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Formula versus maternal breast milk for feeding preterm or low birth weight infants (Review)

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[Intervention Review]

Formula versus maternal breast milk for feeding preterm or low birth weight infants

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ABSTRACT

Background

Artificial formula can be manipulated to contain higher amounts of macro-nutrients than maternal breast milk but breast milk confers important immuno-nutritional advantages for preterm or low birth weight (LBW) infants.

Objectives

To determine the effect of feeding preterm or LBW infants with formula compared with maternal breast milk on growth and developmental outcomes.

Search methods

We used the standard strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL 2018, Issue 9), and Ovid MEDLINE, Ovid Embase, Ovid Maternity & Infant Care Database, and CINAHL to October 2018. We searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles.

Selection criteria

Randomised or quasi-randomised controlled trials that compared feeding preterm or low birth weight infants with formula versus maternal breast milk.

Data collection and analysis

Two review authors planned independently to assess trial eligibility and risk of bias, and extract data. We planned to analyse treatment effects as described in the individual trials and report risk ratios and risk differences for dichotomous data, and mean differences for continuous data, with 95% confidence intervals. We planned to use a fixed-effect model in meta-analyses and to explore potential causes of heterogeneity in subgroup analyses. We planned to use the GRADE approach to assess the certainty of evidence.

Main results

We did not identify any eligible trials.

Authors' conclusions

There are no trials of formula versus maternal breast milk for feeding preterm or low birth weight infants. Such trials are unlikely to be conducted because of the difficulty of allocating an alternative form of nutrition to an infant whose mother wishes to feed with her own breast milk. Maternal breast milk remains the default choice of enteral nutrition because observational studies, and meta-analyses of trials comparing feeding with formula versus donor breast milk, suggest that feeding with breast milk has major immuno-nutritional advantages for preterm or low birth weight infants.

PLAIN LANGUAGE SUMMARY

Formula versus maternal breast milk for feeding preterm or low birth weight infants

Review question

Does feeding preterm or low birth weight infants with formula rather than maternal breast milk affect growth and development?

Background

Artificial formulas can be manipulated to contain higher amounts of important nutrients such as protein than maternal breast milk but newborn infants often find formula difficult to digest. Artificial formulas, furthermore, do not contain the antibodies and other substances present in breast milk that protect the immature gut of preterm or low birth weight infants and reduce the risk of infection and severe bowel problems. If preterm infants are fed with formula rather than maternal breast milk (breast-fed directly or mother's own expressed breast milk), this might increase the risk of these problems and adversely affect growth and development. Given these concerns, we planned to review the evidence from clinical trials that compared formula versus maternal breast milk for feeding preterm or low birth weight infants.

Study characteristics

In searches up to October 2018, we did not find any eligible randomised controlled trials.

Key results and conclusions

There are no trial data to answer this question. Since another Cochrane Review showed that feeding with formula compared to donor breast milk increases the risk of serious gut problems in preterm or low birth weight infants, it is unlikely that families and clinicians would consider it acceptable to allocate an infant to receive formula as an alternative to maternal breast milk when it is available.

BACKGROUND

This review focuses on the comparison of feeding preterm or low birth weight (LBW) infants with artificial formula versus maternal (mother's own) breast milk. The comparison of feeding with formula versus donor breast milk is addressed in a separate review (Quigley 2018). Healthcare professional or peer-led breastfeeding support interventions for mothers of preterm or LBW infants have been addressed in other reviews (McInnes 2008; Renfrew 2009; Ahmed 2010).

Description of the condition

Early enteral feeding strategies, including the type of milk given to infants, can affect important outcomes in preterm or LBW infants, and especially very preterm or very low birth weight (VLBW) infants who have limited nutrient reserves at birth and are subject to physiological and metabolic stresses that increase their nutrient needs (Agostoni 2010; Embleton 2017). Most very preterm or VLBW infants accumulate nutrient deficits during their initial hospital stay and many infants are growth-restricted relative to their term-born peers by the time they are ready to go home (Embleton 2001; Horbar 2015). Growth deficits, which can persist through childhood and adolescence, are associated with adverse neurodevelopmental, cognitive, and educational outcomes (Leppänen 2014).

