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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	4
OBJECTIVES	5
METHODS	5
RESULTS	7
Figure 1.	8
Figure 2.	10
Figure 3.	12
Figure 4.	13
Figure 5.	13
DISCUSSION	14
AUTHORS' CONCLUSIONS	15
ACKNOWLEDGEMENTS	15
REFERENCES	16
CHARACTERISTICS OF STUDIES	19
DATA AND ANALYSES	32
Analysis 1.1. Comparison 1: Hydrolysed versus non-hydrolysed formula, Outcome 1: Feed intolerance	33
Analysis 1.2. Comparison 1: Hydrolysed versus non-hydrolysed formula, Outcome 2: Necrotising enterocolitis	34
Analysis 1.3. Comparison 1: Hydrolysed versus non-hydrolysed formula, Outcome 3: Time to full enteral feeding	34
Analysis 1.4. Comparison 1: Hydrolysed versus non-hydrolysed formula, Outcome 4: Weight gain (g/kg/day)	34
Analysis 1.5. Comparison 1: Hydrolysed versus non-hydrolysed formula, Outcome 5: Length gain (mm/week)	35
Analysis 1.6. Comparison 1: Hydrolysed versus non-hydrolysed formula, Outcome 6: Head circumference growth (mm/week) ..	35
Analysis 1.7. Comparison 1: Hydrolysed versus non-hydrolysed formula, Outcome 7: Serum alkaline phosphatase (IU/L)	35
Analysis 1.8. Comparison 1: Hydrolysed versus non-hydrolysed formula, Outcome 8: Late-onset invasive infection	35
Analysis 1.9. Comparison 1: Hydrolysed versus non-hydrolysed formula, Outcome 9: Any allergic disease	36
APPENDICES	36
WHAT'S NEW	41
HISTORY	42
CONTRIBUTIONS OF AUTHORS	42
DECLARATIONS OF INTEREST	42
SOURCES OF SUPPORT	42
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	43
INDEX TERMS	43

[Intervention Review]

Protein hydrolysate versus standard formula for preterm infants

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ABSTRACT

Background

When human milk is not available for feeding preterm infants, protein hydrolysate, rather than standard cow's milk formulas (with intact proteins), is often used because it is perceived as being tolerated better and less likely to lead to complications. However, protein hydrolysate formulas are more expensive than standard formulas, and concern exists that their use in practice is not supported by high-quality evidence.

Objectives

To assess the effects of feeding preterm infants hydrolysed formula (vs standard cow's milk formula) on risk of feed intolerance, necrotising enterocolitis, and other morbidity and mortality.

Search methods

We used the standard Cochrane Neonatal search strategy including electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 1), in the Cochrane Library; Ovid MEDLINE (1966 to 28 January 2019); Ovid Embase (1980 to 28 January 2019); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (28 January 2019), as well as conference proceedings and previous reviews.

Selection criteria

Randomised and quasi-randomised controlled trials that compared feeding preterm infants protein hydrolysate versus standard (non-hydrolysed) cow's milk formula.

Data collection and analysis

Two review authors assessed trial eligibility and risk of bias and extracted data independently. We analysed treatment effects as described in the individual trials and reported risk ratios and risk differences for dichotomous data, and mean differences for continuous data, with respective 95% confidence intervals (CIs). We used a fixed-effect model in meta-analyses and explored potential causes of heterogeneity in sensitivity analyses. We assessed quality of evidence at the outcome level using the GRADE approach.

Main results

We identified 11 trials for inclusion in the review. All trials were small (total participants 665) and had various methodological limitations including uncertainty about methods to ensure allocation concealment and blinding. Most participants were clinically stable preterm infants of less than about 34 weeks' gestational age or with birth weight less than about 1750 g. Fewer participants were extremely preterm, extremely low birth weight, or growth restricted. Most trials found no effects on feed intolerance, assessed variously as mean pre-feed gastric residual volume, incidence of abdominal distension or other gastrointestinal signs of concern, or time taken to achieve full enteral

Protein hydrolysate versus standard formula for preterm infants (Review)

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feeds (meta-analysis was limited because studies used different measures). Meta-analysis showed no effect on the risk of necrotising enterocolitis (typical risk ratio 1.10, 95% CI 0.36 to 3.34; risk difference 0.00, 95% CI -0.03 to 0.04; 5 trials, 385 infants) (low-certainty evidence; downgraded for imprecision and design weaknesses).

Authors' conclusions

The identified trials provide only low-certainty evidence about the effects of feeding preterm infants protein hydrolysate versus standard formula. Existing data do not support conclusions that feeding protein hydrolysate affects the risk of feed intolerance or necrotising enterocolitis. Additional large, pragmatic trials are needed to provide more reliable and precise estimates of effectiveness and cost-effectiveness.

PLAIN LANGUAGE SUMMARY

Protein hydrolysate versus standard formula for preterm infants

Review question

Does feeding preterm infants cow's milk formula containing predigested (hydrolysed) proteins, rather than whole proteins, improve digestion and reduce the risk of severe bowel problems?

Background

Preterm infants often find cow's milk formula more difficult to digest than human milk, and cow's milk formula may increase the risk of severe bowel problems for preterm (born before their due date) infants. If preterm infants are fed cow's milk formula (when human milk is unavailable), then using a formula in which the protein is already partially digested (called 'hydrolysed') rather than a standard formula (with intact proteins) might reduce the risk of these problems. However, hydrolysed formulas are more expensive than standard formulas, and may have specific side effects not seen with standard formulas. Given these concerns, we have reviewed all available evidence from clinical trials that compared these types of formula for feeding preterm infants.

Study characteristics

In searches of medical databases up to 28 January 2019, we found 11 relevant trials; most were small (involving 665 infants in total) and had methodological weaknesses.

Key results

Currently available evidence suggests that feeding preterm infants hydrolysed formula (rather than standard formula) during their initial hospital admission has no important benefits or harms. However, this finding is not yet conclusive, and larger trials of better quality are needed to provide evidence to help clinicians and families make informed choices about this issue.

Quality of evidence

Data from these trials provide no strong or consistent evidence that feeding preterm infants hydrolysed formula rather than standard formula improved or worsened digestion or changed the risk of severe bowel problems.

SUMMARY OF FINDINGS

Summary of findings 1. Hydrolysed compared to non-hydrolysed formula for feeding preterm infants

Hydrolysed compared to non-hydrolysed formula for feeding preterm infants

Patient or population: feeding preterm infants

Setting: neonatal unit

Intervention: hydrolysed formula (protein hydrolysate)

Comparison: non-hydrolysed formula

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with non-hydrolysed formula	Risk with hydrolysed formula				
Feed intolerance	Study population		RR 2.71 (0.29 to 25.00)	161 (3 RCTs)	⊕⊕⊕⊕ Low	Limited data from 3 small RCTs with imprecise estimate of effect size
	13 per 1000	34 per 1000 (4 to 316)				
Necrotising enterocolitis	Study population		RR 1.10 (0.36 to 3.34)	385 (5 RCTs)	⊕⊕⊕⊕ Low	Methodological limitations of included trials and imprecise effect size estimate
	32 per 1000	35 per 1000 (12 to 107)				

*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; RCT: randomised controlled trial; RR: risk ratio.

BACKGROUND

Hydrolysed cow's milk formulas, originally developed for infants with cow's milk protein allergy or intolerance, are used as enteral feeding alternatives for preterm infants for whom human milk is unavailable. These formulas contain hydrolysed, rather than intact, proteins and may also differ from standard cow's milk formulas in carbohydrate, lipid, and micronutrient type and content (Oldaeus 1997). Their use as a sole, or supplemental, enteral feed source for preterm infants has increased since the late 1990s, particularly in high-income countries, because they are perceived as being tolerated better and less likely to lead to complications than standard cow's milk formulas (Zuppa 2005). However, hydrolysed formulas are more expensive than standard formulas, and concern exists that their use in practice is not supported by high-certainty evidence (Foucard 2005).

Description of the condition

Human breast milk is recommended as the best form of enteral nutrition for preterm infants (AAP 2012). Breast milk proteins, carbohydrates, fats, and micronutrients have been optimised by evolution for neonatal digestion and absorption. Breast milk contains many non-nutrient factors including immunoglobulins and lactoferrin that promote intestinal adaptation and maturation, improve enteral feed tolerance, and protect against infection and inflammatory disorders (Agostoni 2010; Arslanoglu 2013).

