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

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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.

Objectives

To assess the effects of dilute versus full strength formula on the incidence of necrotising enterocolitis, feeding intolerance, weight gain, length of stay 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 methods of the Cochrane Neonatal Review Group. This included searches of the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2013, Issue 1), MEDLINE (1946 to February 2013) and EMBASE (1974 to February 2013).

Selection criteria

Randomised or quasi-randomised trials comparing strengths of formula milk in exclusively formula-fed preterm or low birth weight infants. Studies were excluded 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 the Cochrane Neonatal Review Group, with independent assessment of risk of bias and data extraction. We synthesised mean differences using a fixed-effect meta-analysis model.

Main results

Three studies involving 102 preterm or low birth weight infants were included in the review. The studies compared dilute (double volume, half strength) formula with full strength (20 kcal/oz) formula. We assessed all three studies as being at 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. Two of the studies (88 infants) could be combined in the meta-analysis. Infants in the dilute formula with double volume (half strength) group had significantly fewer episodes of feeding intolerance. Infants in the dilute formula with double volume (half strength) group had fewer episodes of gastric residuals per day (one study, mean difference (MD) -1.20, 95% confidence interval (CI) -2.2 to -0.2), fewer episodes of gastric residuals per baby until attaining 100 kcal/kg (one study, MD -0.80, 95% CI -1.32 to -0.28), fewer episodes of vomiting per day (one study, MD -0.04, 95% CI -0.07 to -0.01) and fewer occurrences of abdominal distension greater than 2 cm (two studies, MD -0.16, 95% CI -0.19 to -0.13). For the secondary outcomes, infants in the dilute formula with double volume (half strength) group attained an adequate energy intake significantly earlier than infants in the full strength group (two studies, MD -2.26, 95% CI -2.85 to -1.67). For weight gain one week after commencement of intragastric feeds, the difference between groups was not statistically significant (one study, MD 0.05 kg, 95% CI -0.06 to 0.15). Data were not reported for length of hospital stay.

Authors' conclusions

There is evidence from three small, old trials at unclear risk of bias that use of dilute formula in preterm or low birth weight formula-fed infants leads to an important reduction in the time taken for these infants to attain an adequate energy intake. There was no evidence of important differences in feeding intolerance. The impact on serious gastrointestinal problems, including necrotising enterocolitis, was not reported. 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

Babies born prematurely (at less than 37 weeks gestation) or with a low birth weight (less than 2500 grams) have special feeding requirements. 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 the severe bowel disorder, necrotising enterocolitis. This review looked at whether dilute formula milk is more effective than full strength formula milk in the initial feeding of preterm babies. The evidence for this review is current up to February 2013. Three studies were included in the review, one small, low-quality trial in 50 preterm infants; a second small, moderate quality trial in 38 preterm infants and a third very small trial of unclear quality in 14 preterm infants. The trials found that infants receiving dilute formula achieved full energy intake earlier than infants receiving full strength formula (20 kcal/oz) and experienced fewer episodes of feeding intolerance. A lack of data on other important outcomes, such as the incidence of necrotising enterocolitis and weight gain, limits the usefulness of the studies and highlights areas that need to be addressed in future trials.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

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)	Quality of the 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 days	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 enterocolitis	**Study population**	Not estimable	0 (0)	See comment	Not reported
	See comment See comment				
	Medium risk population				
All-cause mortality prior to hospital discharge	**Study population**	Not estimable	0 (0)	See comment	Not reported
	See comment See comment				
	Medium risk population				
Incidence of invasive infection	**Study population**	Not estimable	0 (0)	See comment	Not reported
	See comment See comment				
	Medium risk population				

*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% confidence interval) 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 quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: 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 quality: We are very uncertain about the estimate.

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

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

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

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

BACKGROUND

Description of the condition

Preterm infants, especially those who have been growth 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 formula 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 2011a), slow advancement of enteral feed volumes (Morgan 2011b) and minimal enteral nutrition (Bombell 2009) 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 (Premji 2006). 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 thus 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 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

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

Exclusions:

- infants with major congenital malformations, especially abdominal wall defects (e.g. gastroschisis, omphalocoele) or serious gastrointestinal problems (e.g. necrotising enterocolitis)
- infants receiving any breast milk for the duration of the intervention period; and
- 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). 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:
   i) 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);
   ii) 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:
   i) 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);
   ii) neurodevelopmental scores in survivors aged greater than, or equal to, 12 months' of age measured using validated assessment tools;
   iii) cognitive and educational outcomes in survivors aged more than five years old.

