exclusively formula-fed preterm or low birth weight infants

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ABSTRACT

Background

Preterm infants have fewer nutrient reserves at birth than full-term infants and often receive artificial formula feeds in the absence of expressed breast milk. Although it is generally agreed that feeding must be initiated slowly and advanced with much greater deliberation than in a healthy, full-term infant, the way in which feeds are introduced and advanced in preterm infants varies widely. This review focuses on whether dilute or full-strength formula is the preferable mode of introducing feeds in preterm infants for whom expressed breast milk is unavailable.

Objectives

To assess the effects of dilute versus full-strength formula on the incidence of necrotising enterocolitis, feeding intolerance, weight gain, length of stay in hospital and time to achieve full calorie intake in exclusively formula-fed preterm or low birth weight infants. A secondary objective was to assess the effects of different dilution strategies.

Search methods

We used the standard search strategy of Cochrane Neonatal to update the search in the Cochrane Central Register of Controlled Trials (CENTRAL 2018, Issue 9), MEDLINE via PubMed (1966 to 1 October 2018), Embase (1980 to 1 October 2018), and CINAHL (1982 to 1 October 2018).

We searched clinical trials' registries for ongoing or recently completed trials (clinicaltrials.gov; the World Health Organization's International [Trials Registry and Platform](http://trialsregistryandplatform.org); and the [ISRCTN Registry](http://isrctn.com)).

Selection criteria

Randomised or quasi-randomised trials comparing strengths of formula milk in exclusively formula-fed preterm or low birth weight infants. We excluded studies if infants received formula as a supplement to breast milk.

Data collection and analysis

We independently assessed studies for inclusion. We collected data using the standard methods of Cochrane Neonatal, with independent assessment of risk of bias and data extraction. We synthesised mean differences using a fixed-effect meta-analysis model. We used the GRADE approach to assess the certainty of evidence.

Main results

We included three studies involving 102 preterm or low birth weight infants in the review. The studies compared dilute (double-volume, half-strength) formula with full-strength (20 kcal/oz (~ 68 to 70 kcal/100 mL)) formula. We assessed all three studies as having unclear risk of bias due to the likely absence of blinding of study personnel and the potential for selection bias in the largest trial. Data for the primary outcome of necrotising enterocolitis were not reported in any of the studies. We could combine two of the studies (88 infants) in the meta-analysis. The evidence suggests that dilute formula with double-volume (half-strength) may lead to fewer episodes of gastric residuals per day (one study; mean difference (MD) -1.20, 95% confidence interval (CI) -2.20 to -0.20; low-certainty evidence), fewer episodes of gastric residuals per baby until attaining 100 kcal/kg (one study; MD -0.80, 95% CI -1.32 to -0.28; low-certainty evidence), fewer episodes of vomiting per day (one study; MD -0.04, 95% CI -0.07 to -0.01; low-certainty evidence) and fewer occurrences of abdominal distension greater than 2 cm (two studies; MD -0.16, 95% CI -0.19 to -0.13; low-certainty evidence). For the secondary outcomes, data suggest that infants in the dilute formula with double-volume (half-strength) group may have attained an adequate energy intake earlier than infants in the full-strength group (two studies; MD -2.26, 95% CI -2.85 to -1.67; low-certainty evidence). There was no evidence of a difference between groups for weight gain one week after commencement of intragastric feeds (one study; MD 0.05 kg, 95% CI -0.06 to 0.15; low-certainty evidence). Data were not reported for length of hospital stay.

Authors' conclusions

There is low-certainty evidence from three small, old trials that use of dilute formula in preterm or low birth weight formula-fed infants may lead to an important reduction in the time taken for preterm infants to attain an adequate energy intake.

However, our confidence in this result is limited due to uncertainty over risk of bias and sparsity of available data. Dilute formula may reduce incidence of feeding intolerance, but the clinical significance of the reduction is uncertain. The impact on serious gastrointestinal problems, including necrotising enterocolitis, was not reported in any of the trials. Further randomised trials are needed to confirm these results.

PLAIN LANGUAGE SUMMARY

Dilute versus full-strength formula in exclusively formula-fed preterm or low birth weight infants

Review question

Is dilute formula milk (e.g. half the strength at double the volume) better tolerated than full-strength formula milk in the initial feeding of preterm babies for whom breast milk is not available?

Background

Babies born preterm (at less than 37 weeks' gestation) or with a low birth weight (less than 2500 grams) have special feeding requirements. Expressed breast milk is preferred, but preterm babies are often fed with formula milk because breast milk is not always available. The provision of artificial feeds varies considerably in preterm babies and there is concern that introducing full-strength formulas too early may lead to the retention of feed in the stomach, which is associated with feeding intolerance and necrotising enterocolitis, a severe bowel disorder.

Study characteristics

The evidence for this review is current as of 1 October 2018. We included three trials that compared dilute formula milk (half-strength, double-volume) with full-strength formula milk. The trials involved 102 preterm or low birth weight infants; two were conducted in the USA and one in India. The trials were small (14, 38 and 50 infants, respectively) and conducted between 25 and 30 years ago. The quality of two trials was judged to be poor due to insufficient information being provided in the trial publications, but judged to be moderate in the third trial (of 38 infants). None of the trials assessed necrotising enterocolitis as an outcome.

Key results

Infants receiving dilute formula (half-strength, double-volume) experienced fewer episodes of feeding intolerance and achieved full energy intake earlier than infants receiving full-strength formula (20 kcal/oz (~ 68 to 70 kcal/100 mL)).

Feeding intolerance

Two measures of feeding intolerance (abdominal distension and episodes of gastric residuals) were reported across the trials. Two trials (88 infants) provided data for abdominal distension and gastric residuals. Infants fed dilute formula experienced 19% (CI 16% to 23%) fewer episodes of abdominal distension (> 2 cm), equivalent to 0.67 episodes per infant in the half-strength group compared to 0.83 episodes in the full-strength group. It was not possible to combine data on gastric residuals but both trials reported fewer episodes of gastric residuals in the dilute formula group. The third trial (14 infants) only reported that there was no difference between the groups with respect to these two outcomes.

Time to establish full enteral feeding

In two trials (88 infants) infants receiving dilute formula experienced a 22% (CI 16% to 28%) reduction in the number of days required to reach an adequate energy intake (420 joules/kilogram), equivalent to 8 days in the half-strength group compared to 10.3 days in the full-strength group.

Certainty of evidence

In exclusively formula-fed preterm or low birth weight infants, low-certainty evidence shows that diluted formula may lead to an important reduction in the time taken to attain adequate enteral fluid and energy requirements, without increasing indicators of feeding intolerance. The clinical importance of the reduction in episodes of feeding intolerance is unclear. These findings are based on three small, old trials that may be of less relevance to current practice. A lack of data on other important outcomes, such as the incidence of necrotising enterocolitis and weight gain, limits the usefulness of the studies.