Description of the intervention

Maternal breast milk is the recommended form of enteral nutrition for preterm or LBW infants (Agostoni 2010; AAP 2012; Cleminson 2015). In addition to macro- and micro-nutrients that are optimised by evolution for digestion and absorption by human infants, maternal breast milk contains numerous 'immuno-nutrients' such as secretory immunoglobulin (Ig)A, lactoferrin, cytokines, enzymes, growth factors, and leucocytes (Walsh 2019). An important benefit of maternal breast milk for preterm or LBW infants is that delivery of these immunological and growth factors to the immature intestinal mucosa promotes post-natal physiological, neuro-endocrinological, and metabolic adaptation (Jones 2007; Embleton 2017). Evidence from observational studies suggests that feeding with maternal breast milk rather than formula is associated with a reduced risk of serious adverse outcomes including necrotising enterocolitis and infection in very preterm and VLBW infants (Lucas 1990; Battersby 2017). A Cochrane Review of trials that compared feeding preterm or LBW infants with formula versus donor breast milk showed that formula feeding was associated with a near doubling of the risk of severe necrotising enterocolitis (Quigley 2018).

The nutritional requirements of preterm or LBW infants, and especially very preterm and VLBW infants, may not be met by enteral feeding with maternal breast milk alone (Agostoni 2010). Maternal breast milk varies in energy and protein content depending upon the stage of lactation at which it is collected, the duration of lactation, and the method of storage and delivery. Many of the processes involved in handling maternal breast milk, including refrigeration, freeze-thawing, and pasteurisation, can reduce its macro-nutrient and immuno-nutrient content (Zachariassen 2013; Gidrewicz 2014). Supplementation of maternal breast milk with nutrient fortifiers (typically extracted from cow milk) is an option for increasing nutrient density (Klingenberg 2012; Tudehope 2013; Underwood 2013). Although this results in faster short-term growth, uncertainty remains about whether fortification using bovine milk extracts increases the risk of enteral feed intolerance or necrotising enterocolitis in very preterm or VLBW infants (Brown 2016; Ellis 2019).

Intervention ‐ formula

As an alternative to breast milk, a variety of artificial formulas (usually modified cow milk) for feeding preterm or LBW infants are available commercially (Agostoni 2010; Tudehope 2012). These vary in energy, protein and micro-nutrient content and, broadly, can be categorised as:

- standard 'term' formulas; designed for term infants, based on the composition of mature breast milk ‐ the typical energy content is between about 67 and 70 kCal/100 mL;
- nutrient-enriched 'preterm' formulas; designed for preterm infants to provide nutrient intakes to match intra-uterine accretion rates ‐ these are energy-enriched (typically up to about 80 kCal/100 mL) and are variably protein- and mineral-enriched.

How the intervention might work

Artificial formula, particularly nutrient-enriched 'preterm' formula, might provide consistently higher levels of nutrients than maternal breast milk does. However, artificial formulas do not contain the same immuno-nutritional factors that are present in maternal breast milk (Tudehope 2012; Underwood 2013). Furthermore, although bovine proteins, carbohydrates and lipids in artificial formulas are modified to improve digestibility for newborn infants, these are less likely to be tolerated than human milk macro-nutrients, especially by the immature preterm intestine. Formula feeding might therefore delay the functional adaptation of the gastrointestinal tract and disrupt the patterns of microbial colonisation (Embleton 2017). Intestinal dysmotility and dysbiosis might exacerbate feed intolerance and delay the establishment of enteral feeding independent of parenteral nutrition (Pammi 2017). Prolonged parenteral nutrition is associated with infectious and metabolic complications that increase mortality and morbidity, prolong hospital stay, and adversely affect growth and development (Walsh 2019).