Search methods for identification of studies

Electronic searches

We used the standard search strategy of the Cochrane Neonatal Review Group that included searches of the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2013, Issue 1, January 2013), MEDLINE (1946 to 10 February 2013) and EMBASE (1974 to 10 February 2013). No language restrictions were applied.

We used specific subject headings and additional text words describing the intervention and participants to identify relevant trials. The complete search strategy for Ovid MEDLINE is provided in Appendix 1. We adapted this strategy for EMBASE (Appendix 2) and CENTRAL (Appendix 3).

Searching other resources

The search also included checking the reference lists of other reviews and trials for citations to other studies. 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.

Data collection and analysis

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

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search. We resolved any disagreement through discussion. Specifically we:

1. merged search results using reference management software and removed duplicate records of the same report;
2. examined titles and abstracts to remove irrelevant reports;
3. retrieved the full text of the potentially relevant reports;
4. linked together multiple reports of the same study;
5. examined full-text reports for compliance of studies with eligibility criteria;
6. corresponded with investigators, when appropriate, to clarify study eligibility;
7. noted reasons for inclusion and exclusion of studies;
8. made final decisions on study inclusion and proceeded with data collection;
9. resolved discrepancies through a consensus process.

Data extraction and management

Two review authors independently extracted data from the full-text articles using a specifically designed spreadsheet to manage the information. We resolved discrepancies through discussion. We entered data into Review Manager 5.1 (RevMan 2011) and checked them for accuracy. When information regarding any of the above was missing or unclear, we tried to contact the authors of the original report to provide further details.

Assessment of risk of bias in included studies

All authors independently assessed study quality and risk of bias using the following criteria documented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

1. Sequence generation: was the allocation sequence adequately generated?
2. Allocation concealment: was allocation adequately concealed?
3. Blinding of participants, personnel and outcome assessors for each main outcome or class of outcomes: was knowledge of the allocated intervention adequately prevented during the study?
4. Incomplete outcome data for each main outcome or class of outcomes: were incomplete data adequately addressed?
5. Selective outcome reporting: was the report of the study free of suggestion of selective outcome reporting?
6. Other sources of bias: was the study apparently free of other problems that could put it at a high risk of bias?

For each criterion listed above we assessed the risk of bias as low, unclear or high. We gave particular attention to completeness of follow-up of all randomised infants and to the length of follow-up to identify whether any benefits claimed were robust. We requested additional information and clarification of published data from the authors of the included studies.

Measures of treatment effect

We analysed the results of the studies using Review Manager (RevMan 2011). 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 the number needed to treat (NNT) based on the risk difference.

Unit of analysis issues

If cluster-randomised trials had been identified and selected for inclusion, their sample sizes would have been adjusted 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. The use of ICCs from other sources would have been reported and sensitivity analyses conducted to investigate the effect of variation in the ICC. If both cluster-randomised trials and individually randomised trials were identified, we planned to synthesise the relevant information. The results from both would be combined if there was little heterogeneity and interaction between the effect of the intervention and the choice of randomisation unit was considered to be unlikely. Cross-over trials were not eligible.

Dealing with missing data

The authors of all published studies were to be contacted if such clarifications were required, or to provide additional information. In the case of missing data, the number of participants with missing data would have been described 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 suspected reporting bias we planned to contact the study authors to obtain missing data from them. Where this was not possible, and the missing data were thought to introduce serious bias, we planned to explore the impact of including such studies in the overall assessment of results by a sensitivity analysis. Reporting bias was not suspected.

Data synthesis

We ran statistical analyses according to the recommendations of the Cochrane Neonatal Review Group (http://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 subgroup analyses would have been conducted.

Sensitivity analysis

We planned to explore methodological heterogeneity through the use of sensitivity analysis. Studies 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.