SUMMARY OF FINDINGS

Summary of findings 1. Half-strength formula compared to full-strength formula for exclusively formula-fed preterm or low birth weight infants

Half-strength formula compared to full-strength formula for exclusively formula-fed preterm or low birth weight infants

Patient or population: exclusively formula-fed preterm or low birth weight infants

Settings: neonatal intensive care units (NICUs)

Intervention: half-strength formula

Comparison: full-strength formula

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Full-strength formula	Half-strength formula				
Episodes of abdominal distention > 2 cm	The mean episodes of abdominal distention > 2 cm in the control groups was 0.83 episodes ⁴	The mean episodes of abdominal distention > 2 cm in the intervention groups was 0.16 lower (0.19 to 0.13 lower) ⁴		88 (2 studies)	⊕⊕⊕⊕ low 1,2	
Episodes of gastric residuals ³ > 50% of last feed remaining	See comment	See comment	Not estimable ³	88 (2 studies)	⊕⊕⊕⊕ low 1,2	Episodes of gastric residuals were lower in the half-strength formula group in both studies (MD -1.20, 95% CI -2.20 to -0.20; and MD -0.80, 95% CI -1.32 to -0.28)
Days until 420 joules per kilogram	The mean days until 420 joules per kilogram in the control groups was 10.3 days ⁴	The mean days until 420 joules per kilogram in the intervention groups was 2.26 lower (2.85 to 1.67 lower) ⁴		88 (2 studies)	⊕⊕⊕⊕ low 1,2	

Necrotising entero-colitis	Data for this outcome were not reported
All-cause mortality prior to hospital discharge	Data for this outcome were not reported
Incidence of invasive infection	Data for this outcome were not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

¹Inadequate method of randomisation and allocation concealment unlikely in one study. Limited information to assess design in both studies.

²We are aware of at least one study which was not published due to inability to recruit sufficient numbers of formula-fed infants.

³Studies used different units (residuals per baby per day and residuals per baby until attaining 100 kcal/day) and so could not be combined.

⁴Assumed risk calculated from mean of control groups in both included studies.

BACKGROUND

Description of the condition

Preterm infants, especially those whose growth has been restricted in utero, have fewer nutrient reserves at birth than term infants. Furthermore, preterm infants are subject to physiological and metabolic stresses, such as respiratory distress or infection, that can affect their nutritional needs. Despite optimal maternal support, expressed breast milk may not always be available and, as an alternative, preterm infants may be fed with a variety of artificial formulas given enterally. Nutritional requirements for preterm infants assume that the optimal rate of postnatal growth should be similar to that of normal fetuses of the same postnatal age. In practice, these target levels of nutrient input are not always achieved and this may result in important nutritional deficits (McGuire 2004).

Increased milk osmolality has been suggested as a risk factor for developing feeding intolerance and necrotising enterocolitis (NEC), either through damaging the bowel mucosa or by influencing the development or growth of the gut. However, the evidence to support either mechanism is limited (Pearson 2011). The osmolality of breast milk from mothers of term babies is 300 mOsmol/kg, and from mothers of preterm babies is 276 mOsmol/kg. Preterm formulas vary in osmolality from 250 to 350 mOsmol/kg. The addition of fortifiers increases the osmolality of milk (Pearson 2011). Dilution of formula might be one way of reducing osmolality and, therefore, feeding intolerance and NEC.

Another concern is that delayed enteral feeding could diminish the functional adaptation of the gastrointestinal tract and result in feeding intolerance later on because gut hormone secretion and motility have not been stimulated, compromising growth and prolonging hospital stay (Lucas 1986). Feeding intolerance is extremely common in the preterm infant, and although its relationship to NEC is poorly understood, it is often considered a precursor to NEC. Feeding intolerance is usually characterised by gastric residuals or aspirates before feeding, emesis and abdominal distension (Cobb 2004).

Despite several Cochrane Reviews on the topic, evidence is lacking that different feeding approaches affect the incidence of necrotising enterocolitis. Reviews of delayed enteral feeding (Morgan 2014), slow advancement of enteral feed volumes (Oddie 2017) and minimal enteral nutrition (Morgan 2013) all conclude that there is no significant effect on the incidence of NEC. Other reviews have compared the effect of different protein intakes on weight gain and neurodevelopmental outcomes (Fenton 2014). This review focuses on an alternative approach for infants receiving formula milk, namely the dilution of full-strength formula feeds during feeding advancement.

Description of the intervention

Important decisions about the care of preterm infants include when to start oral feeding and what quantity and concentration to use. It is generally agreed that feeding must be initiated slowly and advanced with much greater deliberation than in full-term infants. One question in beginning feeding for preterm infants is whether to use full-strength formula with standard volume, slowly increasing the volume of each feeding, or whether there is an advantage in

initially presenting the intestine with dilute formula with greater volume (Stern 1982).

How the intervention might work

There is concern that high osmolality formulas may lead to gastric retention in preterm infants, increasing physiological strain on the gastrointestinal tract and leading to the development of feeding intolerance and NEC. It has been suggested that dilute formulas may be more easily digested than full-strength formulas and may thus be beneficial during the initial feeding of preterm infants (Duritz 1979).

Why it is important to do this review

Establishing feeding is a central component of care for preterm or low birth weight infants. As several Cochrane Reviews have demonstrated, there is limited evidence for which feeding methods are most beneficial in avoiding feeding intolerance and reducing the risk of NEC. A key question in considering initiating feeding for these infants is whether using full-strength formula and slowly increasing the volume of each feed is more beneficial than presenting the intestine initially with larger volumes of more dilute formula.

OBJECTIVES

To assess the effects of dilute versus full-strength formula on the incidence of necrotising enterocolitis, feeding intolerance, weight gain, length of stay in hospital and time to achieve full calorie intake in exclusively formula-fed preterm or low birth weight infants. A secondary objective was to assess the effects of different dilution strategies.

METHODS

Criteria for considering studies for this review

Types of studies

We searched for randomised or quasi-randomised trials, including cluster-randomised trials, in exclusively formula-fed preterm or low birth weight infants. Cross-over trials were not eligible for inclusion.

Types of participants

Exclusively formula-fed infants weighing less than 2500 grams or preterm infants (< 37 weeks' gestational age at birth) in whom enteral feeds are being initiated.

Exclusions

1. Infants with major congenital malformations, especially abdominal wall defects (e.g. gastroschisis, omphalocele) or serious gastrointestinal problems (e.g. necrotising enterocolitis).
2. Infants receiving any breast milk for the duration of the intervention period.
3. Infants receiving formula fortified with additives such as vitamins, minerals or iron during the study (i.e. supplemental additives which were not included in the formula by the manufacturer or the formula preparation room in the hospital).

Types of interventions

Any dilution of formula compared to full-strength formula during feeding advancement in which the total enteral nutrient intake was the same in both groups. That is, infants receiving dilute formula received greater volumes (e.g. half-strength formula at twice the volume). Any type of formula was eligible for assessment, whether designed for full-term or preterm infants. In each trial, criteria for initiating, advancing and stopping feeds had to be identical.