Why it is important to do this review

Given the potential for the type of enteral nutrition to affect important outcomes for preterm or LBW infants, and since uncertainty exists about the balance between the putative benefits and harms, an attempt to detect, appraise and synthesise evidence from randomised controlled trials is merited.

OBJECTIVES

To determine the effect of feeding preterm or LBW infants with formula compared with maternal breast milk on growth and developmental outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Controlled trials utilizing either random or quasi-random patient allocation.

Types of participants

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

Types of interventions

Feeding with formula milk versus maternal (mother's own) expressed milk.

Types of outcome measures

Primary outcomes

Growth

- Rates of weight gain, linear growth, head growth or skinfold thickness growth during initial hospitalisation, and z-score at 36 weeks' or longer post-menstrual age
- Weight, height or head circumference (or proportion of infants who remain below the 10th percentile for the index population's distribution), assessed at intervals following hospital discharge

Neurodevelopment

- Death or severe neurodevelopmental disability defined as any one or combination of the following: non-ambulant cerebral palsy, developmental quotient more than two standard deviations below the population mean, and blindness (visual acuity < 6/60) or deafness (any hearing impairment requiring or unimproved by amplification)
- Neurodevelopmental scores in children aged at least 12 months, measured using validated assessment tools such as main domains (cognitive, motor, language) of Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III)
- Cognitive and educational outcomes in children ≥ five years old

Necrotising enterocolitis confirmed at surgery or autopsy or diagnosed by at least two of the following clinical features (Kliegman 1987).

- 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)
- Blood in stool
- Lethargy, hypotonia or apnoea (or combination of these)

Secondary outcomes

- Death in the neonatal period (up to 28 days) and death prior to hospital discharge
- Feed intolerance during the trial intervention period that results in cessation in enteral feeding for > 4 hours
- Time after birth to establish full enteral feeding (independently of parenteral nutrition)
- Invasive infection as determined by culture of bacteria or fungus from blood, cerebrospinal fluid, or from a normally sterile body space
- Duration of birth hospitalisation (days)

Search methods for identification of studies

We used the Cochrane Neonatal standard search strategy.

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 9) in the Cochrane Library, Ovid MEDLINE (1946 to 1 October 2018), OVID Embase (1980 to 1 October 2018), and OVID Maternity & Infant Care Database (1971 to 1 October 2018)**,** and the Cumulative Index to Nursing and Allied Health Literature Plus (CINAHL) via Ebsco (1982 to 21 September 2018) using a combination of text words and MeSH terms described in Appendix 1. We limited the search outputs with relevant search filters for clinical trials as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We did not apply any language restrictions.
We searched ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform (www.who.int/ictrp/en) for completed or 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 2019), the European Society for Paediatric Research (1995 to 2019), the Royal College of Paediatrics and Child Health (2000 to 2019), and the Perinatal Society of Australia and New Zealand (2000 to 2019). Trials reported only as abstracts were eligible if sufficient information was available from the report, or from contact with the authors, to fulfil the inclusion criteria.