When sufficient human breast milk is unavailable, cow's milk-based formulas are used in feeding preterm infants, either as the sole enteral diet or as a supplement to human breast milk (Klingenberg 2012). Feeding preterm infants standard cow's milk formulas, rather than human breast milk, is, however, associated with higher rates of feed intolerance and necrotising enterocolitis (Quigley 2014). Feed intolerance and interruption of enteral feeds are major contributors to cumulative nutrient deficits and postnatal growth restriction in very preterm infants (Cooke 2016; Embleton 2001). Slow postnatal growth is associated with neurodevelopmental impairment in later childhood and with poorer cognitive and educational outcomes (Brandt 2003; Embleton 2013a; Leppanen 2014). Necrotising enterocolitis affects about 5% of very preterm infants. Infants who develop necrotising enterocolitis experience more infections, have lower levels of nutrient intake, grow more slowly, have longer durations of intensive care and hospital stay, and are more likely to die or be disabled than gestation-comparable infants who do not develop necrotising enterocolitis (Morgan 2011; Pike 2012; Yee 2012).

Description of the intervention

Standard cow's milk formulas can be grouped broadly as 'term' formulas (designed for term infants; nutrient content based on the composition of mature breast milk) and nutrient-enriched 'preterm' formulas (designed for preterm or low birth weight infants; energy enriched and variably protein and mineral enriched) (Fewtrell 1999). Concern exists that standard cow's milk formulas (both 'term' and 'preterm') are poorly tolerated, especially by very preterm infants, because the immature infant's gastrointestinal tract is less efficient than that of term infants in digesting intact cow's milk proteins and fats (Ewer 1994; Lindberg 1998).

Hydrolysed formulas

'Hydrolysed' protein formulas containing protein digested chemically (acid/alkali) or enzymatically (protease) to oligopeptides are often used in feeding preterm infants, especially infants with feed intolerance or clinical features (such as episodic apnoea, oxygen desaturation, or bradycardia) that are attributed to gastro-oesophageal reflux, or following gastrointestinal surgery or necrotising enterocolitis (Zuppa 2005).

Several brands of hydrolysed formulas (both 'term' and 'preterm') are available commercially, and these are grouped broadly depending on degree of hydrolysis.

- Extensively hydrolysed: residual free amino acids and peptides with molecular weights less than 1.5 kDa to 3.0 kDa.
- Partially hydrolysed: residual peptides with molecular weights of 3.0 kDa to 10.0 kDa.

This distinction is mainly relevant to the putative hypo-allergenic properties of hydrolysed formulas, and limited data show its functional relevance to preterm infants. Formulas also vary by the predominant protein source (casein vs whey-casein), as well as by carbohydrate (lactose, maltodextrin) and fat (cow, vegetable) type and content (BNFC 2016).

How the intervention might work

Although hydrolysed formulas have been developed as hypo-allergenic alternatives to standard cow's milk formulas for infants at risk of cow's milk protein intolerance or allergy, evidence for this effect in term infants is very weak (Boyle 2016; Osborn 2017). In preterm infants, hydrolysed formulas are used mostly for their perceived benefits in reducing the risk of feed intolerance and necrotising enterocolitis. When human milk is unavailable, hydrolysed formulas may be used empirically (starter formula) and therapeutically to improve feeding tolerance or reduce gastro-oesophageal reflux. Possible mechanisms for these effects include accelerated gastric emptying and intestinal transit, more efficient enteric peptide digestion, and stimulation of small intestinal enzymatic and motilin activity (Mihatsch 2001b; Zuppa 2005). If better feed tolerance reduces the time taken to establish full enteral feeding in very preterm infants, this may reduce the adverse infectious or metabolic consequences of prolonged exposure to parenteral nutrition.

Several potential adverse effects of hydrolysed formulas are recognised. Osmolality is increased when protein is hydrolysed into smaller peptides, and these higher-osmolality fluids delivered to the small intestine may increase the risk of necrotising enterocolitis. Furthermore, if bioactive proteins such as immunoglobulin or lactoferrin are hydrolysed, this may reduce their putative benefits in reducing the risk of infection or necrotising enterocolitis. It is possible that some peptides created by artificial hydrolysis may have diminished or harmful functional activities (Embleton 2013b). Concern about micronutrient bioavailability in hydrolysed formulas exists, particularly regarding whether bone minerals are well absorbed in the absence of intact casein proteins (Zuppa 2005). Another theoretical long-term risk is that the high levels of "advanced glycation end-products" in most hydrolysed formulas might be associated with development of chronic inflammatory, metabolic, or neurodegenerative diseases (Uribarri 2015).

Why it is important to do this review

Given the potential for protein hydrolysate formulas (rather than standard cow's milk formulas) to improve enteral feed tolerance and prevent adverse outcomes in preterm infants, we undertook a systematic review of the randomised trial data to help to inform practice and research.

OBJECTIVES

To assess the effects of feeding preterm infants hydrolysed formula (vs standard cow's milk formula) on risk of feed intolerance, necrotising enterocolitis, and other morbidity and mortality.

METHODS

Criteria for considering studies for this review

Types of studies

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

Types of participants

Preterm (less than 37 weeks' gestation) newborn infants who received cow's milk formula as their sole or supplemental enteral diet.

Types of interventions

Hydrolysed cow's milk formula versus standard (non-hydrolysed) cow's milk formula or another type of hydrolysed cow's milk formula. Formula was to be allocated as at least 20% of the intended enteral diet for at least two weeks to discern measurable effects on growth rates and episodes of feed intolerance. Trials should have compared formulas with similar energy and protein levels (i.e. hydrolysed 'preterm' formula vs non-hydrolysed 'preterm' formula, or hydrolysed 'term' formula vs non-hydrolysed 'term' formula).

We planned separate comparisons of trials that assessed:

- *empirical* use of hydrolysed formulas; and
- *indicated* (therapeutic) use of hydrolysed formulas to treat infants with feed intolerance or gastro-oesophageal reflux (and associated apnoea, desaturation, or bradycardia), or following gastrointestinal surgery or necrotising enterocolitis (as defined by the primary investigators).

Types of outcome measures

Primary outcomes

- Infants with at least one episode of feed intolerance that resulted in cessation of, or reduction in, enteral feeding (enteral feeds were reduced or ceased for longer than four hours), or mean number of episodes of feed intolerance during the trial period, or both
- Infants with at least one episode of necrotising enterocolitis (modified Bell stage 2/3) (Walsh 1986) (unless indicated for use following necrotising enterocolitis)

Secondary outcomes

- Time to full enteral feeding independent of parenteral fluids (days)

- Growth: time to regain birth weight, and subsequent rates of weight (grams/kilogram/d), length (millimetre/week), and head growth (millimetre/week) during hospital admission
- Duration of hospital admission (days)
- Measures of bone mineralisation
  - * Serum alkaline phosphatase level at 36 to 40 weeks' postmenstrual age or
  - * Bone mineral content assessed post term by dual energy X-ray absorptiometry (DEXA) or
  - * Clinical or radiological evidence of rickets on long-term follow-up
- Late-onset invasive infection diagnosed more than 72 hours after birth, as determined by culture from a normally sterile site: cerebrospinal fluid, blood, bone or joint, peritoneum, pleural space, or central venous line tip; or findings on autopsy examination consistent with invasive microbial infection
- Mortality: all-cause until 28 days and during hospital admission
- Neurodevelopmental outcomes assessed by a validated test after 12 months post term: neurological evaluations, developmental scores, and classifications of disability, including auditory and visual disability
- Allergy or atopy diagnosed after 12 months post term: asthma, eczema, allergic rhinitis or conjunctivitis, food allergy, allergic sensitisation (skin prick, or specific or total immunoglobulin E level) (Boyle 2016)

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 the specialised register).

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 1), in the Cochrane Library; Ovid MEDLINE (1946 to 28 January 2019); Ovid Embase (1974 to 28 January 2019); Ovid Maternity & Infant Care Database (1971 to January 2019); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to 28 January 2019) using a combination of the following text words and medical subject heading (MeSH) terms as described in [Appendix 1](#). We limited search outputs by using relevant search filters for clinical trials, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We did not apply language restrictions.