Types of outcome measures

Primary outcomes

1. Necrotising enterocolitis confirmed by at least two of the following features: abdominal radiograph showing pneumatosis intestinalis or gas in the portal venous system or free air in the abdomen; abdominal distension with abdominal radiograph with gaseous distension or frothy appearance of bowel lumen (or both); gross blood in stool; lethargy, hypotonia or apnoea (or combination of these); or a diagnosis confirmed at surgery or autopsy (Walsh 1986).
2. Feed intolerance, as defined by the included studies.

Secondary outcomes

1. Growth
 - a. Time to regain birth weight and subsequent rates of weight gain, linear growth, head growth or skinfold thickness, growth up to six months (from date of birth).
 - b. Long-term growth: weight, height or head circumference (and/or proportion of infants who remain below the 10th percentile for the index population's distribution) assessed at intervals from six months of age.
2. Duration of hospital stay (days).
3. Time to establish full enteral feeding: as defined by the included studies.
4. All-cause mortality prior to hospital discharge.
5. Incidence of invasive infection as determined by culture of bacteria or fungi from blood, cerebrospinal fluid, urine or from a normally sterile body space.
6. Neurodevelopment
 - a. Death or severe neurodevelopmental disability defined as any one or a combination of the following: non-ambulant cerebral palsy; developmental delay (developmental quotient less than 70); auditory and visual impairment (each component will be analysed individually as well as part of the composite outcome).
 - b. Neurodevelopmental scores in survivors aged greater than, or equal to, 12 months of age measured using validated assessment tools.
 - c. Cognitive and educational outcomes in survivors aged more than five years old.

Search methods for identification of studies

We used the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal [search strategy](#) for specialized register).

Electronic searches

We conducted a comprehensive search to update the previous searches including: Cochrane Central Register of Controlled Trials

(CENTRAL 2018, Issue 9) in the Cochrane Library; MEDLINE via PubMed (1966 to 1 October 2018); Embase (1980 to 1 October 2018); and CINAHL (1982 to 1 October 2018). We used the following search terms: (Infant Formula[MeSH] OR formula*), plus database-specific limiters for RCTs and neonates (see [Appendix 1](#) for the full search strategies for each database). We did not apply language restrictions.

We searched clinical trials' registries for ongoing or recently completed trials ([clinicaltrials.gov](#); World Health Organization's International Trials Registry and Platform [www.who.int/ictrp/search/en](#); and [ISRCTN Registry](#)). We searched clinical trials' registries for relevant studies using the search words (formula OR formulas) AND (infant OR neonate).

Searches for the previously published review were conducted in 2013 and are detailed in [Appendix 2](#).

Searching other resources

We also checked the reference lists of other reviews and trials for citations to other studies.

Data collection and analysis

We used the standard method of Cochrane Neonatal and Cochrane, as documented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

At least two review authors (from FB, DH, TT and SM) independently assessed for inclusion all citations retrieved by the searches. We resolved any disagreement through discussion. Specifically for this update we:

1. merged search results using reference management software and removed duplicate records of the same report;
2. applied machine learning using Cochrane Classifier tools in the Cochrane Register of Studies (CRS) to remove reports with the least (0% to 2%) probability of being randomised trials and the least (0% to 2%) probability of having infants in the population; we double-checked those with 1% to 2% probability for accuracy;
3. imported records into Covidence and examined titles and abstracts to remove irrelevant reports;
4. retrieved the full text of potentially relevant reports;
5. linked together multiple reports of the same study;
6. examined full-text reports for compliance of studies with eligibility criteria;
7. noted reasons for inclusion and exclusion of studies;
8. made final decisions on study inclusion;
9. resolved disagreements through a consensus process.

Data extraction and management

Two review authors (FB and DH) independently extracted data from the full-text articles using a specifically designed spreadsheet to manage the information. We resolved disagreements through discussion. We entered data into Review Manager 5 and checked for accuracy (Review Manager 2014). When information regarding any

of the above was missing or unclear, we attempted to contact the authors of the original report to provide further details.

Assessment of risk of bias in included studies

Two review authors (FB and DH) independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool for the following domains (Higgins 2017).

1. Sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Any other bias

We resolved any disagreements by discussion or, if necessary, by asking a third assessor to arbitrate. See [Appendix 3](#) for a more detailed description of risk of bias for each domain.

Measures of treatment effect

We analysed the results of the studies using Review Manager 5 (Review Manager 2014). We summarised data in a meta-analysis in the absence of moderate or serious clinical and statistical heterogeneity. For continuous data we used the mean difference (MD) with 95% confidence intervals. We planned to present dichotomous data as risk ratios with 95% confidence intervals and to calculate number needed to treat for an additional beneficial outcome (NNTB) based on the risk difference.

Unit of analysis issues

If we had identified cluster-randomised trials and selected them for inclusion, we would have adjusted their sample sizes according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using an estimate of the intra-cluster correlation co-efficient (ICC) derived from the trial or other source. We would have reported the use of ICCs from other sources and would have conducted sensitivity analyses to investigate the effect of variation in the ICC. If we had identified both cluster-randomised trials and individually randomised trials, we planned to synthesise the relevant information. We would have combined the results from both if there was little heterogeneity and if we considered interaction between the effect of the intervention and the choice of randomisation unit to be unlikely. Cross-over trials were not eligible.

Dealing with missing data

We planned to contact the authors of all published studies if clarification regarding missing data was required, or if we required additional information. In the case of missing data, we would have described the number of participants with missing data in the Results section and the [Characteristics of included studies](#) table.

Assessment of heterogeneity

We assessed the heterogeneity of treatment effects between trials using the Chi² test and the I² statistic. For I² we planned to grade the degree of heterogeneity as minimal (0% to 30%), moderate (31% to 50%), substantial (51% to 75%) and excessive (76% to 100%). Where there was evidence of apparent or statistical heterogeneity,

we planned to assess the source of the heterogeneity using sensitivity and subgroup analysis looking for evidence of bias or methodological differences between trials.

Assessment of reporting biases

We tried to obtain the study protocol for each included study and planned to compare outcomes reported in the protocol to those reported in the study; however protocols were not available. If we had suspected reporting bias we planned to contact the study authors to obtain missing data from them. Where this was not possible, and we thought the missing data introduced serious bias, we planned to explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

It turned out that we had no cause to suspect reporting bias.

Data synthesis

We ran statistical analyses according to the recommendations of Cochrane Neonatal (neonatal.cochrane.org/en/index.html). We analysed all infants randomised on an intention-to-treat basis, and planned to contact the study authors whenever it was necessary to clarify whether the analysis was performed as intention-to-treat. We analysed treatment effects in the individual trial and used a fixed-effect model to combine the data in the meta-analysis. When meta-analysis was not suitable to analyse the data in these studies, we analysed and interpreted individual trials separately.

Subgroup analysis and investigation of heterogeneity

We combined studies where the concentration, energy density and composition of the formula provided was the same or similar across studies. If the concentration, energy density or composition of the formula had varied between studies then we would have conducted subgroup analyses.