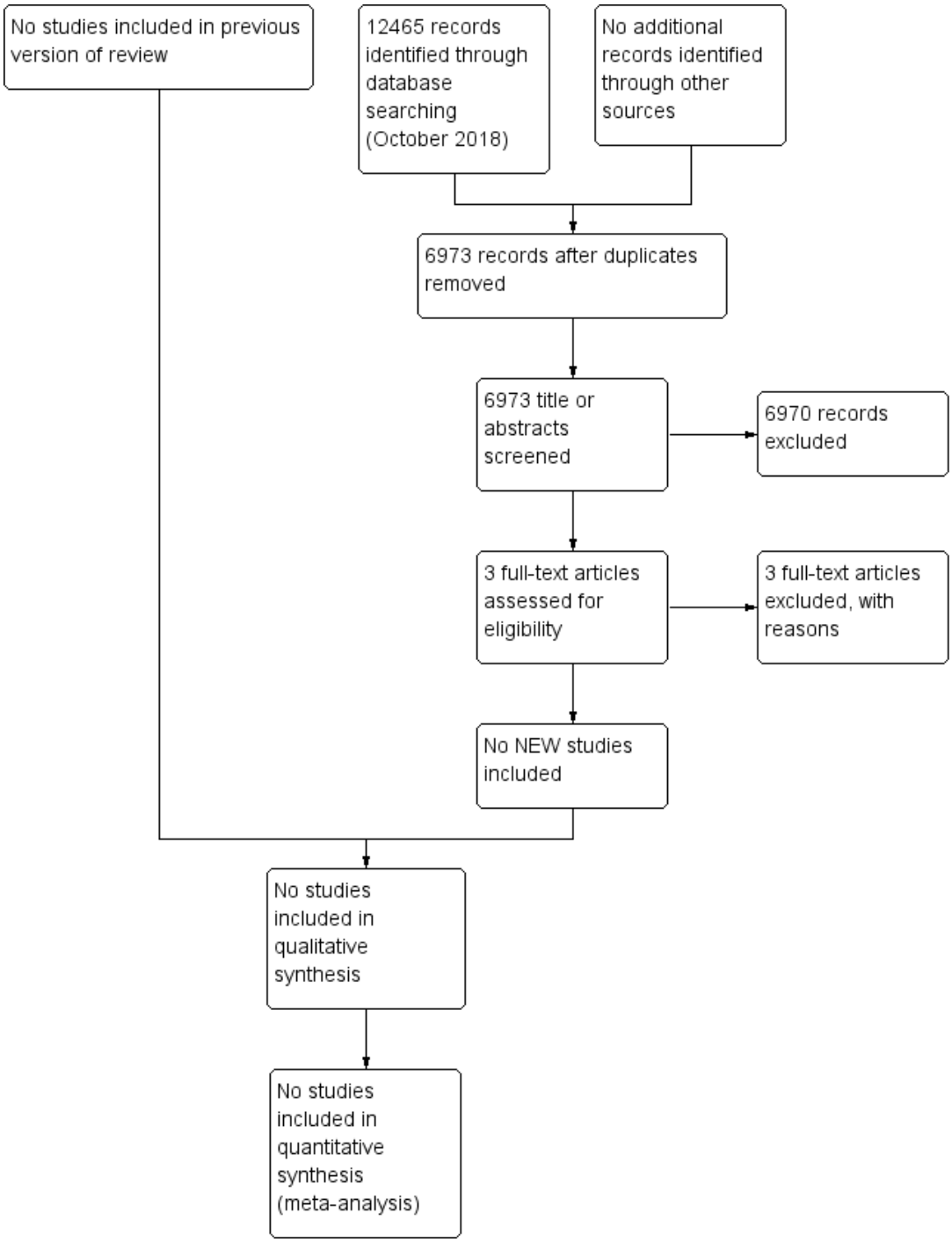
Data collection and analysis

We used the standard methods of Cochrane Neonatal (neonatal.cochrane.org).

Selection of studies

We screened the title and abstract of all studies identified by the above search strategy and two review authors (JB, VW) 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 reason for exclusion. We discussed any disagreements until consensus was achieved. We illustrated the screening and selection outcomes in a flowchart (Figure 1).

Figure 1. Study flow diagram: review update



Data extraction and management

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

Assessment of risk of bias in included studies

Two review authors (JB and VW) planned to independently assess the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2011) for the following domains.

- 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

We planned to resolve disagreements by discussion or by including a third review author (WM). See Appendix 2 for a detailed description of risk of bias for each domain.

Measures of treatment effect

We planned to calculate risk ratios and risk differences for dichotomous data and mean differences for continuous data, with respective 95% confidence intervals. If deemed appropriate to combine two or more study arms, we planned to obtain the treatment effects from the combined data using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to determine the number needed to treat for an additional beneficial outcome or the number needed to treat for an additional harmful outcome for each statistically significant risk difference.