We searched ClinicalTrials.gov and the World Health Organization's International Trials Registry and Platform (www.who.int/ictrp/en/) for completed and ongoing trials.

Searching other resources

We examined reference lists in previous reviews and included studies. We searched the proceedings of the annual meetings of the Pediatric Academic Societies (1993 to 29 January 2019), the European Society for Paediatric Research (1995 to 28 January 2019), the Royal College of Paediatrics and Child Health (2000 to 28 January 2019), and the Perinatal Society of Australia and New Zealand (2000 to 28 January 2019). Trials reported only as abstracts were eligible if sufficient information was available from the report, or from contact with study authors, to fulfil the inclusion criteria.

Data collection and analysis

We used the standard methods of Cochrane Neonatal.

Selection of studies

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

Data extraction and management

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

Assessment of risk of bias in included studies

Two review authors (DN and JK) 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 2011).

- Sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Any other bias.

Any disagreements were resolved by discussion or by consultation with a third assessor (WM). See [Appendix 2](#) for a more detailed description of risk of bias for each domain. We requested additional information from the trial authors to clarify methods and results when necessary. We did not exclude trials on the basis of risk of bias, but we did plan to conduct sensitivity analyses if applicable to explore the consequences of synthesising evidence of variable quality (Higgins 2011).

Measures of treatment effect

We analysed treatment effects in individual trials using Review Manager 5 (RevMan 2014), and we reported risk ratio (RR) and risk difference (RD) for dichotomous data, and mean difference (MD) for continuous data, with respective 95% confidence intervals (CIs). We determined the number needed to treat for an additional beneficial outcome (NNTB) or an additional harmful outcome (NNTH) for analyses with a statistically significant difference in the RD.

Unit of analysis issues

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

Dealing with missing data

Where data were missing and could not be derived as described, we approached the analysis of missing data as follows.

- We contacted the original study investigators to request the missing data.
- Where possible, we imputed missing standard deviations (SDs) using the coefficient of variation (CV) or calculated from other available statistics including standard errors, CIs, t values, and P values.
- If data were assumed to be missing at random, we analysed the data without imputing any missing values.
- If this could not be assumed, then we planned to impute the missing outcomes with replacement values, assuming all to have a poor outcome. We planned sensitivity analyses to assess any changes in the direction or magnitude of effect resulting from data imputation.

Assessment of heterogeneity

Two review authors assessed clinical heterogeneity, with a meta-analysis conducted only when both authors agreed that study participants, interventions, and outcomes were sufficiently similar.

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

Assessment of reporting biases

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

Data synthesis

We used the fixed-effect model in Review Manager 5 for meta-analyses (as per Cochrane Neonatal recommendations) (RevMan 2014). Where moderate or high heterogeneity existed, we planned to examine the potential causes in subgroup and sensitivity analyses.

Quality of evidence

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, as outlined in the *GRADE Handbook* (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes: feed tolerance and incidence of necrotising enterocolitis.

Two review authors (DN and JK) independently assessed the quality of evidence for each of the outcomes above. We considered evidence from randomised controlled trials (RCTs) as high quality 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 evidence, precision of estimates, and presence of publication bias. We used the *GRADEpro Guideline Development Tool* to create [Summary of findings table 1](#) to report the quality of evidence (GRADEpro GDT).

The GRADE approach yields an assessment of the quality of a body of evidence using one of four grades.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- 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.
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses by:

- gestational age at birth: very preterm (less than 32 weeks' gestation) infants versus infants born at 32 weeks' gestation or later;

- indication (for therapeutic use): post surgery versus post necrotising enterocolitis versus feeding intolerance or gastro-oesophageal reflux; and
- extent of protein hydrolysis (as defined by manufacturers): extensively versus partially hydrolysed formula.

Sensitivity analysis

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

RESULTS

Description of studies

Results of the search

See [Figure 1](#).

Figure 1. Study flow diagram (updated January 2019).

We screened the title and abstract (if available) of 946 unique records identified by the searches.

We identified two ongoing trials ([ACTRN12613000481774](#); Yin 2015).

We excluded 920 articles outright and screened the full text of 24 study reports.

We included 11 trials - [Characteristics of included studies](#) - and excluded eight full-text reports - [Characteristics of excluded studies](#).

Five reports await classification. One is awaiting further data ([del Moral 2017](#)), and four reports await full text and English language translation to allow assessment of eligibility for inclusion ([Dobryansky 2015](#); [Gu 2017](#); [Kwinta 2002](#); [Luo 2016](#)).

Included studies

We included 11 trials ([Baldassarre 2017](#); [Florendo 2009](#); [Huston 1992](#); [Maggio 2005](#); [Mihatsch 2002](#); [Pauls 1996](#); [Picaud 2001](#); [Raupp 1995](#); [Riezzo 2001](#); [Schweizer 1993](#); [Szajewska 2004](#)). Most of the included trials were undertaken during the 1990s and 2000s by investigators in neonatal units in Europe (mainly Germany and Italy) and North America. For further details, see the [Characteristics of included studies](#) table.

Participants

In total, 665 infants participated in the included trials. Most participants were clinically stable preterm infants of gestational age less than about 34 weeks' gestation or birth weight less than about 1750 g. Few participants were extremely preterm, extremely low birth weight, or growth restricted. Most of the trials specifically excluded infants with congenital anomalies or gastrointestinal or neurological problems.

Interventions

All trials assessed the *empirical* use of protein hydrolysate formulas; none assessed *indicated* use.

Trials varied according to the brand of formula studied. All trials except one assessed a "preterm" (nutrient-enriched) hydrolysed formula; [Schweizer 1993](#) assessed a "term" hydrolysed formula.

Most trials used a whey-casein-based hydrolysate. Two trials used a predominantly casein-based hydrolysate ([Huston 1992](#); [Riezzo 2001](#)). Most studies assessed a partially hydrolysed formula. Three trials used an extensively hydrolysed formula ([Baldassarre 2017](#); [Mihatsch 2002](#); [Schweizer 1993](#)). One (three-arm) trial randomly allocated infants to receive a partially hydrolysed formula, an extensively hydrolysed formula, or a standard preterm formula ([Szajewska 2004](#)). Control diets were preterm non-hydrolysed formulas in all except [Riezzo 2001](#), where the control diet was a standard term formula.

No trials compared hydrolysed cow's milk formula versus another type of hydrolysed cow's milk formula.

Trial participants received the intervention or control formulas on commencing enteral feeds either as a sole diet or as a supplement when mother's own milk was not available or was insufficient. One trial specifically excluded participants post hoc if mother's own milk formed more than 10% of enteral intake ([Mihatsch 2002](#)). In general, trial feeds were allocated for several weeks (at least two weeks), or until participating infants reached a specified weight (typically about 1.8 kg).

Outcomes

Outcomes reported most commonly were feed intolerance (reported in various ways but often without accompanying numerical data), growth parameters during the study period or until hospital discharge, and adverse events (including mortality and necrotising enterocolitis). None of the trials reported long-term growth and neurodevelopmental outcomes.

Excluded studies

We excluded eight studies ([Agosti 2003](#); [Corvaglia 2013](#); [Logarajaha 2015](#); [Mihatsch 1999](#); [Mihatsch 2001a](#); [Rigo 1994](#); [Rigo 1995](#); [Yu 2014](#)). Reasons for exclusion are described in the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

Quality assessments are detailed in the [Characteristics of included studies](#) table and are summarised in [Figure 2](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias 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): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Baldassarre 2017	+	+	+	+	+	?	?
Florendo 2009	+	+	+	+	+	?	?
Huston 1992	?	?	-	-	+	?	?
Maggio 2005	?	+	+	+	+	?	?
Mihatsch 2002	+	?	?	?	-	?	?
Pauls 1996	?	?	-	-	+	?	?
Picaud 2001	?	?	?	?	+	?	?
Raupp 1995	?	?	-	-	+	?	?
Riezzo 2001	?	?	-	-	+	?	?
Schweizer 1993	?	?	+	+	+	?	?
Szajewska 2004	?	+	?	?	+	?	?

Allocation

Three trials reported adequate allocation concealment methods (sealed, numbered envelopes; central randomisation in blocks) and were at low risk of bias (Florendo 2009; Maggio 2005; Szajewska 2004). None of the remaining trials reported sufficient details for assessment of whether or how allocation concealment was achieved.