RESULTS

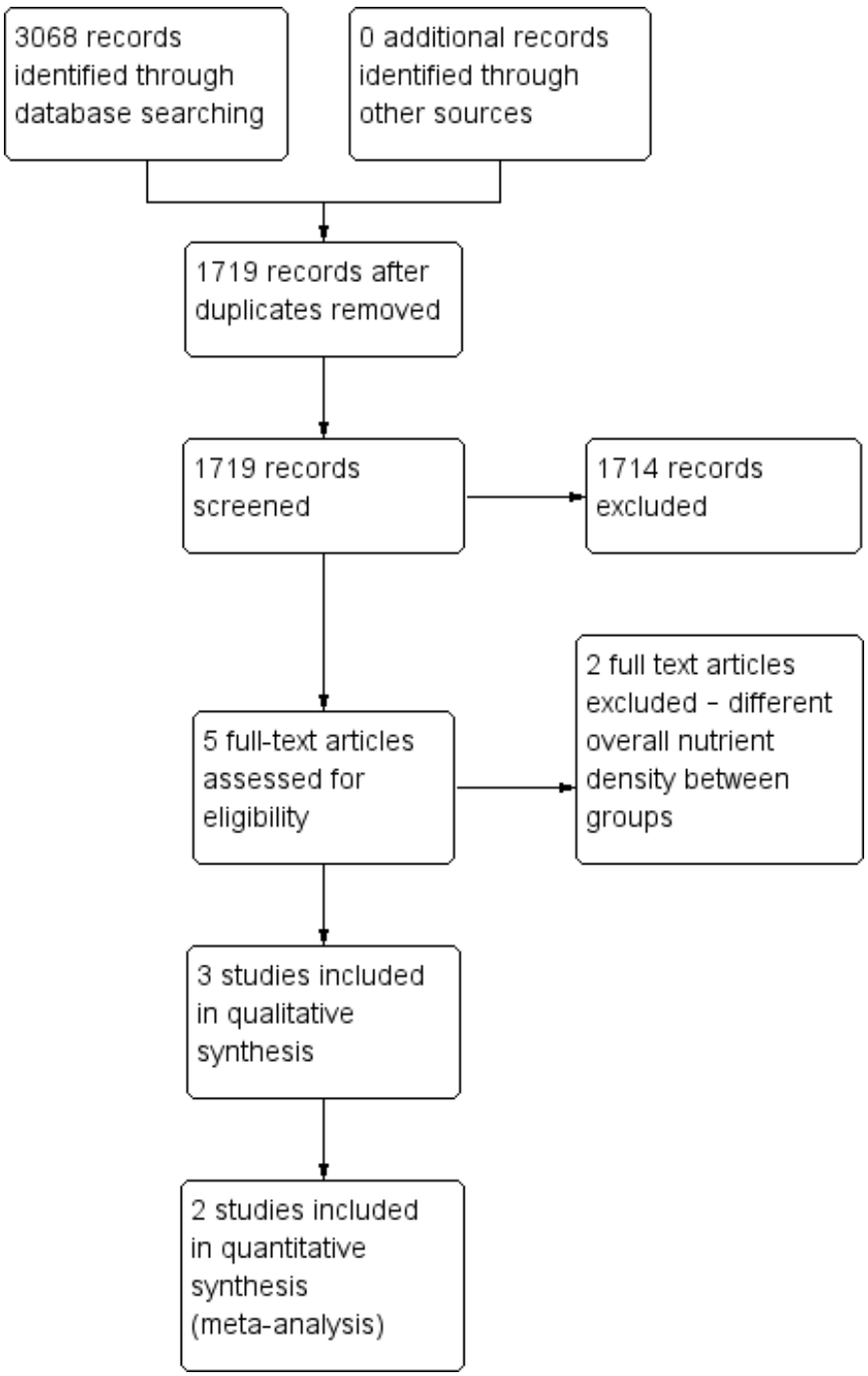
Description of studies

See: Characteristics of included studies and Characteristics of excluded studies.

Results of the search

The searches of MEDLINE, EMBASE and CENTRAL were conducted in February 2013 and retrieved 3068 records. Following deduplication, 1349 records were removed, leaving 1719 records to screen. From reading the titles and abstracts, we excluded 1714 and identified five studies as potentially eligible. Having retrieved these five studies two met the inclusion criteria (Anderson 1995; Currao 1988), one of which was only reported as a conference abstract (Anderson 1995). One further study was included after contacting the author to confirm the study was randomised (Sarna 1990). Two studies were excluded because the total enteral nutrient intake varied between the groups (Fewtrell 1997; Postolow 2000). See flow chart in Figure 1.

Figure 1. Study flow diagram.