Sensitivity analysis

We planned to explore methodological heterogeneity through the use of sensitivity analysis. Studies we deemed to be at low risk of bias were those with adequate sequence generation, allocation concealment and less than 10% losses with intention-to-treat analysis. However both included studies had similar risk of bias.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the certainty of evidence for the following (clinically relevant) outcomes: episodes of abdominal distention; episodes of gastric residuals; time to achieve full enteral feeding. We had planned to assess the certainty of evidence for the following additional outcomes had there been trial data: necrotising enterocolitis; all-cause mortality prior to hospital discharge; and incidence of invasive infection.

All authors participated in assessing the certainty of the evidence for each of the outcomes above. We considered evidence from randomised trials as high certainty but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias. We used the [GRADEpro GDT](#) Guideline Development Tool to create a 'Summary of findings' table to report the certainty of the evidence ([GRADEpro GDT](#)).

The GRADE approach results in an assessment of the certainty of a body of evidence in one of the four following grades.

1. High: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. 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.

RESULTS

Description of studies

See: [Characteristics of included studies](#) and [Characteristics of excluded studies](#).

Results of the search

We give details of the searches conducted for the first version of this review published in 2013 in [Figure 1](#). We included three studies in the earlier version of the review ([Anderson 1995](#); [Currao 1988](#); [Sarna 1990](#)). One was included after contacting the author to confirm the study was randomised ([Sarna 1990](#)); and another was only reported as a conference abstract ([Anderson 1995](#)). Two studies were excluded because the total enteral nutrient intake varied between the groups ([Fewtrell 1997](#); [Postolow 2000](#)).

Figure 1. Study flow diagram for review version published in 2013.

For this update, we searched CENTRAL, MEDLINE, Embase and CINAHL on 1 October 2018 and retrieved 4591 records (see [Figure 2](#)). We removed 1541 records with de-duplication, leaving 3050 records to which we applied the Cochrane Classifier tools in the Cochrane Register of Studies (CRS). This resulted in the exclusion

of a further 1204 records (904: 0% to 2% probability as RCTs; 300: 0% to 2% probability as relating to infants), leaving 1846 records to screen from the database searches. The searches of the three trials registers yielded a further 140 unique records.

Figure 2. Study flow diagram: review update 2018

Figure 2. (Continued)

synthesis
(meta-analysis)

We imported 1986 records into Covidence for screening. From reading the titles and abstracts, we excluded 1983 records and identified three as potentially eligible. On reading the full text, we excluded two studies because the interventions and comparators were not appropriate ([Armanian 2013](#); [Hodgson 1983](#)); and a third record was a commentary on the earlier version of this review ([Hale 2014](#)). Since none of the records was eligible, we identified no new studies for this update.

Included studies

Population

[Currao 1988](#) was conducted in the USA and involved 50 very low birth weight infants (< 1500 grams) who were exclusively fed with formula. Infants were excluded if they had serious medical problems, such as necrotising enterocolitis; if they were growth retarded; or if they were receiving maternal breast milk. Comparison between these two groups showed no significant differences in birth weight or gestational age at the time of entry into the study.

[Sarna 1990](#) was conducted in India and involved 38 preterm infants weighing less than 1750 grams who were exclusively fed with formula. Only infants without clinical features or laboratory evidence of infection were included in the study. Infants with birth asphyxia, meconium aspiration, heart disease, respiratory distress or other significant problems were excluded. There were no significant differences between the groups with respect to birth weight or gestational age at the time of entry into the study.

[Anderson 1995](#) was conducted in the USA and involved 14 very low birth weight infants (not defined) who were appropriately grown and had feeding introduced within the first seven days of life. There were no significant differences between the groups with respect to birth weight or gestational age at the time of entry into the study.

Interventions

In [Currao 1988](#), of the 50 preterm or very low birth weight infants who were exclusively formula-fed, 28 began on a regimen of full-strength (20 kcal/oz (~ 68 to 70 kcal/100 mL)) formula (Enfamil 20) and 22 on Enfamil 20 formula diluted with water to half strength and provided at twice the volume. The actual amounts of formula differed depending on the size of the infant. Feeds were given every two hours by nasogastric tube (slow push or gravity feed). The feeds of half-strength formula at double volume provided the same caloric and other nutrient intake as full-strength formula intake, but with twice the fluid. The groups were compared until infants reached an enteral nutrient intake of 420 joules (100 kcal) per kilogram.

During the initiation of the feeds, all infants received parenteral nutrition of fluids and energy calculated to maintain adequate fluid and energy intake while the feeds were being advanced. The parenteral nutrition was progressively reduced as enteral feeds were tolerated and was finally discontinued after enteral feeds were fully established.

In [Sarna 1990](#), of the 38 preterm or low birth weight infants who were exclusively formula-fed, 20 infants were given double-volume (half-strength) formula (Lactogen Infant formula) (10 kcal/oz (~ 34 kcal/100 mL)) diluted with water to twice the volume, and 18 infants were fed with full-strength formula (20 kcal/oz (~ 68 to 70 kcal/100 mL)) at the standard volume. Feeds were given at three-hourly intervals. The two groups were compared until infants reached an enteral nutrient intake of 100 kcal per kilogram per day.

Infants in both groups received clear fluids for the first 12 hours followed by the dilute formula with double-volume (half-strength) or full-strength formula. Infants were supplemented with intravenous fluids to maintain adequate fluid intake. The intravenous infusion was progressively reduced as enteral feedings were tolerated and was finally discontinued after enteral feedings were fully established.

In [Anderson 1995](#), six infants were given double-volume, half-strength 24 kcal Enfamil Premature formula and eight were given full-strength 24 kcal Enfamil Premature formula. Feeds were given as three-hourly bolus feeds. The two groups were compared until infants reached an enteral nutrient intake of 80 kcal per kilogram per day. No further details were provided on the feeding regimen.

Major outcomes assessed

The primary outcome in two studies was time to achieve full enteral feeding (measuring time required to reach enteral nutrient intake of 420 joules (100 kcal per kilogram) ([Currao 1988](#); [Sarna 1990](#)). In [Anderson 1995](#) the primary outcome was enteral nutrient feeds of 80 kcal per kilogram per day. Secondary outcomes in all three studies included various measures of feeding intolerance, including gastric residuals, vomiting and abdominal distension. None of the studies reported effects on mortality, necrotising enterocolitis, sepsis or neurodevelopment.

Excluded studies

We excluded four studies because the overall enteral nutrient density between groups was different ([Armanian 2013](#); [Fewtrell 1997](#); [Hodgson 1983](#); [Postolow 2000](#)). A fifth exclusion was a commentary on the earlier version of this review ([Hale 2014](#)).

Risk of bias in included studies

We assessed the studies as having an unclear risk of bias ([Figure 3](#); [Figure 4](#)). [Currao 1988](#) used a quasi-random method of allocation (odd/even number) and therefore it was unlikely that allocation was concealed. Personal communication with the first author of [Sarna 1990](#) confirmed that the study was randomised; however, allocation concealment was unclear. The blinding of outcome assessors was not described. Outcome data were reported for all infants but without access to the original trial protocols we do not know if all the planned and measured outcomes were reported in the trial publications. [Anderson 1995](#) was reported only as an abstract and so information on the methods of the trial was very limited.