Blinding

Four trials reported blinding of investigators and carers or parents (Baldassarre 2017; Florendo 2009; Maggio 2005; Schweizer 1993). It is probable that the other trials were not blinded as the reports did not describe any methods that might achieve this.

Incomplete outcome data

Most trials were likely to be at low risk of bias because of incomplete assessment of the trial cohort. In one trial, investigators recruited 129 infants initially, then excluded 42 participants post hoc because they had received more than 10% of their enteral intake as human milk (Mihatsch 2002).

Selective reporting

We were unable to assess reliably whether selective reporting occurred as we did not have protocols or other indicators of prespecified outcomes for any of the trials.

Other potential sources of bias

We did not identify any other potential sources of bias in the reports.

Effects of interventions

See: [Summary of findings 1](#) Hydrolysed compared to non-hydrolysed formula for feeding preterm infants

Empirical use of protein hydrolysate versus standard formula (Comparison 1)

1. Feed intolerance (Outcome 1.1)

Three trials reported numerical data on the incidence of feed intolerance (Baldassarre 2017; Florendo 2009; Maggio 2005). Meta-analysis found no statistically significant effect (typical risk ratio (RR) 2.71, 95% confidence interval (CI) 0.29 to 25.00; typical risk difference (RD) 0.02, 95% CI -0.03 to 0.08) (I^2 not applicable) (Analysis 1.1).

The other trials did not report any numerical data but described their findings in a narrative format. These trials found no differences in measures of gastric residual volumes (Mihatsch 2002; Pauls 1996), frequency of regurgitation (Riezzo 2001), or vomiting or diarrhoea (Szajewska 2004). Raupp 1995 reported that "both formulas were well tolerated". The remaining trials did not report any measures of feed intolerance (Huston 1992; Picaud 2001; Schweizer 1993).

2. Incidence of necrotising enterocolitis (Outcome 1.2)

Meta-analysis of data from five trials (385 infants) revealed no differences (typical RR 1.10, 95% CI 0.36 to 3.34; typical RD 0.00, 95% CI -0.03 to 0.04; $I^2 = 0\%$) (Analysis 1.2; Figure 3).

Figure 3. Forest plot of comparison: 1 Hydrolysed versus non-hydrolysed formula, outcome: 1.2 Necrotising enterocolitis.

The other trials did not report this outcome, although in most, it seems likely that none of the participants developed necrotising enterocolitis.

The quality of evidence for the primary outcomes was low because of methodological limitations of the included trials (including uncertainty about allocation concealment and blinding) and imprecision of effect size estimates (Summary of findings 1).

3. Time to full enteral feeding (Outcome 1.3)

Most trials did not report time to full enteral feeds (Florendo 2009; Huston 1992; Maggio 2005; Raupp 1995; Riezzo 2001; Szajewska 2004).

Mihatsch 2002 reported that the median time to full enteral feeding was shorter in the intervention group (10 days vs 12 days in the control group).

Four trials reported no difference.

- Schweizer 1993: 24 days versus 25 days (standard deviation (SD) not reported).
- Pauls 1996; no data reported.
- Picaud 2001: 16 (SD 8) days versus 17 (SD 8) days (mean difference (MD) -1.00 days, 95% CI -8.36 to 6.36).

- Baldassarre 2017: 11 days versus 10 days (SD not reported).

4. Growth: time to regain birth weight, and subsequent rates of growth during hospital admission (Outcomes 1.4 to 1.6)

Four trials did not report any growth data (Baldassarre 2017; Pauls 1996; Riezzo 2001; Szajewska 2004). The other trials reported some data on growth parameters during the study period or until hospital discharge, but most did not provide sufficient data for inclusion in the meta-analysis (Huston 1992; Mihatsch 2002; Raupp 1995; Schweizer 1993).

Time to regain birth weight

One trial reported days to regain birth weight (Schweizer 1993). This trial found no difference (10 days in the intervention group vs 9 days in the control group; SD not reported).

Weight gain

Three trials reported rates of weight gain over the study period or until hospital discharge (Florendo 2009; Maggio 2005; Picaud 2001). Meta-analysis showed that weight gain was slower among infants fed hydrolysed formula (MD -3.02 g/kg/d, 95% CI -4.66 to -1.38) (Analysis 1.4; Figure 4).

Figure 4. Forest plot of comparison: 1 Hydrolysed versus non-hydrolysed formula, outcome: 1.4 Weight gain (g/kg/d). **Length change**

Meta-analysis of data from two trials (97 infants) showed no difference in length change (MD -0.04 mm/week, 95% CI -1.24 to 1.15) ([Analysis 1.5](#)).

Head circumference growth

Meta-analysis of data from two trials (97 infants) revealed no difference in head circumference growth (MD 0.27 mm/week, 95% CI -0.39 to 0.94) ([Analysis 1.6](#)).

5. Duration of hospital admission

No trials reported the duration of hospital admission.

6. Measures of bone mineralisation (Outcome 1.7)

Two trials reported measures of bone mineralisation ([Florendo 2009](#); [Raupp 1995](#)). Neither trial nor a meta-analysis of data from both trials showed a difference in serum alkaline phosphatase level at 36 to 40 weeks' postmenstrual age (MD 16.6 IU/L, 95% CI -34.1 to 67.4) ([Analysis 1.7](#); [Figure 5](#)). None of the trials reported bone mineral content assessed post term nor clinical or radiological evidence of rickets on long-term follow-up.

Figure 5. Forest plot of comparison: 1 Hydrolysed versus non-hydrolysed formula, outcome: 1.7 Serum alkaline phosphatase (IU/L). **7. Late-onset invasive infection (Outcome 1.8)**

Only one trial reported the incidence of late-onset invasive infection ([Baldassarre 2017](#)), describing no difference in the incidence of microbiologically confirmed bacteraemia (typical RR 1.50, 95% CI 0.27 to 8.34; typical RD -0.03, 95% CI -0.11 to 0.17) ([Analysis 1.8](#)).

8. Mortality

No trials reported the incidence of mortality.

9. Neurodevelopmental outcomes

No trials reported neurodevelopmental outcomes.

10. Allergy or atopy diagnosed after 12 months post term (Outcome 1.8)

One trial assessed allergy or atopy (Szajewska 2004). This trial found no difference in the incidence of "any allergic disease" (atopic dermatitis, gastrointestinal symptoms, wheezing) at 12 months (RR 0.62, 95% CI 0.27 to 1.42; RD -0.13, 95% CI -0.36 to 0.10) (Analysis 1.9).

Subgroup analyses

- Gestational age at birth: very preterm (less than 32 weeks) infants versus infants born at 32 weeks or later: subgroup data not available
- Indication (for therapeutic use): post surgery versus post necrotising enterocolitis versus feeding intolerance or gastro-oesophageal reflux: not applicable as all trials assessed empirical use
- Extent of protein hydrolysis (as defined by manufacturers): data for subgroup analysis sufficient for necrotising enterocolitis (Outcome 1.2) only. Three trials used a partially hydrolysed preterm formula (Florendo 2009; Pauls 1996; Raupp 1995). Two trials used an extensively hydrolysed formula (Baldassarre 2017; Mihatsch 1999). Meta-analysis showed no evidence of a subgroup effect (test for subgroup differences: $\chi^2 = 0.75$, $df = 1$ ($P = 0.39$), $I^2 = 0\%$) (Figure 3).

Indicated use of protein hydrolysate versus standard formula (Comparison 2)

We found no trials comparing protein hydrolysate versus standard formula.

DISCUSSION

Summary of main results

Data from 11 small randomised controlled trials provided only low-certainty evidence about how feeding preterm infants (typically stable infants less than 34 weeks' gestation at birth) protein hydrolysate rather than standard cow's milk formula affects the risk of feed intolerance, necrotising enterocolitis, or other adverse outcomes. Limited data did not indicate any important effects on growth, although a meta-analysis of data from three trials suggested that weight gain was slower among infants fed protein hydrolysate compared with isocaloric preterm formula. Currently no data are available to assess effects on growth and neurodevelopmental outcomes beyond the initial hospital admission.