Included studies

Population

Currao 1988 was conducted in the United States 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 United States 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) 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) diluted with water to twice the volume, and 18 infants were fed with full strength formula (20 kcal/oz) 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 (Currao 1988; Sarna 1990) was time to achieve full enteral feeding (measuring time required to reach enteral nutrient intake of 420 joules (100 kcal per kilogram). 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

There were two excluded studies in which the overall enteral nutrient density between groups was different (Fewtrell 1997; Postolow 2000).

Risk of bias in included studies

We assessed the studies as having an unclear risk of bias (Figure 2; Figure 3). 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 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

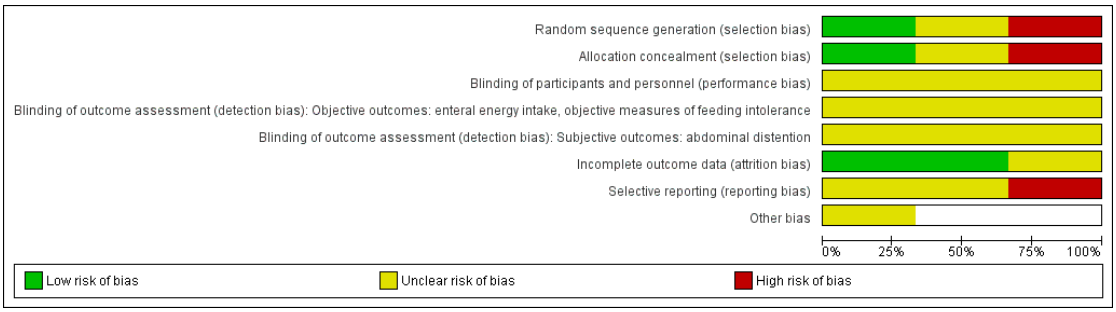
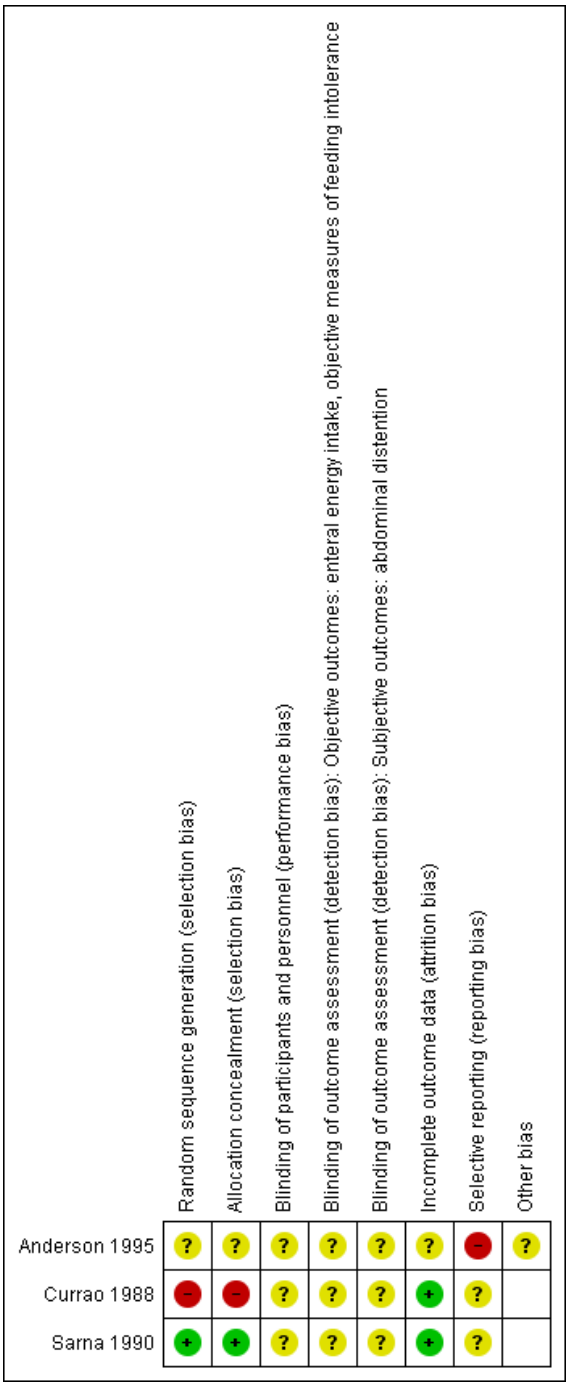


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Effects of interventions

See: **Summary of findings for the main comparison** 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 > 2 cm in the dilute formula with 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 and/or gastric residuals > 50% of previous feeding) 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 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 premature ($\leq$ 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. Overall, 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.