Figure 3. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

Figure 4. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): Objective outcomes: enteral energy intake, objective measures of feeding intolerance	Blinding of outcome assessment (detection bias): Subjective outcomes: abdominal distention	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Anderson 1995	?	?	?	?	?	?	+	?
Currao 1988	+	+	?	?	?	+	?	

Figure 4. (Continued)

Currao 1988	-	-	?	?	?	+	?
Sarna 1990	+	+	?	?	?	+	?

Effects of interventions

See: [Summary of findings 1](#) Half-strength formula compared to full-strength formula for exclusively formula-fed preterm or low birth weight infants

Primary outcomes

Necrotising enterocolitis

None of the trials assessed necrotising enterocolitis as an outcome.

Feed intolerance (indicated by gastric residuals, abdominal distension and/or vomiting)

Both [Currao 1988](#) and [Sarna 1990](#) reported reductions in episodes of abdominal distension of greater than 2 cm in the dilute formula with the double-volume (half-strength) group compared to the full-strength group (mean difference (MD) -0.16, 95% confidence interval (CI) -0.19 to -0.13; [Analysis 1.1](#)). These reductions were statistically significant but of unclear clinical importance. Both studies found significant reductions in episodes of gastric residuals in the dilute formula with the double-volume (half-strength) group as measured by episodes per infant per day in [Currao 1988](#) (MD -1.20, 95% CI -2.20 to -0.20; [Analysis 1.2](#)) and episodes per infant until attaining 100 kcal/kg in [Sarna 1990](#) (MD -0.80, 95% CI -1.32 to -0.28; [Analysis 1.2](#)). Due to different methods of measurement we could not combine the studies in the meta-analysis. [Currao 1988](#) also reported fewer episodes of vomiting per day (MD -0.04, 95% CI -0.07 to -0.01; [Analysis 1.3](#)) in the half-strength group. [Anderson 1995](#) only reported that the incidence of feed intolerance (abdominal distension > 2 cm or gastric residuals > 50% of previous feeding, or both outcomes) did not differ between groups.

Secondary outcomes

Growth

Only [Sarna 1990](#) measured our secondary outcome of weight gain. One week after commencement of intragastric feeds there was no statistically significant important difference in weight gain between the groups (MD 0.05 kg, 95% CI -0.06 to 0.15; [Analysis 1.4](#)).

Duration of hospital stay (days)

None of the trials assessed duration of hospital stay.

Time to establish full enteral feeding

Both [Currao 1988](#) and [Sarna 1990](#) found statistically significant reductions in the number of days required to reach full calorie intake by enteral nutrient feeds (420 joules/kilogram) in the half-strength group compared to the full-strength group (MD -2.26 days, 95% CI -2.85 to -1.67; [Analysis 1.5](#)). No adverse effects were reported. [Anderson 1995](#) reported that the half-strength feeds group reached the goal of 80 kcal/kg/day sooner than the full-strength group (8.2 ± 2.4 days versus 16.9 ± 7.9 days (the publication

does not define these statistics); however it was not clear if this was considered attainment of full enteral nutrient feeding.

All-cause mortality prior to hospital discharge

None of the trials assessed mortality prior to hospital discharge.

Invasive infection

Incidence of invasive infection, as determined by culture of bacteria or fungus from blood, cerebrospinal fluid, urine or from a normally sterile body space, was not assessed in any of the included trials.

Neurodevelopment

None of the trials assessed neurodevelopmental outcomes.

DISCUSSION

The primary outcome of interest was not reported in any of the included studies and positive findings were restricted to a few secondary outcomes. The two small studies included in the meta-analysis found that infants on dilute formula with double-volume (half-strength) feeds attained their required energy intake earlier and had fewer complications, such as abdominal distension and persistent gastric aspirates, compared to infants on full-strength feeds. However none of the included studies reported important outcomes like length of hospital stay or the incidence of serious gastrointestinal problems, such as necrotising enterocolitis. Overall, the evidence is limited for assessing the benefits and harms of dilute versus full-strength formula in preterm or low birth weight infants.

Summary of main results

The results of the included studies suggest a benefit in advancing formula intake for small preterm infants using a dilute formula. The attainment of adequate energy intake by enteral feeds was on average two to three days earlier in the infants receiving dilute formula. Two studies reported reductions in episodes of gastric residuals and abdominal distension in the infants receiving half-strength feeds and no adverse effects were reported. The reasons for the earlier establishment of enteral feeds are not clear from the studies, but may be related to lower incidence of feed intolerance.

Overall completeness and applicability of evidence

The results were applicable to exclusively formula-fed preterm and low birth weight infants and do not apply to either exclusively breast-milk-fed infants or to those infants who are fed a combination of breast milk and formula. No data were found for length of hospital stay or serious gastrointestinal problems, such as necrotising enterocolitis. Information on these outcomes is very important to understand the effects of using dilute formula with double volume (half the strength). The intervention was carried out in the context of adjustments to the intravenous fluid and energy intakes of the infants and as such it may not be applicable

for infants on standardised parenteral nutrition. Additionally, since the two studies enrolled stable infants without serious co-existing medical problems, the findings should be applied cautiously to sick, extremely preterm (≤ 28 weeks) or extremely low birth weight (< 1000 g) infants. These studies are from a different era of neonatal care and may have little relevance to the populations and practices of today.

Quality of the evidence

Evidence was only available from three small studies involving 102 infants. All of the studies were considered at unclear risk of bias; blinding (performance bias and detection bias) of study personnel and outcome assessor was not described but is unlikely given the nature of the trials. The overall GRADE assessment was low-certainty evidence (downgraded due to concerns over bias) and thus our confidence in the effects observed in these trials is limited.

Potential biases in the review process

We designed the methods of the review to minimise the introduction of additional bias. It is possible that we might have found additional studies with additional literature searches, such as searching non-English language databases. Had more detail about the methods of the included studies been available, we might have been able to draw clearer conclusions about the certainty of the evidence.

Agreements and disagreements with other studies or reviews

Several other Cochrane Reviews address related aspects of feeding for preterm infants (as outlined in the Background). This is the only systematic review we are aware of that focuses on the effects of dilution of full-strength formula feeds during feeding advancement.

AUTHORS' CONCLUSIONS

Implications for practice

The primary outcome of interest was not reported in any of the studies and positive findings were restricted to a few secondary outcomes. There was insufficient data for us to determine whether dilute or full-strength formula, in exclusively formula-fed preterm or low birth weight infants, affects length of hospital stay, necrotising enterocolitis or other clinically important outcomes. The included trials are quite old and may have little relevance to current practice. However, in the three included studies diluted formula did result in the more rapid attainment of enteral fluid and energy requirements without increasing indicators of feeding intolerance.

Implications for research

Further randomised trials are needed to assess the effect of dilute versus full-strength formula in preterm or low birth weight infants who are fed formula. Future studies should probably compare dilute versus full-strength formula in populations of infants at increased risk of necrotising enterocolitis. They could also enrol infants on a combination of human and formula feeds, as this is a common scenario in nurseries that support lactation. Necrotising enterocolitis, death, hospital length of stay, sepsis, adverse events (including hyponatraemia) and neurodevelopmental outcomes should also be considered. Trials should attempt to ensure carers and assessors are blind to the intervention.