Overall completeness and applicability of evidence

These findings should be interpreted and applied cautiously. The primary outcome, feed intolerance, was reported in various ways, and together with the paucity of numerical data, this precluded meta-analysis. Trials generally reported that feeding with protein hydrolysate did not affect measures such as the pre-feed gastric residual volume or the need to cease enteral feeding. Similarly, few trials reported the impact of the intervention on time to achieve full enteral feeding, and trials that did report this outcome found no statistically significant or clinically important effects.

Although a meta-analysis of five trials (385 participants) found no effect on the risk of necrotising enterocolitis, data were insufficient to exclude a more modest but still important effect size. The lower

bound of the 95% confidence interval (CI) was consistent with a 3% absolute risk reduction (i.e. one fewer infant developing necrotising enterocolitis for every 33 infants who received protein hydrolysate formula). Because necrotising enterocolitis is a relatively rare outcome, affecting about 5% of very preterm infants, much larger trials would be needed to obtain a more precise estimate of the effect of feeding with protein hydrolysate versus standard formula (Yee 2012).

Data on growth parameters are limited, as are data on other adverse outcomes. Furthermore, uncertainty remains about longer-term impact on growth or development. As concerns exist that hydrolysed proteins may be utilised less efficiently than intact proteins by preterm infants, and that concomitant mineral uptake may be lower, trials that assess effects on both short- and long-term growth and body composition (including bone health) may help to inform policy and practice (Senterre 2016).

Another major applicability limitation of this review is that all included trials were undertaken at healthcare facilities in high-income countries, and none in low-income countries. Therefore, this evidence may be of limited applicability to practices in resource-limited settings, where, globally, most preterm and low birth weight infants are cared for (Imdad 2013).

All included trials assessed the effects of empirical (primary) use of protein hydrolysate for feeding preterm infants. We found no trials that assessed the indicated use of protein hydrolysate versus standard formula for preterm infants with feed intolerance or gastro-oesophageal reflux (and associated apnoea, desaturation, or bradycardia), or following gastrointestinal surgery or necrotising enterocolitis. Although indicated use of protein hydrolysate is common, based on perceptions that formulas with intact proteins may be tolerated poorly by infants with intestinal trauma or compromise, trials have provided no evidence to inform this practice (Lapillonne 2016).

Quality of the evidence

The GRADE assessments indicated that the quality of evidence for the primary outcomes was 'low' because of methodological limitations of the included trials (including uncertainty about allocation concealment and blinding) and imprecision of effect size estimates (Summary of findings 1).

Most of the included trials were funded or supported by the manufacturers of the formulas being assessed, but the funders were not involved in trial design or analysis. However, there remains some concern that formula manufacturers may promote study findings of trials of specialist formulas selectively as part of a marketing strategy that subverts UNICEF Baby Friendly Initiative regulations (Clemenson 2015).

Potential biases in the review process

It is possible that our findings were subject to publication and other reporting biases. We attempted to minimise this by screening the reference lists of included trials and related reviews and by searching the proceedings of major international perinatal conferences to identify trial reports that were not (or were not yet) published in full form in academic journals. The meta-analyses that we performed did not include sufficient trials to explore symmetry of funnel plots as a means of identifying possible publication or reporting bias.

AUTHORS' CONCLUSIONS

Implications for practice

This review provides only low-certainty evidence regarding any benefits or harms of feeding preterm infants with protein hydrolysate versus standard formula. Although no trial data suggest an effect on the risk of feed intolerance or necrotising enterocolitis, the total number of infants studied was small (665 infants), and the data that could be abstracted from published studies for inclusion in meta-analyses were limited.

Implications for research

Further high-quality randomised controlled trials are needed to assess the benefits and safety of protein hydrolysate versus standard cow's milk formulas for feeding very preterm infants when maternal breast milk is insufficient or is not available. Trials could assess primary (empirical) use and secondary (indicated)

use in infants with feed intolerance or gastro-oesophageal reflux, or following gastrointestinal surgery or necrotising enterocolitis. Trials should aim to ensure the participation of extremely preterm, extremely low birth weight, or growth-restricted infants, so that subgroup analyses can be planned for these infants at higher risk of necrotising enterocolitis. Given that protein hydrolysate preterm formula is more expensive than standard preterm formula, trials could justifiably include a cost-benefit analysis.

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Ng 2017

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Baldassarre 2017

Study characteristics	
Methods	RCT
Participants	Preterm infants (28 to 33 weeks' gestational age; birth weight 700 to 1750 g and appropriate to gestational age) within 24 hours of first enteral feeding (and whose mother did not plan to exclusively breast feed)
Interventions	Extensively hydrolysed casein infant formula (n = 33) Standard cow's milk-based preterm infant formula (n = 35)
Outcomes	Enteral intake (mL/kg/d) during first 14 days after birth Feed intolerance measures (abdominal distension, regurgitation/emesis, feedings withheld $\geq$ 4 hours, or bloody stools) Necrotising enterocolitis Invasive infection
Notes	University of Bari-Policlinico Hospital, Neonatology and Neonatal Intensive Care Unit, Department of Biomedical Science and Human Oncology, Bari, Italy Trial dates: 2014 to 2016 Trial registration: clinicaltrials.gov/ct2/show/NCT01987154

Baldassarre 2017 (Continued)

Further information provided by investigators (August 2017)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	60/68 enrolled infants completed trial and contributed to outcome analysis
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funded by Mead Johnson Nutrition

Florendo 2009

Study characteristics

Methods	RCT
Participants	Preterm infants (≤ 32 weeks' gestational age, ≤ 1750 g at birth) receiving $\leq 25\%$ breast milk as total enteral intake
Interventions	Empirical use of partially hydrolysed whey-casein preterm formula (n = 42) Intact preterm formula (n = 38)
Outcomes	Feed intolerance (interruption of enteral feeds) Necrotising enterocolitis
Notes	Division of Neonatology, University of Tennessee Center for Health Sciences, Memphis, TN, USA Trial dates: 2004 to 2005

Risk of bias

Bias	Authors' judgement	Support for judgement

Florendo 2009 (Continued)

Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Sequentially labelled, sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"; ready-to-feed, colour-coded cartons
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data for 74/80 participants 1 infant in the control group developed sepsis; 1 infant from the hydrolysed formula group developed necrotising enterocolitis and was withdrawn
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funded by Nestle (manufacturer of the trial formula)

Huston 1992

Study characteristics

Methods	RCT
Participants	Preterm very low birth weight infants
Interventions	Empirical use of partially hydrolysed casein hydrolysate formula (with 40% or 60% medium-chain triglyceride) Non-hydrolysed preterm formula Total N = 60
Outcomes	Food tolerance Growth rates
Notes	Department of Pediatrics, Emanuel Children's Health Care Centre, Portland, OR, USA Trial date: early 1990s Reported as abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information - only abstract available

Huston 1992 (Continued)

Allocation concealment (selection bias)	Unclear risk	Insufficient information - only abstract available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unlikely to be blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unlikely to be blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all participants
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funder: Mead Johnson Nutritional Group

Maggio 2005
Study characteristics

Methods	RCT
Participants	Preterm infants (≤ 34 weeks' gestational age, ≤ 1750 g at birth)
Interventions	Empirical use of partially hydrolysed whey-based formula* (n = 10) Conventional preterm formula* (n = 11)
Outcomes	Growth rates from inclusion until hospital discharge Feed intolerance (no infants had enteral feeds interrupted)
Notes	Division of Neonatology, Department of Paediatrics, Catholic University of the Sacred Heart, Rome, Italy Trial dates: 1998 to 2000 * Energy content of both formulas: 75 kcal/100 mL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised schedule generated - not specified how
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias)	Low risk	Study and control formulas identical in colour and smell

Protein hydrolysate versus standard formula for preterm infants (Review)

Maggio 2005 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study and control formulas identical in colour and smell
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all participants
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funded by Humana (manufacturer of the trial formula)

Mihatsch 2002
Study characteristics

Methods	RCT
Participants	Very low birth weight (< 1500 g) infants
Interventions	Empirical use of extensively hydrolysed (whey-casein) preterm formula* (n = 41) Standard preterm formula* (n = 46)
Outcomes	Necrotising enterocolitis Proportion of enteral feeds with gastric residual volumes > 5 mL/kg birth weight
Notes	Division of Neonatology and Pediatric Critical Care, Department of Pediatrics, Ulm University, 89070 Ulm, Germany Trial dates: 1999 to 2001 * Energy content of both formulas: 80 kcal/100 mL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes - unclear whether opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind"; same appearance, but investigators acknowledged different tastes
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind"