Potential biases in the review process

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

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 were insufficient data to determine whether, in exclusively formula-fed preterm or low birth weight infants, dilute or full strength formula 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.

ACKNOWLEDGEMENTS

Fauziah Basuki wrote the protocol as part of a SEA-ORCHID Project Fellowship at the Australasian Cochrane Centre. The review was completed at a review completion workshop, also at the Australasian Cochrane Centre. Thanks to Miranda Cumpston, Madeleine Hill and Jann Foster for their support and advice.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Anderson 1995

Methods	Randomised trial
Participants	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 grams) ; full strength group (n = 8; gestational age 29.5 ± 2 weeks; birth weight 1185 ± 286 grams). (Whether these statistics are means and standard deviations is not described in the abstract) 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
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 per kilogram per 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 ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: not described
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

Anderson 1995 (*Continued*)

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

Methods	Quasi-randomised trial
Participants	50 preterm infants with birth weight less than 1500 grams. Dilute formula with double volume (half strength) group (n = 28; mean gestational age 30.2 weeks (SD 1.2); mean birth weight 1189 grams (SD 23.1)); full strength group (n = 22; mean gestational age 30.3 weeks (SD 1.3); mean birth weight 1269 grams (SD 45.4)) 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
Interventions	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 Rate of feeding advancement varied with weight (< 1000 g, 1000 to 1250 g, 1250 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
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

Risk of bias		***Risk of bias***

Currao 1988 (*Continued*)

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

Methods	Randomised trial
Participants	38 preterm infants with birth weight less than 1750 grams. Dilute formula with double volume (half strength) group (n = 20; mean gestational age 32.05 weeks (SD 2.08); mean birth weight 1420 grams (SD 200)); full strength group (n = 18; mean gestational age 32.5 weeks (SD 1.54); mean birth weight 1410 grams (SD 200)) The ratio of male to female infants was not significantly different. All infants in the 2 groups were between 1000 grams and 1750 grams except 2 infants who weighed less than 1000 grams. 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
Interventions	Dilute formula with double volume (half strength) group received Lactogen infant formula (10 kcal/oz) but fed in twice the volume 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

Sarna 1990 (*Continued*)

	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, 1000 to 1250 g, 1250 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

Risk of bias ***Risk of bias***

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

SD: standard deviation

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

Study	Reason for exclusion
Fewtrell 1997	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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Episodes of abdominal distention > 2 cm	2	88	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.19, -0.13]
2 Episodes of gastric residuals	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Episodes of gastric residuals per baby per day	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Episodes of gastric residuals per baby until attaining 100 kcal/kg	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Episodes of vomiting per day	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Weight gain one week after starting feeds (kg)	1	38	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.06, 0.15]
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, Outcome 1 Episodes of abdominal distention > 2 cm.

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

Comparison: 1 Half strength formula versus full strength

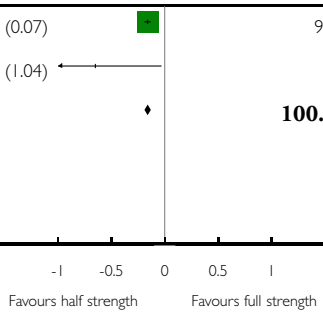
Outcome: 1 Episodes of abdominal distention > 2 cm

Study or subgroup	Half strength formula N	Mean(SD)	Full strength formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Currao 1988	22	0.25 (0.03)	28	0.41 (0.07)		99.8 %	-0.16 [-0.19, -0.13]
Sarna 1990	20	0.85 (0.88)	18	1.5 (1.04)		0.2 %	-0.65 [-1.27, -0.03]
Total (95% CI)	**42**		**46**			**100.0 %**	**-0.16 [-0.19, -0.13]**

Heterogeneity: Chi² = 2.42, df = 1 (P = 0.12); I² =59%

Test for overall effect: Z = 10.97 (P < 0.00001)

Test for subgroup differences: Not applicable



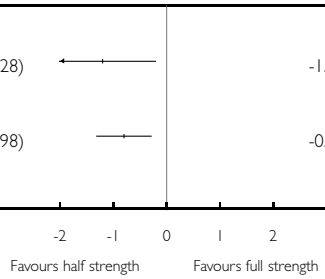
Analysis 1.2. Comparison 1 Half strength formula versus full strength, Outcome 2 Episodes of gastric residuals.