Unit of analysis issues

We specified the unit of analysis as the participating infant in individually randomised trials and the neonatal unit (or subunit) for cluster-randomised controlled trials. For cluster trials, we planned to undertake analyses at the level of the individual while accounting for the clustering in the 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 planned to approach the analysis of missing data as follows.

- Contact the original study investigators to request the missing data
- Where possible, impute missing standard deviations (SD) using the coefficient of variation or calculate the SD from other statistics including standard errors, confidence intervals, t values and P values
- If the data were likely to be missing at random, analyse the data without imputing any missing values
- If the data were not likely to be missing at random, impute the missing outcomes with replacement values, assuming all to have a poor outcome

Assessment of heterogeneity

Two review authors (JB and VW) planned to assess clinical heterogeneity, with a meta-analysis conducted only when both agreed that study participants, interventions and outcomes were sufficiently similar.

We planned to examine the treatment effects of individual trials and heterogeneity between trial results by inspecting the forest plots. We planned to calculate the I^2 statistic for each analysis to quantify inconsistency across studies and describe the percentage of variability in effect estimates that may be due to heterogeneity rather than to sampling error. If we detected moderate or high heterogeneity ($I^2 > 50\%$), we planned to explore the possible causes (for example, 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 planned to use a fixed-effect model for meta-analysis (as per Cochrane Neonatal policy). Where moderate or high heterogeneity existed, we planned to examine the potential causes in subgroup and sensitivity analyses.

Quality of evidence

We planned to use the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the certainty of evidence for the primary outcomes (Appendix 3). We planned

to use the GRADEpro GDT Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence.

Subgroup analysis and investigation of heterogeneity

We planned these analyses of trials to assess subgroup differences for:

- (i) 'term' formula milk (up to 72 kCal/100 mL) or (ii) 'preterm' formula milk (> 72 kCal/100 mL) versus maternal breast milk;
- formula versus (i) unfortified or (ii) nutrient-fortified maternal breast milk.

RESULTS

Description of studies

We did not find any studies that fulfilled the eligibility criteria. We excluded nine studies (Characteristics of excluded studies). Six were not randomised trials on review of the full text (Carey 1987; Greer 1988; Lucas 1990; Armand 1996; O'Connor 2003; Marseglia 2014). One was a trial of early versus later use of breast milk (Tewari 2018). Two studies were excluded because the infants were allocated to receive formula versus a mixture of maternal and donor breast milk (Narayanan 1982; Svenningsen 1982).

Risk of bias in included studies

We were unable to assess risk of bias as there were no eligible trials.

Effects of interventions

We were not able to calculate the effects of interventions as there were no eligible trials.

DISCUSSION

Summary of main results

We did not identify any randomised controlled trials of formula versus maternal breast milk for feeding preterm or low birth weight (LBW) infants. This is likely to be due to reluctance of families, clinicians, caregivers, and researchers to assess an intervention that results in infants not receiving the immuno-nutritional benefits of breast milk (Walsh 2019). Observational studies have found higher rates of necrotising enterocolitis in infants fed formula compared with maternal breast milk (Lucas 1990; Battersby 2017). Meta-analysis of data from randomised controlled trials indicates that feeding with formula, compared with donor breast milk, leads to higher rates of feed intolerance and necrotising enterocolitis in preterm infants (Quigley 2018). Since maternal breast milk contains higher levels of putative immuno-protective factors (secretory IgA, lysozyme, lactoferrin, epidermal growth factors) than donor breast milk, it is plausible that feeding with maternal breast milk will have the same or greater protective effect. Furthermore, if there is concern regarding the nutritional adequacy of maternal breast milk, infants can receive supplemental nutrition via multicomponent fortification although it is uncertain if this compromises the non-nutritional benefits of breast milk (Brown 2016). In resource-poor countries, where the risk of infection in the neonatal period is much higher than in resource-rich countries, the anti-infective properties of maternal breast milk might confer further advantages for preterm or LBW infants. In India, a randomised trial in LBW infants "at risk of infection" found that serious infections (diarrhoea, pneumonia, septicaemia) were less common in infants allocated to receive "expressed human milk" versus formula (Narayanan 1982). "Expressed human milk" in this trial referred to a mixture of maternal and donor breast milk. As these could not be separated into subgroups, the data could not be included in the review.