Protein hydrolysate versus standard formula for preterm infants (Review)

Mihatsch 2002 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	129 infants recruited initially, then 42 excluded post hoc because they received > 10% of enteral intake as human milk
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funder: Milupa GmbH, Germany (manufacturer of the trial formula)

Pauls 1996

Study characteristics

Methods	RCT
Participants	Very low birth weight (< 1500 g) infants
Interventions	Empirical use of partially hydrolysed whey-casein formula* (n = 25) Non-hydrolysed protein formula* (n = 25)
Outcomes	Mean gastric residual volume (% of intake) Time to full enteral feeds Necrotising enterocolitis
Notes	Kinderklinik, Freie Universitat Berlin, Germany Trial date: early 1990s Reported as an abstract only * Energy content of both formulas: 80 kcal/100 mL; protein content: hydrolysed formula 2.9 g/100 mL vs non-hydrolysed formula 2.7 g/100 mL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information - only abstract available
Allocation concealment (selection bias)	Unclear risk	Insufficient information - only abstract available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unlikely to be blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unlikely to be blinded
Incomplete outcome data (attrition bias)	Low risk	Outcomes reported for all participants

Protein hydrolysate versus standard formula for preterm infants (Review)

Pauls 1996 (Continued)

All outcomes

Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funder: not stated

Picaud 2001
Study characteristics

Methods	RCT
Participants	Preterm newborns with birth weight < 1500 g and aged < 15 days when enteral feeds commenced
Interventions	Empirical use of partially hydrolysed formula* (n = 9) Standard preterm formula* (n = 7) Until 40 weeks' postmenstrual age
Outcomes	Rate of weight gain during initial hospital admission Nitrogen balance studies
Notes	Edouard Herriot Hospital, Claude Bernard University, Lyon, France Trial date: late 1990s * Energy content of both formulas: 80 kcal/100 mL, but nitrogen content 10% higher in standard preterm formula

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes - unclear whether opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Investigators unaware of formula; unclear if carers or parents aware
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Investigators unaware of formula; unclear if carers or parents aware
Incomplete outcome data (attrition bias) All outcomes	Low risk	All infants assessed for primary outcomes
Selective reporting (reporting bias)	Unclear risk	Protocol not available

Protein hydrolysate versus standard formula for preterm infants (Review)

Picaud 2001 (Continued)

Other bias	Unclear risk	Funder: Nestle (manufacturer of the trial formula)

Raupp 1995
Study characteristics

Methods	RCT
Participants	Neonates; body weight 1000 to 1799 g
Interventions	Empirical use of partially hydrolysed whey-casein formula* (n = 56) Non-hydrolysed preterm formula* (n = 52)
Outcomes	Biochemistry Bone mineralisation Blood/serum Necrotising enterocolitis
Notes	University Children's Hospital of Düsseldorf * Energy content of both formulas: 80 kcal/100 mL

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All infants assessed for primary outcomes
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funder: Nestle (manufacturer of the trial formula)

Riezzo 2001

Study characteristics

Methods	RCT
Participants	Preterm infants (n = 36)
Interventions	Partially hydrolysed casein preterm formula* (n = 18) Standard (whey-casein) formula* (n = 18)
Outcomes	Proportion of infants who had > 1 episode of regurgitation or vomiting per day
Notes	Department of Pediatrics, Neonatology Section, University of Bari, Bari, Italy Trial date: 2000 Energy content of hydrolysed formula (80 kcal/100 mL) higher than control standard term formula (68 kcal/100 mL). Because trial did not report growth rates (the reason for specifying similar energy levels in comparison formulas), we made a consensus decision to include the trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear evidence provided - stated only that infants were randomly assigned
Allocation concealment (selection bias)	Unclear risk	Unclear evidence provided - stated only that infants were randomly assigned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All infants assessed for primary outcomes
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funder: not stated

Schweizer 1993

Study characteristics

Methods	RCT
Participants	Preterm infants (formula fed)

Protein hydrolysate versus standard formula for preterm infants (Review)

Schweizer 1993 (Continued)

Interventions	Extensively hydrolysed whey-casein term formula (Alfare)* (n = 26) Non-hydrolysed preterm formula (Prematil)* (n = 26)
Outcomes	Time to regain birth weight Time to full enteral feeding Mean number of high gastric residual volumes per day
Notes	Kinderklinik der Stadt, Kliniken, Dortmund Trial dates: 1991 to 1993 * Energy content of hydrolysed formula (70 kcal/100 mL) lower than control standard preterm formula (80 kcal/100 mL). Because trial did not report growth rates (the reason for specifying similar energy levels in comparison formulas), we made a consensus decision to include the trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information - only abstract available
Allocation concealment (selection bias)	Unclear risk	Insufficient information - only abstract available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blinded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double-blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all participants
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funder: not stated

Szajewska 2004

Study characteristics

Methods	RCT
Participants	Preterm infants, body weight < 2500 g with ≥ 1 first-degree relative with atopy
Interventions	Extensively (n = 26) or partially hydrolysed whey-casein preterm formula* (n = 32) Standard preterm formula* (n = 32)

Protein hydrolysate versus standard formula for preterm infants (Review)

Szajewska 2004 (Continued)

Outcomes	Allergic disease in infancy Feed intolerance
Notes	Primary aim: to assess effects on allergy and atopic disease In-hospital feed tolerance, growth, and adverse outcomes not reported. We contacted corresponding author in December 2016 to seek these data * Energy content of both formulas: 80 kcal/100 mL 33% "dropout" before assessment at 4 to 5 months post term

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised schedule generated - unspecified how
Allocation concealment (selection bias)	Low risk	Sealed numbered envelopes - not stated whether opaque, but codes concealed from investigators until trial completed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Double-blind" but study and control formulas not identical in texture and smell
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Double-blind" but study and control formulas not identical in texture and smell
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all participants
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funded by Ovita Nutricia Research Foundation

n: number of infants.

RCT: randomised controlled trial.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Agosti 2003	Not an RCT
Corvaglia 2013	Cross-over RCT with cross-over at each enteral feed
Logarajaha 2015	Cross-over RCT with cross-over at 24 hours
Mihatsch 1999	Cross-over RCT with initial formula allocation for 5 days only

Study	Reason for exclusion
Mihatsch 2001a	Cross-over RCT with initial formula allocation for 5 days only
Rigo 1994	5-Arm RCT with term infants receiving different types of hydrolysed formula (3 different whey hydrolysate formulas, a soy-collagen hydrolysate formula, or a whey-casein hydrolysate formula)
Rigo 1995	Not an RCT
Yu 2014	Cross-over study with initial formula allocation for 10 days, and cross-over occurring only if feeds not well tolerated Unclear whether randomised

RCT: randomised controlled trial.

Characteristics of studies awaiting classification *[ordered by study ID]*

del Moral 2017

Methods	RCT (double blind) Randomisation sequence generated by computer, allocation by sealed envelopes
Participants	Very low birth weight or very preterm infants (stratified by 2 birth weight categories (500 to 1000 g and 1001 to 1500 g)) who survived > 3 days after birth and for whom breast milk was not available or was insufficient for requirements
Interventions	Empirical use of 100% whey protein partially hydrolysed preterm formula (n = 62) vs intact preterm formula (n = 73) Breast milk allowed if available; different formulas given to supplement when no breast milk available (postrandomisation exclusion if breast milk > 25% of total enteral intake)
Outcomes	Time to achieve full feeds Number of days from initiating oral feeds to achieving full feeds Mortality Necrotising enterocolitis
Notes	Principal investigator: Teresa del Moral, Department of Pediatrics, Miller School of Medicine, University of Miami, FL, USA Contacted tdelmoral@miami.edu in July 2017 seeking data Trial dates: 2004 to 2005 Funded by Nestle Study discontinued because the increasingly common use of breast milk meant recruitment was much slower than planned (remains unreported June 2019)

Dobryansky 2015

Methods	RCT
Participants	Very low birth weight (< 1500 g) infants
Interventions	Hydrolysed formula (n = 35) vs standard preterm formula (n = 25)
Outcomes	Feed intolerance Time to full enteral feeding