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The Methods section of this review is based on a standard template used by Cochrane Neonatal.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Anderson 1995

Study characteristics		
Methods	Randomised trial	
Participants	<p>14 very low birth weight infants (not defined). Dilute formula with double volume (half-strength) group (n = 6; gestational age 29.2 ± 2 weeks; birth weight 1235 ± 243 g); full-strength group (n = 8; gestational age 29.5 ± 2 weeks; birth weight 1185 ± 286 g). (Whether these statistics are means and standard deviations is not described in the abstract.)</p> <p>Day of life on which feeding was initiated did not differ between the groups. The ratio of male to female infants was not reported. The proportion of infants that were small for gestational age, or who had central venous catheters was not described</p>	
Interventions	Half- versus full-strength preterm formula. Dilute group received double-volume, half-strength 24 kcal Enfamil Premature formula. Full-strength group received undiluted 24 kcal Enfamil Premature formula. Feeds were given as 3-hourly bolus feeds. The 2 groups were compared until infants reached an enteral nutrient intake of 80 kcal/kg/day. No further details were provided on the feeding regimen.	
Outcomes	Feeding intolerance (abdominal girth increased by > 2 cm and/or residuals > 50% of previous feed), time to reach goal feeds of 80 kcal/kg/day	
Notes	Location: Charleston, South Carolina, USA. Reported as a conference abstract only. The study was not published in full as trial investigators could not recruit enough babies who were being fed formula (personal communication).	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not described

Anderson 1995 (Continued)

Allocation concealment (selection bias)	Unclear risk	Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: blinding of study personnel or participants was not described but is unlikely given the nature of the trial
Blinding of outcome assessment (detection bias) Objective outcomes: enteral energy intake, objective measures of feeding intolerance	Unclear risk	Comment: not described but is unlikely given the nature of the trial
Blinding of outcome assessment (detection bias) Subjective outcomes: abdominal distention	Unclear risk	Comment: not described but is unlikely given the nature of the trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: difficult to assess since trial reported as an abstract only
Selective reporting (reporting bias)	High risk	Comment: trial reported as an abstract only. Actual data not given for some outcomes even though outcomes narratively reported
Other bias	Unclear risk	Comment: not enough information to assess since trial reported as an abstract only

Currao 1988

Study characteristics

Methods	Quasi-randomised trial
Participants	<p>50 preterm infants with birth weight < 1500 g. Dilute formula with double-volume (half-strength) group (n = 28; mean gestational age 30.2 weeks (SD 1.2); mean birth weight 1189 g (SD 23.1)); full-strength group (n = 22; mean gestational age 30.3 weeks (SD 1.3); mean birth weight 1269 g (SD 45.4)).</p> <p>There were no significant differences between the full-strength group and half-strength group in terms of birth weight, gestational age or weight at the time of entry into the study. The ratio of male to female infants was also similar. The proportion of infants that were small for gestational age, or who had central venous catheters, was not described in the study.</p>
Interventions	<p>The dilute formula with double-volume (half-strength) group received formula (Enfamil 20) diluted with water but fed in twice the volume (10 kcal/oz), thus maintaining the same enteral caloric and nutrient intake as the full-strength group. During the initiation of the feeds, all infants received parenteral nutrition calculated to maintain adequate fluid and nutrient intake while the feeds were being advanced. The parenteral nutrition was progressively reduced as enteral feeds were tolerated and was finally discontinued after enteral feeds were fully established. The groups were compared until infants reached an enteral nutrient intake of 420 joules (100 kcal) per kilogram</p> <p>Rate of feeding advancement varied with weight (< 1000 g, 1000 to 1250 g, 1251 to 1500 g) and followed an established pattern of introduction over 4 days (Table 1). Feeds were provided 2-hourly. No further details on the feeding regimen were provided.</p>

Currao 1988 (Continued)

Outcomes	Time to achieve full enteral feeding; gastric residuals; incidence of apnoea and/or bradycardia; episodes of vomiting; abdominal distension; guaiac-positive stools.	
Notes	Location: New York, USA	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"... randomly assigned to one of two groups based on whether the last digit of their hospital identification number was odd or even."
Allocation concealment (selection bias)	High risk	Comment: it is unlikely that allocation was concealed due to odd/even number assignment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: blinding of study personnel or participants was not described but is unlikely given the nature of the trial.
Blinding of outcome assessment (detection bias) Objective outcomes: enteral energy intake, objective measures of feeding intolerance	Unclear risk	Comment: blinding of outcome was not described but is unlikely given the nature of the trial.
Blinding of outcome assessment (detection bias) Subjective outcomes: abdominal distention	Unclear risk	Comment: blinding of outcome assessor(s) not described, but is unlikely given the nature of the trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: outcome data were reported for all babies.
Selective reporting (reporting bias)	Unclear risk	Comment: there is no protocol to access so we do not know the original planned outcomes.

Sarna 1990

Study characteristics	
Methods	Randomised trial
Participants	<p>38 preterm infants with birth weight < 1750 g. Dilute formula with double-volume (half-strength) group (n = 20; mean gestational age 32.05 weeks (SD 2.08); mean birth weight 1420 g (SD 200)); full-strength group (n = 18; mean gestational age 32.5 weeks (SD 1.54); mean birth weight 1410 g (SD 200)).</p> <p>The ratio of male to female infants was not significantly different. All infants in the 2 groups were between 1000 g and 1750 g except 2 infants who weighed less than 1000 g. Gestational age of most infants was between 29 weeks and 34 weeks. The proportion of infants that were small for gestational age, or who had central venous catheters, was not described in the study</p>
Interventions	Dilute formula with double-volume (half-strength) group received Lactogen infant formula (10 kcal/oz) but fed in twice the volume.

Dilute versus full-strength formula in exclusively formula-fed preterm or low birth weight infants (Review)

Sarna 1990 (Continued)

Infants in both groups received clear fluids for the first 12 hours followed by the dilute formula with double-volume (half-strength) formula or full-strength formula. Infants were supplemented with intravenous fluids initially to maintain adequate fluid intake. The intravenous infusion was progressively reduced as enteral feeds were tolerated and was finally discontinued after enteral feeds were fully established. The groups were compared until infants reached an enteral nutrient intake of 420 joules (100 kcal) per kilogram.

Rate of feeding advancement varied with weight (≤ 1000 g, 1001 to 1250 g, 1251 to 1500 g, > 1500 g) and followed an established pattern of introduction over 4 days (Table 2). Feeds were provided 3-hourly. No further details on the feeding regimen were provided.