Potential biases in the review process

The main concern with the review process is the possibility that we did not detect trials that are not indexed in the major bibliographic electronic databases. We attempted to minimise this threat by screening the reference lists of included trials and related reviews and searching the proceedings of the major international perinatal conferences to identify trial reports that are not published in full form in academic journals. However, we cannot be sure whether other trials have been undertaken, but not reported or indexed, and the concern remains that unpublished trials are not likely to have detected statistically significant or clinically important effects.

Agreements and disagreements with other studies or reviews

We did not identify another systematic review of randomised controlled trials of feeding preterm or VLBW infants with formula versus maternal breast milk.

AUTHORS' CONCLUSIONS

Implications for practice

There are no data from randomised controlled trials to determine whether feeding preterm or LBW infants with formula versus maternal breast milk affects growth, development, or other important outcomes. Maternal breast milk remains the default choice of nutrition for feeding preterm or LBW infants because of its putative immuno-nutrient advantages, and because nutrient fortification of breast milk can address concerns about nutrient content and growth rates.

Implications for research

Mothers who wish to breast feed, and their health care advisors, would require very clear evidence that feeding with formula had major advantages for their infants before electing not to feed (or to reduce feeding) with maternal breast milk. It is unlikely that equipoise exists amongst families, mothers, clinicians and caregivers to undertake such a trial. Data from observational studies, and meta-analyses of trials that compared feeding with formula milk versus donor breast milk, suggest that feeding with breast milk has important advantages for preterm or LBW infants.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Armand 1996	Not randomised
Carey 1987	Not randomised
Greer 1988	Not randomised
Lucas 1990	Not randomised
Marseglia 2014	Not randomised
Narayanan 1982	Human-milk-fed infants received a mixture of maternal and donor breast milk
O'Connor 2003	Not randomised
Svenningsen 1982	Control group received maternal and donor breast milk
Tewari 2018	Randomised trial of early versus late feeding of very preterm infants with breast milk

APPENDICES

Appendix 1. Electronic search strategy

Milk or formula search strategies

Database	Date of search	Results	Results after deduplication
MEDLINE (Ovid)	1 October 2018	2537	2480
Embase (Ovid)	1 October 2018	2947	1471
Maternity and Infant Care (Ovid)	1 October 2018	2336	1068
CINAHL Plus (Ebsco)	21 September 2018	2770	1505
CENTRAL (Wiley)	1 October 2018	1875	449

(*Continued*)

total	12465	6973

MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily
via Ovid (ovidsp.ovid.com)
1946 to 28 September 2018
Searched on: 1 October 2018
Records retrieved: 2537
1 exp Infant, Premature/ (51111)
2 exp Infant, Low Birth Weight/ (31685)
3 Premature Birth/ (11274)
4 (preterm or preterms or pre term or pre terms).ti,ab. (65706)
5 (preemie$ or premie or premies).ti,ab. (150)
6 prematur$.ti,ab. (131848)
7 (low adj3 (birthweight$ or birth weight$)).ti,ab. (31674)
8 (lbw or vlbw or elbw).ti,ab. (7485)
9 or/1-8 (219368)
10 Infant Formula/ (3933)
11 formula$.ti,ab. (277253)
12 10 or 11 (278195)
13 9 and 12 (4365)
14 Milk, Human/ (17874)
15 Milk Banks/ (422)
16 (breastmilk$ or milk$).ti,ab. (116057)
17 or/14-16 (119637)
18 9 and 17 (5756)
19 13 or 18 (8298)
20 randomized controlled trial.pt. (468895)
21 controlled clinical trial.pt. (92668)
22 randomized.ab. (422504)
23 placebo.ab. (192035)
24 drug therapy.fs. (2050146)
25 randomly.ab. (297839)
26 trial.ab. (440111)
27 groups.ab. (1836626)
28 or/20-27 (4287670)
29 exp animals/ not humans/ (4499073)
30 28 not 29 (3706627)
31 19 and 30 (2537)