Dobryansky 2015 *(Continued)*

	Necrotising enterocolitis
	9 additional infants (originally randomised) who died were excluded
Notes	Article in Ukrainian; awaiting translation

Gu 2017

Methods	Unclear whether RCT or observational study
Participants	Very low birth weight infants
Interventions	Extensively hydrolysed formula (n = 187) vs standard preterm formula (n = 188)
Outcomes	Feed intolerance Time to full enteral feeding Time to complete meconium excretion Number of spontaneous bowel movements Growth and development Motilin level at 4 days and 10 days after feeding Incidence rate of infection
Notes	Article in Chinese language; awaiting full text and translation

Kwinta 2002

Methods	RCT
Participants	Very low birth weight infants
Interventions	Hydrolysed protein formula vs preterm formula
Outcomes	Feed intolerance Gram-negative sepsis Weight gain Duration of parenteral nutrition
Notes	Article in Polish; awaiting full text and translation Author contacted January 2019 (kwintap@mp.pl)

Luo 2016

Methods	RCT

Protein hydrolysate versus standard formula for preterm infants (Review)

Luo 2016 (Continued)

Participants	"Very/extremely" low birth weight infants
Interventions	Hydrolysed protein formula vs preterm formula
Outcomes	Feed intolerance Growth rates
Notes	Article in Chinese language; awaiting full text and translation

RCT: randomised controlled trial.

Characteristics of ongoing studies [ordered by study ID]

ACTRN12613000481774

Study name	Effects of a New Hydrolyzed Powdered Formula on Feeding Tolerance in Preterm Neonates: A Randomised Placebo-Controlled Study
Methods	RCT
Participants	60 newborns with birth weight < 1500 g
Interventions	Powdered hydrolysed formula vs standard preterm formula
Outcomes	Time to reach full enteral feeding (120 kcal/kg/d)
Starting date	2013
Contact information	Professor Gianluca Terrin, University of Rome "La Sapienza", Italy
Notes	Trial has not yet started due to lack of funding (personal communication from Professor Terrin)

RCT: randomised controlled trial.

DATA AND ANALYSES
Comparison 1. Hydrolysed versus non-hydrolysed formula

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Feed intolerance	3	161	Risk Ratio (M-H, Fixed, 95% CI)	2.71 [0.29, 25.00]
1.2 Necrotising enterocolitis	5	385	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.03, 0.04]
1.2.1 Partially hydrolysed	3	238	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.03, 0.06]
1.2.2 Extensively hydrolysed	2	147	Risk Difference (M-H, Fixed, 95% CI)	-0.02 [-0.07, 0.04]

Protein hydrolysate versus standard formula for preterm infants (Review)

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Time to full enteral feeding	1	16	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-8.36, 6.36]
1.4 Weight gain (g/kg/day)	3	113	Mean Difference (IV, Fixed, 95% CI)	-3.02 [-4.66, -1.38]
1.5 Length gain (mm/week)	2	97	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-1.24, 1.15]
1.6 Head circumference growth (mm/week)	2	97	Mean Difference (IV, Fixed, 95% CI)	0.27 [-0.39, 0.94]
1.7 Serum alkaline phosphatase (IU/L)	2	88	Mean Difference (IV, Fixed, 95% CI)	16.61 [-34.15, 67.37]
1.8 Late-onset invasive infection	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.27, 8.34]
1.9 Any allergic disease	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.27, 1.42]

Analysis 1.1. Comparison 1: Hydrolysed versus non-hydrolysed formula, Outcome 1: Feed intolerance

Analysis 1.2. Comparison 1: Hydrolysed versus non-hydrolysed formula, Outcome 2: Necrotising enterocolitis

Analysis 1.3. Comparison 1: Hydrolysed versus non-hydrolysed formula, Outcome 3: Time to full enteral feeding

Analysis 1.4. Comparison 1: Hydrolysed versus non-hydrolysed formula, Outcome 4: Weight gain (g/kg/day)

Analysis 1.5. Comparison 1: Hydrolysed versus non-hydrolysed formula, Outcome 5: Length gain (mm/week)

Analysis 1.6. Comparison 1: Hydrolysed versus non-hydrolysed formula, Outcome 6: Head circumference growth (mm/week)

Analysis 1.7. Comparison 1: Hydrolysed versus non-hydrolysed formula, Outcome 7: Serum alkaline phosphatase (IU/L)

Analysis 1.8. Comparison 1: Hydrolysed versus non-hydrolysed formula, Outcome 8: Late-onset invasive infection

Analysis 1.9. Comparison 1: Hydrolysed versus non-hydrolysed formula, Outcome 9: Any allergic disease

APPENDICES

Appendix 1. Electronic search strategy

Database: **CENTRAL**

Searched via Cochrane Library 28 January 2019

437 records identified

ID Search

#1 MeSH descriptor: [Infant, Newborn] explode all trees

#2 MeSH descriptor: [Premature Birth] explode all trees

#3 neonat*:ti,ab,kw (Word variations have been searched)

#4 neo-nat*:ti,ab,kw (Word variations have been searched)

#5 newborn or new born* or newly born*:ti,ab,kw (Word variations have been searched)

#6 preterm or preterms or (pre term) or (pre terms):ti,ab,kw (Word variations have been searched)

#7 preemie* or premie or preemies:ti,ab,kw (Word variations have been searched)

#8 prematur* near/3 (birth* or born or deliver*):ti,ab,kw (Word variations have been searched)

#9 low near/3 (birthweight* or birth weight*):ti,ab,kw (Word variations have been searched)

#10 lbw or vlbw or elbw:ti,ab,kw (Word variations have been searched)

#11 infan* or baby or babies:ti,ab,kw (Word variations have been searched)

#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

#13 (hydroly* near/3 (formula* or milk or protein* or whey)):ti,ab,kw (Word variations have been searched)

#14 (hypoallergen* near/3 (formula* or milk or protein* or whey)):ti,ab,kw (Word variations have been searched)

#15 (Nutramigen or Nutriprem or Pregestamil or Profylac or Nan or Aptamil Pepti or Pepti-Junior or Pepdite or Infatrini or Similac or Gold Prem Pro or Alimentum):ti,ab,kw (Word variations have been searched)

#16 #13 or #14 or #15

#17 #12 and #16

CINAHL Complete

Searched via EBSCO, 28 January 2019, 210 records identified

Search ID#	Search Terms	Search Options
S1	(MH "Infant, Newborn+")	Search modes - Boolean/ Phrase
S2	TX ((neonat* or neo nat*)) OR TX ((newborn* or new born* or newly born*)) OR TX ((preterm or preterms or pre term or pre terms)) OR TX ((preemie\$ or premie or premies)) OR TX ((prematur* N3 (birth* or born or deliver*))) OR TX ((low N3 (birthweight* or birth weight*))) OR TX ((lbw or vlbw or elbw)) OR TX infan* OR TX ((baby or babies))	Search modes - Boolean/ Phrase
S3	S1 OR S2	Search modes - Boolean/ Phrase
S4	TX ((hydroly* N3 (formula* or milk or protein* or whey))) OR TX ((hypoallergen* N3 (formula* or milk or protein* or whey))) OR TX ((Nutramigen or Nutripem or Pregestamil or Profylac or Nan or Aptamil Pepti or Pepti-Junior or Pepdite or Infatrini or Similac or Gold Prem Pro or Alimentum))	Search modes - Boolean/ Phrase
S5	S3 AND S4	Search modes - Boolean/ Phrase
S6	S3 AND S4	Limiters - Clinical Queries: Therapy - High Sensitivity Search modes - Boolean/ Phrase (210 records)

Embase

Searched via OVID 28 January 2019 443 records

Database: Embase <1974 to 2019 January 25>

Search Strategy:

-
- 1 exp Infant, Newborn/ (494224)
  - 2 Premature Birth/ (48011)
  - 3 (neonat\$ or neo nat\$).ti,ab. (314056)
  - 4 (newborn\$ or new born\$ or newly born\$).ti,ab. (179767)
  - 5 (preterm or preterms or pre term or pre terms).ti,ab. (93664)
  - 6 (preemie\$ or premie or premies).ti,ab. (234)
  - 7 (prematur\$ adj3 (birth\$ or born or deliver\$)).ti,ab. (19781)
  - 8 (low adj3 (birthweight\$ or birth weight\$)).ti,ab. (40166)
  - 9 (lbw or vlbw or elbw).ti,ab. (10334)
  - 10 infan\$.ti,ab. (459564)