Outcomes	Time to achieve full enteral feeding; episodes of gastric aspirate; episodes of abdominal distension; weight gain.	
Notes	Location: New Delhi, India	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The allocation of subjects to the two groups was through a simple randomisation. The random numbers were generated through the random numbers table." (personal communication with trialist)
Allocation concealment (selection bias)	Low risk	Quote: "The random number sequence was with one of the medical personnel not connected with the study. The numbers were made available to the PI (MS Sarna) at the time of enrolment of each subject." (personal communication with trialist)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: blinding of study personnel or participants was not described but is unlikely given the nature of the trial
Blinding of outcome assessment (detection bias) Objective outcomes: enteral energy intake, objective measures of feeding intolerance	Unclear risk	Comment: blinding of outcome was not described but is unlikely given the nature of the trial
Blinding of outcome assessment (detection bias) Subjective outcomes: abdominal distention	Unclear risk	Comment: blinding of outcome assessor(s) not described, but is unlikely given the nature of the trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: outcome data were reported for all babies
Selective reporting (reporting bias)	Unclear risk	Comment: there is no protocol to access so we do not know the original planned outcomes

g: grams

SD: standard deviation

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Armanian 2013	Compared low volume with routine volume formula. The overall nutrient density was different between the groups.
Fewtrell 1997	Different overall nutrient density between groups.
Hale 2014	Commentary on existing systematic review.
Hodgson 1983	Different overall nutrient density between groups.
Postolow 2000	Compared half-strength regular formula with full-strength preterm formula. The overall nutrient density was different between the groups.

DATA AND ANALYSES

Comparison 1. Half-strength formula versus full-strength formula

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Episodes of abdominal distention > 2 cm	2	88	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.19, -0.13]
1.2 Episodes of gastric residuals	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2.1 Episodes of gastric residuals per baby per day	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2.2 Episodes of gastric residuals per baby until attaining 100 kcal/kg	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.3 Episodes of vomiting per day	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4 Weight gain one week after starting feeds (kg)	1	38	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.06, 0.15]
1.5 Days until 420 joules per kilogram	2	88	Mean Difference (IV, Fixed, 95% CI)	-2.26 [-2.85, -1.67]

Analysis 1.1. Comparison 1: Half-strength formula versus full-strength formula, Outcome 1: Episodes of abdominal distention > 2 cm

Analysis 1.2. Comparison 1: Half-strength formula versus full-strength formula, Outcome 2: Episodes of gastric residuals

Analysis 1.3. Comparison 1: Half-strength formula versus full-strength formula, Outcome 3: Episodes of vomiting per day

Analysis 1.4. Comparison 1: Half-strength formula versus full-strength formula, Outcome 4: Weight gain one week after starting feeds (kg)

Analysis 1.5. Comparison 1: Half-strength formula versus full-strength formula, Outcome 5: Days until 420 joules per kilogram

ADDITIONAL TABLES

Table 1. Feeding schedule for Currao 1988

Birth weight (< 1000 g)		Birth weight (1000 to 1250 g)		Birth weight (1251 to 1500 g)	
Full-strength formula	Diluted formula (double volume)	Full-strength formula	Diluted formula (double volume)	Full-strength formula	Diluted formula (double volume)
Day 1					
2 mL 5% dextrose × 2	2 mL 5% dextrose × 2	3 mL 5% dextrose × 2	3 mL 5% dextrose × 2	5 mL 5% dextrose × 2	5 mL 5% dextrose × 2
2 mL ¼S × 3	2 mL ¼S × 3	3 mL ¼S × 3	3 mL ¼S × 3	5 mL ¼S × 3	5 mL ¼S × 3
2 mL ½S × 3	2 mL ½S × 7	3 mL ½S × 3	3 mL ½S × 7	5 mL ½S × 3	5 mL ½S × 7
2 mL ¾S × 3	[n/a]	3 mL ¾S × 4	[n/a]	5 mL ¾S × 4	[n/a]
Day 2					
2 mL FS × 12	3 mL ½S × 6	3 mL FS × 12	5 mL ½S × 12	5 mL FS × 12	7 mL ½S × 6
	4 mL ½S × 6				10 mL ½S × 6
Day 3					
3 mL FS × 12	5 mL ½S × 6	4 mL FS × 12	6 mL ½S × 6	7 mL FS × 12	12 mL ½S × 6
	6 mL ½S × 6		8 mL ½S × 6		14 mL ½S × 6
Day 4					
4 mL FS × 12	7 mL ½S × 6	6 mL FS × 12	10 mL ½S × 6	9 mL FS × 12	16 mL ½S × 6
	8 mL ½S × 6		12 mL ½S × 6		18 mL ½S × 6

Feeds were given every two hours. After day 4, the schedule remained the same.

S = strength; FS = full strength.

Multiplication factor indicates the number of feeds.

Table 2. Feeding schedule for Sarna 1990

Schedule	Birth weight (≤ 1000 g)		Birth weight (1001 to 1250 g)		Birth weight (1251 to 1500 g)		Birth weight (> 1500 g)	
	Diluted formula (double volume)	Full-strength formula	Diluted formula (double volume)	Full-strength formula	Diluted formula (double volume)	Full-strength formula	Diluted formula (double volume)	Full-strength formula
First 24 hours	CF	CF	CF	CF	CF	CF	CF	CF
	1 cc $\times$ 4	1 cc $\times$ 4	2 cc $\times$ 4	2 cc $\times$ 4	3 cc $\times$ 4	3 cc $\times$ 4	4 cc $\times$ 4	4 cc $\times$ 4
	HSM	FSM	HSM	FSM	HSM	FSM	HSM	FSM
	2 cc $\times$ 4	1 cc $\times$ 4	4 cc $\times$ 4	2 cc $\times$ 4	5 cc $\times$ 4	3 cc $\times$ 4	7 to 8 cc $\times$ 4	4 cc $\times$ 4
24 to 48 hours	3 cc $\times$ 4	2 cc $\times$ 4	6 cc $\times$ 4	3 cc $\times$ 4	8 cc $\times$ 4	4 cc $\times$ 4	12 cc $\times$ 4	7 cc $\times$ 4
	4 cc $\times$ 4	2 cc $\times$ 4	8 cc $\times$ 4	4 cc $\times$ 4	10 cc $\times$ 4	6 cc $\times$ 4	16 cc $\times$ 4	8 cc $\times$ 4

Feeding continued until a volume of 150 mL/kg per day was reached. The end point of the study was achieved when the caloric intake became 100 kcal/kg/day. Then the strength in the dilute formula group was changed to full strength.

CF = clear fluid (5% dextrose)

HSM = half-strength milk (double volume)

FSM = full-strength milk

Multiplication factor indicates the number of feeds.

APPENDICES

Appendix 1. Standard search methodology

Searches were run on 1 October 2018.

PubMed

((Infant, Newborn [mh] 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])) AND (Infant Formula [mh] or formula*[tiab]))

Embase

#1 (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*).mp
#2 exp infant
#3 (#1 OR #2)
#4 (human not animal) .mp
#5 (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial).mp
#6 (#3 and #4 and #5)
#7 formula.mp.
#8 exp Artificial milk
#9 (#7 or #8)
#10 (#6 and #9)

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) AND (Infant formula OR formula*)

Cochrane Central Register of Controlled Trials

(infant or newborn or neonate or neonatal or premature or preterm or very low birth weight or low birth weight or VLBW or LBW) and (formula or formulas)

Appendix 2. Previous search strategies

Searches were run for the previously published review on 1 February 2013.