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

Comparison: 1 Half strength formula versus full strength

Outcome: 2 Episodes of gastric residuals

Study or subgroup	Half strength formula N	Mean(SD)	Full strength formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Episodes of gastric residuals per baby per day						
Currao 1988	22	0.41 (1.3)	28	1.61 (2.28)		-1.20 [-2.20, -0.20]
2 Episodes of gastric residuals per baby until attaining 100 kcal/kg						
Sarna 1990	20	0.6 (0.6)	18	1.4 (0.98)		-0.80 [-1.32, -0.28]



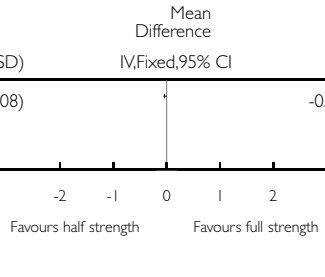
Analysis 1.3. Comparison 1 Half strength formula versus full strength, Outcome 3 Episodes of vomiting per day.

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

Comparison: 1 Half strength formula versus full strength

Outcome: 3 Episodes of vomiting per day

Study or subgroup	Half strength formula N	Mean(SD)	Full strength formula N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Currao 1988	22	0.32 (0.009)	28	0.36 (0.08)		-0.04 [-0.07, -0.01]

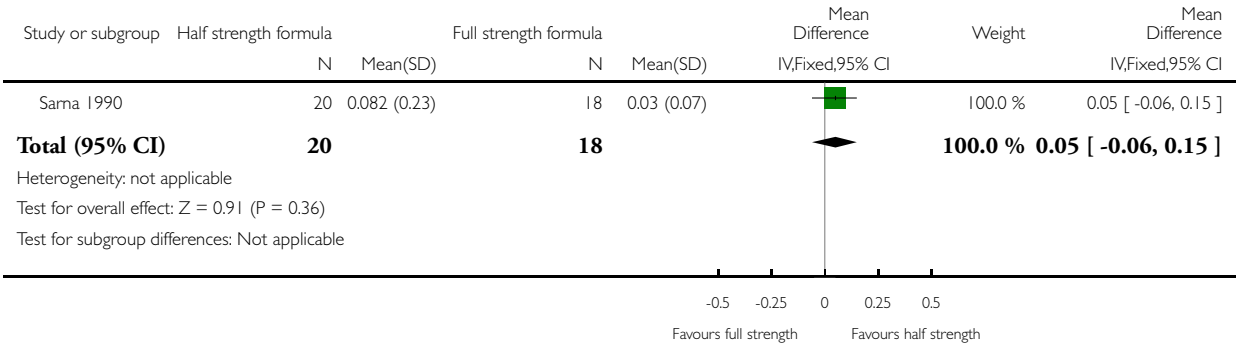


Analysis 1.4. Comparison 1 Half strength formula versus full strength, Outcome 4 Weight gain one week after starting feeds (kg).

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

Comparison: 1 Half strength formula versus full strength

Outcome: 4 Weight gain one week after starting feeds (kg)

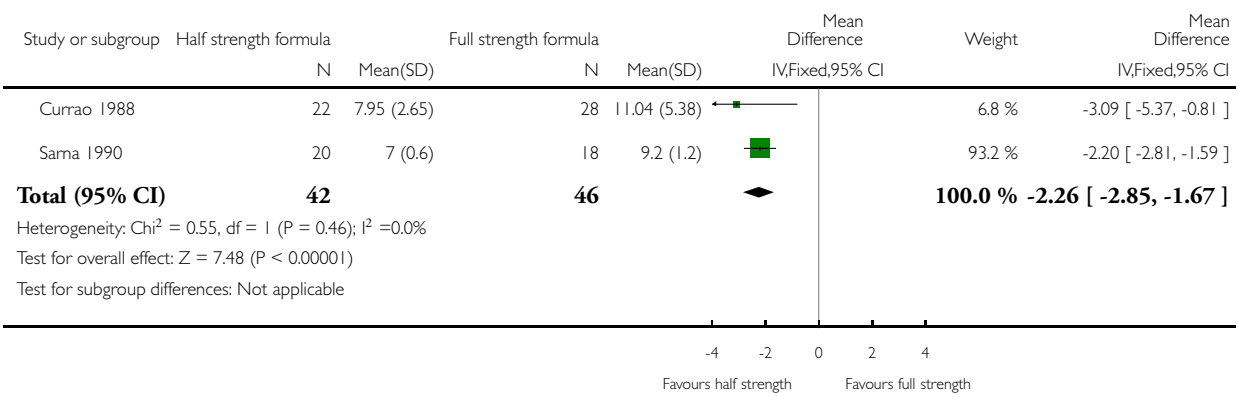


Analysis 1.5. Comparison 1 Half strength formula versus full strength, Outcome 5 Days until 420 joules per kilogram.