Protein hydrolysate versus standard formula for preterm infants (Review)

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- 11 (baby or babies).ti,ab. (89325)
- 12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (1048188)
- 13 (hydroly\$ adj3 (formula\$ or milk or protein\$ or whey)).ti,ab. (9398)
- 14 (hypoallergen\$ adj3 (formula\$ or milk or protein\$ or whey)).ti,ab. (463)
- 15 (Nutramigen or Nutriprem or Pregestamil or Profylac or Nan or Aptamil Pepti or Pepti-Junior or Pepdite or Infatrini or Similac or Gold Prem Pro or Alimentum).ti,ab. (1811)
- 16 13 or 14 or 15 (11365)
- 17 clinical trial/ (953847)
- 18 randomized controlled trial/ (533609)
- 19 randomization/ (81009)
- 20 single blind procedure/ (33779)
- 21 double blind procedure/ (157592)
- 22 crossover procedure/ (58047)
- 23 placebo/ (329701)
- 24 randomi?ed controlled trial\$.tw. (195584)
- 25 rct.tw. (31133)
- 26 random allocation.tw. (1905)
- 27 randomly allocated.tw. (31798)
- 28 allocated randomly.tw. (2419)
- 29 (allocated adj2 random).tw. (879)
- 30 single blind\$.tw. (22298)
- 31 double blind\$.tw. (194704)
- 32 ((treble or triple) adj blind\$).tw. (912)
- 33 placebo\$.tw. (284340)
- 34 prospective study/ (498156)
- 35 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (1999977)
- 36 case study/ (58844)
- 37 case report.tw. (372753)
- 38 abstract report/ or letter/ (1093127)
- 39 36 or 37 or 38 (1515434)
- 40 35 not 39 (1949209)
- 41 12 and 16 and 40 (443)

Maternity and Infant Care**Searched via Ovid 28 January 2019 22 records identified**

Database: Maternity & Infant Care Database (MIDIRS) <1971 to December 2018FF

Search Strategy:

-
- 1 (neonat\$ or neo nat\$).ti,ab. (43123)
  - 2 (newborn\$ or new born\$ or newly born\$).ti,ab. (19566)
  - 3 (preterm or preterms or pre term or pre terms).ti,ab. (25419)
  - 4 (preemie\$ or premie or premies).ti,ab. (53)
  - 5 (prematur\$ adj3 (birth\$ or born or deliver\$)).ti,ab. (3927)
  - 6 (low adj3 (birthweight\$ or birth weight\$)).ti,ab. (10548)
  - 7 (lbw or vlbw or elbw).ti,ab. (2974)
  - 8 infan\$.ti,ab. (62846)
  - 9 (baby or babies).ti,ab. (28609)
  - 10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (116422)
  - 11 (hydroly\$ adj3 (formula\$ or milk or protein\$ or whey)).ti,ab. (157)
  - 12 (hypoallergen\$ adj3 (formula\$ or milk or protein\$ or whey)).ti,ab. (32)
  - 13 (Nutramigen or Nutriprem or Pregestamil or Profylac or Nan or Aptamil Pepti or Pepti-Junior or Pepdite or Infatrini or Similac or Gold Prem Pro or Alimentum).ti,ab. (36)
  - 14 11 or 12 or 13 (205)
  - 15 10 and 14 (195)
  - 16 limit 15 to randomised controlled trial (22)

MEDLINE searched 28 January 2019 465 records identified

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Database: Ovid MEDLINE(R) ALL <1946 to January 25, 2019>

Search Strategy:

-
- 1 exp Infant, Newborn/ (577694)
  - 2 Premature Birth/ (11711)
  - 3 (neonat\$ or neo nat\$).ti,ab. (245408)
  - 4 (newborn\$ or new born\$ or newly born\$).ti,ab. (156950)
  - 5 (preterm or preterms or pre term or pre terms).ti,ab. (67233)
  - 6 (preemie\$ or premie or premies).ti,ab. (155)
  - 7 (prematur\$ adj3 (birth\$ or born or deliver\$)).ti,ab. (14660)
  - 8 (low adj3 (birthweight\$ or birth weight\$)).ti,ab. (32141)
  - 9 (lbw or vlbw or elbw).ti,ab. (7634)
  - 10 infan\$.ti,ab. (409379)
  - 11 (baby or babies).ti,ab. (65510)

Protein hydrolysate versus standard formula for preterm infants (Review)

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12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (996498)

13 (hydroly\$ adj3 (formula\$ or milk or protein\$ or whey)).ti,ab. (8524)

14 (hypoallergen\$ adj3 (formula\$ or milk or protein\$ or whey)).ti,ab. (287)

15 (Nutramigen or Nutriprem or Pregestamil or Profylac or Nan or Aptamil Pepti or Pepti-Junior or Pepdite or Infatrini or Similac or Gold Prem Pro or Alimentum).ti,ab. (1851)

16 13 or 14 or 15 (10495)

17 randomized controlled trial.pt. (475348)

18 controlled clinical trial.pt. (92893)

19 randomized.ab. (433287)

20 placebo.ab. (195102)

21 drug therapy.fs. (2078948)

22 randomly.ab. (304542)

23 trial.ab. (452332)

24 groups.ab. (1875742)

25 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (4366018)

26 exp animals/ not humans.sh. (4541052)

27 25 not 26 (3775428)

28 12 and 16 and 27 (465)

Appendix 2. Risk of bias

'Risk of bias' tool

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

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

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

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

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

- low risk (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); 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 categorised 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 classes of outcomes. We categorised the methods as:

- low risk, high risk, or unclear risk for participants; and
- 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 categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or classes of outcomes. We categorised the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- 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 described the completeness of data including attrition and exclusions from the analysis. We noted 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 re-included missing data in the analyses. We categorised the methods as:

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

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

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

- 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);
- high risk (where not all of the study's prespecified outcomes have been reported; 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); or
- unclear risk.

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

For each included study, we described 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, whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk; or
- unclear risk.

If needed, we explored the impact of the level of bias through undertaking sensitivity analyses.

WHAT'S NEW

Date	Event	Description
8 July 2020	Amended	Typo corrected in Declarations of interest section

HISTORY

Protocol first published: Issue 10, 2016

Review first published: Issue 10, 2017

Date	Event	Description
7 August 2019	Amended	Declaration of interest updated for Dr. Nicholas D Embleton.
26 February 2019	New citation required but conclusions have not changed	Conclusions remain consistent with the previously published version of the review (Ng 2017)
29 January 2019	New search has been performed	Search has been updated - no new trials are included

CONTRIBUTIONS OF AUTHORS

All authors developed the protocol.

DN and WM: screened search outputs, assessed study eligibility, and extracted and synthesised data.

DN and JK assessed risk of bias across key domains and undertook the GRADE assessment with WM.

All review authors revised the final review.

DECLARATIONS OF INTEREST

NDE declares the following: receiving a research grant award for an RCT of breast milk products by Prolacta Bioscience, 2017; receiving a grant from Danone Early Life Nutrition to support a study on feeding in late and moderately preterm infants, 2018; receiving a grant from Nestle Nutrition for transcriptomic analyses of gut tissue, 2016; lectures with Wyeth Nutrition in 2017, Nestle Nutrition Institute in 2017 and 2018, Philipps in 2017, and Fresenius, 2017.

DN has no interest to declare.

JK has no interest to declare.

WM has no interest to declare.

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To maintain the utmost editorial independence for this Cochrane Review, an editor outside of the Cochrane Neonatal core editorial team who is not receiving any financial remuneration from the grant, Jann Foster, was the Sign-off Editor for this review. Additionally, a Senior Editor from the Cochrane Children and Families Network, Robert Boyle, assessed and signed off on this Cochrane Review.

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- Vermont Oxford Network, USA

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- The Gerber Foundation, USA

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Two trials compared formulas with different energy densities ([Riezzo 2001](#); [Schweizer 1993](#)). These trials did not report growth rates (the reason for prespecified similar energy levels), so we made a consensus decision to include them in the review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant Formula; Infant Nutritional Physiological Phenomena [*physiology]; Infant, Premature [*growth & development]; Protein Hydrolysates [*administration & dosage] [metabolism]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant; Infant, Newborn