Embase
via Ovid (ovidsp.ovid.com)
1974 to 28 September 2018
Searched on: 1 October 2018
Records retrieved: 2947
1 prematurity/ (89190)
2 exp low birth weight/ (54784)
3 (preterm or preterms or pre term or pre terms).ti,ab. (90499)
4 (preemie$ or premie or premies).ti,ab. (224)
5 prematur$.ti,ab. (168322)
6 (low adj3 (birthweight$ or birth weight$)).ti,ab. (39175)

7 (lbw or vlbw or elbw).ti,ab. (10058)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (288691)
9 artificial milk/ (12531)
10 formula$.ti,ab. (344884)
11 9 or 10 (348727)
12 8 and 11 (6305)
13 breast milk/ (24259)
14 milk bank/ (110)
15 (breastmilk$ or milk$).ti,ab. (125678)
16 or/13-15 (130935)
17 8 and 16 (7348)
18 12 or 17 (11077)
19 randomized controlled trial/ (513947)
20 controlled clinical trial/ (457995)
21 Random$.ti,ab. (1330412)
22 randomization/ (79416)
23 intermethod comparison/ (238126)
24 placebo.ti,ab. (275734)
25 (compare or compared or comparison).ti. (459192)
26 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (1792923)
27 (open adj label).ti,ab. (65919)
28 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. (209762)
29 double blind procedure/ (153064)
30 parallel group$1.ti,ab. (22153)
31 (crossover or cross over).ti,ab. (93846)
32 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. (287519)
33 (assigned or allocated).ti,ab. (337932)
34 (controlled adj7 (study or design or trial)).ti,ab. (299382)
35 (volunteer or volunteers).ti,ab. (225794)
36 human experiment/ (413882)
37 trial.ti. (251429)
38 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 (4358702)
39 (rat or rats or mouse or mice or rodent or rodents or swine or porcine or murine or sheep or lamb or lambs or ewe or ewes or pig or pigs or piglet or piglets or sow or sows or rabbit or rabbits or cat or cats or kitten or kittens or dog or dogs or puppy or puppies or monkey or monkeys or horse or horses or foal or foals or equine or calf or calves or cattle or heifer or heifers or hamster or hamsters or chicken or chickens or livestock or panda or pandas or buffalo$ or baboon$).ti. (2142499)
40 38 not 39 (4076303)
41 18 and 40 (2947)

Maternity & Infant Care Database (MIDIRS)

via Ovid (ovidsp.ovid.com)
1971 to August 2018
Searched on: 1 October 2018
Records retrieved: 2336
1 (preterm or preterms or pre term or pre terms).mp. (24799)
2 (preemie$ or premie or premies).mp. (52)
3 prematur$.mp. (22144)
4 (low adj3 (birthweight$ or birth weight$)).mp. (11391)
5 (lbw or vlbw or elbw).mp. (2911)
6 1 or 2 or 3 or 4 or 5 (39839)
7 formula$.mp. (6112)
8 6 and 7 (1052)
9 (breastmilk$ or milk$).mp. (8742)

10 6 and 9 (1857)
11 8 or 10 (2336)