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

Comparison: 1 Half strength formula versus full strength

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 (1250 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						**Day 1**
2 mL 5% dextrose x 2	2 mL 5% dextrose x 2	3 mL 5% dextrose x 2	3 mL 5% dextrose x 2	5 mL 5% dextrose x 2	5 mL 5% dextrose x 2	
2 mL ¼S x 3	2 mL ¼S x 3	3 mL ¼S x 3	3 mL ¼S x 3	5 mL ¼S x 3	5 mL ¼S x 3	
2 mL ½S x 3	2 mL ½S x 7	3 mL ½S x 3	3 mL ½S x 7	5 mL ½S x 3	5 mL ½S x 7	
2 mL ¾S x 3	[n/a]	3 mL ¾S x 4	[n/a]	5 mL ¾S x 4	[n/a]	
Day 2						**Day 2**
2 mL FS x 12	3 mL ½S x 6	3 mL FS x 12	5 mL ½S x 12	5 mL FS x 12	7 mL ½S x 6	
	4 mL ½S x 6				10 mL ½S x 6	
Day 3						**Day 3**
3 mL FS x 12	5 mL ½S x 6	4 mL FS x 12	6 mL ½S x 6	7 mL FS x 12	12 mL ½S x 6	
	6 mL ½S x 6		8 mL ½S x 6		14 mL ½S x 6	
Day 4						**Day 4**
4 mL FS x 12	7 mL ½S x 6	6 mL FS x 12	10 mL ½S x 6	9 mL FS x 12	16 mL ½S x 6	
	8 mL ½S x 6		12 mL ½S x 6		18 mL ½S x 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.

Feeds were given
ule remained the
S = strength; FS
Multiplication fa

Table 2. Feeding schedule for Sarna 1990

Schedule	Birth weight (< 1000 g)		Birth weight (1000 to 1250 g)		Birth weight (1250 to 1500 g)		Birth weight (> 1500 g)	
	Diluted formula (dou-	**Full strength formula**	**Diluted formula (dou-**	**Full strength formula**	**Diluted formula (dou-**	**Full strength**	**Diluted for-**	**Full strength**

Table 2. Feeding schedule for Sarna 1990 (*Continued*)

	ble volume)		ble volume)		ble volume)	formula	mula (double volume)	formula
First 24 hours	CF 1cc x 4	CF 1cc x 4	CF 2cc x 4	CF 2cc x 4	CF 3cc x 4	CF 3cc x 4	CF 4cc x 4	CF 4cc x 4
	HSM 2cc x 4	FSM 1cc x 4	HSM 4cc x 4	FSM 2cc x 4	HSM 5cc x 4	FSM 3cc x 4	HSM 7-8cc x 4	FSM 4cc x 4
24 to 48 hours	3cc x 4	2cc x 4	6cc x 4	3cc x 4	8cc x 4	4cc x 4	12cc x 4	7cc x 4
	4cc x 4	2cc x 4	8cc x 4	4cc x 4	10cc x 4	6cc x 4	16cc x 4	8cc x 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.

Feeding continu
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caloric intake be
kg/day. Then th
the dilute formu
changed to full s
CF = clear fluid
HSM = half stren
ble volume)
FSM = full stren
Multiplication f
the number of fe

APPENDICES

Appendix 1. 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

Appendix 2. 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

Appendix 3. 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

HISTORY

Protocol first published: Issue 3, 2008

Review first published: Issue 11, 2013

Date	Event	Description
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 and analysis. All authors commented on the draft and approved the final version.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

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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.

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant, Low Birth Weight; *Infant, Premature; Energy Intake [*physiology]; Enterocolitis, Necrotizing [epidemiology]; Gastrointestinal Diseases [epidemiology]; Infant Formula [administration & dosage; *chemistry]; Infant, Premature, Diseases [epidemiology]; Length of Stay; Randomized Controlled Trials as Topic; Time Factors; Weight Gain [*physiology]

MeSH check words

Humans; Infant, Newborn