MEDLINE search strategy

1 Premature Birth/
2 Infant, Premature/
3 exp Infant, Low Birth Weight/
4 Fetal Growth Retardation/
5 (preterm or pre-term or prematur\$ or "low birth weight").tw.
6 (IUGR or SGA or "small for gestational age" or "growth retard\$" or "growth restrict\$").tw.
7 or/1-6
8 Infant Formula/
9 exp Milk Substitutes/
10 formula\$.tw.
11 Randomized Controlled Trial/
12 Controlled Clinical Trial/

13 (randomi?ed or placebo or randomly or trial or groups).tw.

14 or/11-13

15 (animals not (humans and animals)).sh.

16 or/8-10

17 7 and 14 and 16

18 17 not 15

EMBASE search strategy

1 'prematurity'/exp

2 'low birth weight'/exp

3 'intrauterine growth retardation'/exp

4 preterm:ab,ti OR 'pre term':ab,ti OR prematur*:ab,ti OR 'low birth weight':ab,ti

5 iugr:ab,ti OR sga:ab,ti OR 'small for gestational age':ab,ti OR 'growth retarded':ab,ti OR 'growth restricted':ab,ti

6 #1 OR #2 OR #2 OR #4 OR #5

7 'artificial milk'/exp

8 'artificial milk':ab,ti OR formula*:ab,ti

9 #7 OR #8

10 'randomized controlled trial'/exp

11 random*:ab,ti OR placebo:ab,ti OR trial:ab,ti OR groups:ab,ti

12 #10 or #11

13 #6 and #9 and #12

CENTRAL search strategy

1 [Premature Birth] explode all trees

2 [Infant, Low Birth Weight] explode all trees

3 [Infant, Premature] explode all trees

4 [Fetal Growth Retardation] explode all trees

5 #1 or #2 or #3 or #4

6 [Infant Formula] explode all trees

7 [Milk Substitutes] explode all trees

8 [Milk] explode all trees

9 #6 or #7 or #8

10 (preterm or pre-term or prematur* or "low birth weight")

11 (IUGR or SGA or "small for gestational age" or "growth retard*" or "growth restrict*")

12 #10 or #11

13 (formula*)

14 #5 or #12

15 #9 or #13

16 #14 and #15

We also searched the WHO International Clinical Trials Registry Platform (<http://apps.who.int/trialsearch/>) in May 2012. Part of the Cochrane Neonatal Review Group's search includes the proceedings of the Perinatal Society of Australia and New Zealand and Pediatric Academic Societies (American Pediatric Society, Society for Pediatric Research and European Society for Pediatric Research) from 1990 to 2011.

Appendix 3. Risk of bias tool

We planned to use the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality of the trials. For each trial, we planned to seek information regarding the method of randomisation, blinding, and reporting of all outcomes of all the infants enrolled in the trial. We planned to assess each criterion as being at either low, high, or unclear risk of bias. Two review authors separately planned to assess each study and resolve any disagreements through discussion. We planned to add this information to the 'Characteristics of included studies' table. We planned to evaluate the following issues and enter the findings into the 'Risk of bias' table.

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we planned to categorise the method used to generate the allocation sequence as:

1. low risk (any truly random process e.g. random number table; computer random number generator);
2. high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
3. unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we planned to categorise the method used to conceal the allocation sequence as:

1. low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
2. high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
3. or unclear risk.

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we planned to categorise the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

1. low risk, high risk or unclear risk for participants; and
2. low risk, high risk or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we planned to categorise the methods used to blind outcome assessment. Blinding was to be assessed separately for different outcomes or class of outcomes. We planned to categorise the methods as:

1. low risk for outcome assessors;
2. high risk for outcome assessors; or
3. unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we planned to describe the completeness of data including attrition and exclusions from the analysis. We planned to note whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we planned to re-include missing data in the analyses. We planned to categorise the methods as:

1. low risk (< 20% missing data);
2. high risk ($\geq$ 20% missing data);
3. or unclear risk.

6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we planned to describe how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we planned to compare prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we planned to contact study authors to gain access to the study protocol. We planned to assess the methods as:

1. low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);

2. high risk (where not all the study's prespecified outcomes have been reported;
3. one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
4. or unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we planned to describe any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We planned to assess whether each study was free of other problems that could put it at risk of bias as:

1. low risk;
2. high risk;
3. unclear risk.

If needed, we planned to explore the impact of the level of bias through undertaking sensitivity analyses.

WHAT'S NEW

Date	Event	Description
21 July 2020	Amended	<p>1. The Gerber Foundation was added to Sources of support, and referenced in Declarations of interest.</p> <p>2. The text under the 'Certainty of evidence' heading has been moved to the 'Summary of findings and assessment of the certainty of the evidence' section.</p>

HISTORY

Protocol first published: Issue 3, 2008

Review first published: Issue 11, 2013

Date	Event	Description
10 April 2019	New citation required but conclusions have not changed	New search performed in October 2018. No new studies identified. Text of review updated accordingly.
24 February 2019	New search has been performed	New search performed in October 2018. No new studies identified.
17 February 2019	New search has been performed	This updates the review of Basuki 2013 .
15 November 2012	Amended	Title amended by inclusion of '...in exclusively formula-fed...' to make clear that studies in which infants received both formula milk and breast milk were excluded.
15 February 2009	Amended	The original protocol restricted the intervention to preterm formula only. To improve the usefulness of the review, we broadened the inclusion criteria to include regular strength formula. The title of the protocol was modified to 'Dilute versus full-strength formula in preterm or very low birth weight infants'. The text of the protocol was updated and we added type of formula as a subgroup.

CONTRIBUTIONS OF AUTHORS

Fauziah Basuki and Diah Hadiati wrote the first draft of the review. Tari Turner and Steve McDonald helped with risk of bias assessment, data extraction, analysis and GRADE assessment. All authors commented on the draft and approved the final version.

DECLARATIONS OF INTEREST

FB: none known

DH: none known

TT: none known

SM: none known

MH: none known

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SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

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- Vermont Oxford Network, USA

Cochrane Neonatal Reviews are produced with support from Vermont Oxford Network, a worldwide collaboration of health professionals dedicated to providing evidence-based care of the highest quality for newborn infants and their families.

- Wellcome Trust (SEA-ORCHID Project), UK

This review is an output of the SEA-ORCHID project (2004-09), a collaborative project that aimed to improve clinical practice during pregnancy and childbirth in centres across Thailand, Malaysia, Philippines and Indonesia. SEA-ORCHID was jointly funded by NHMRC in Australia and Wellcome Trust, UK.

- The Gerber Foundation, USA

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The secondary outcome measures were expanded to include mortality, sepsis and neurodevelopment to align with related Cochrane Reviews.

We added the methodology and plan for 'Summary of findings' tables and GRADE recommendations, which were not included in the original protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Energy Intake; *Enterocolitis, Necrotizing [epidemiology] [prevention & control]; *Infant Formula; *Infant Nutritional Physiological Phenomena; *Infant, Low Birth Weight; *Infant, Premature; Length of Stay; Weight Gain

MeSH check words

Humans; Infant; Infant, Newborn