CINAHL Complete

via Ebsco (www.ebsco.com/products/research-databases)
Inception to 20180919
Searched on: 21 September 2018
Records retrieved: 2770
S1 (MH "Infant, Premature") 18,840
S2 (MH "Infant, Low Birth Weight+") 11,604
S3 TI (preterm or preterms or pre-term or pre-terms) OR AB (preterm or preterms or pre-term or pre-terms) 24,932
S4 TI (preemie* or premie or premies) OR AB (preemie* or premie or premies) 254
S5 TI prematur* OR AB prematur* 23,780
S6 TI (low N3 (birthweight* or birth-weight*)) OR AB (low N3 (birthweight* or birth-weight*)) 9,526
S7 TI (lbw or vlbw or elbw) OR AB (lbw or vlbw or elbw) 2,560
S8 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 57,624
S9 (MH "Infant Formula") 3,535
S10 TI formula* OR AB formula* 36,707
S11 S9 OR S10 38,406
S12 S8 AND S11 1,355
S13 (MH "Milk, Human+") 4,886
S14 (MH "Milk Banks") 434
S15 TI (breastmilk* or milk*) OR AB (breastmilk* or milk*) 13,874
S16 S13 OR S14 OR S15 15,557
S17 S8 AND S16 2,069
S18 S12 OR S17 2,817
S19 TI (rat or rats or mouse or mice or hamster or hamsters or dog or dogs or cat or cats or sheep or lamb or lambs or pig or pigs or baboon*) 64,810
S20 S18 not S19 2,770

CENTRAL

via Wiley (www.wiley.com)
Issue 9 of 12, September 2018
Searched on: 1 October 2018
Records retrieved: 1875
#1 MeSH descriptor: [Infant, Premature] explode all trees 3387
#2 MeSH descriptor: [Infant, Low Birth Weight] explode all trees 2036
#3 MeSH descriptor: [Premature Birth] this term only 1028
#4 (preterm or preterms or pre next term or pre next terms):ti,ab,kw 10114
#5 (preemie* or premie or premies):ti,ab,kw 34
#6 prematur*:ti,ab,kw 18080
#7 (low near/3 (birthweight* or birth next weight*)):ti,ab,kw 4473
#8 (lbw or vlbw or elbw):ti,ab,kw 1377
#9 {OR #1-#8} 23404
#10 MeSH descriptor: [Infant Formula] this term only 531
#11 formula*:ti,ab,kw 30754
#12 #10 or #11 30754
#13 #9 and #12 1252
#14 MeSH descriptor: [Milk, Human] this term only 926
#15 MeSH descriptor: [Milk Banks] this term only 5
#16 (breastmilk* or milk*):ti,ab,kw 8086
#17 #14 or #15 or #16 8086
#18 #9 and #17 1339
#19 #13 or #18 2017

#20 #13 or #18 in Trials 1875

Appendix 2. '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 randomisation; 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 class 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 class 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 in 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 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 a 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 or 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;
- unclear risk.

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

Appendix 3. GRADE

GRADE considers that evidence from randomised controlled trials is high quality, but that assessment may be downgraded based on consideration of any of five areas.

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

This results in an assessment of the quality of a body of evidence in one of four grades.

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

WHAT'S NEW

Date	Event	Description
2 July 2019	New citation required but conclusions have not changed	No trials identified. Conclusions are unchanged.
2 July 2019	New search has been performed	Search updated in October 2018.

HISTORY

Protocol first published: Issue 1, 2001

Review first published: Issue 3, 2001

Date	Event	Description
12 June 2008	Amended	Converted to new review format.
9 July 2007	New search has been performed	This review updates the review "Formula milk versus preterm human milk for feeding preterm or low birth weight infants" published in The Cochrane Library, Issue 3, 2001 (Henderson 2001). In this update, the structure of the review has been revised in the following manner: 1. The comparison description is now "formula milk versus maternal breast milk." A companion review addresses the comparison of "formula milk versus donor breast milk" (Quigley 2007). 2. The inclusion criteria includes trials that compared feeding with formula versus maternal breast milk as a sole diet or as a supplement to formula milk (previous review restricted to sole diet). No eligible trials were identified on updated search. The previous review had identified a trial that compared feeding with formula milk versus donor preterm milk. This trial is no longer eligible for inclusion but is now included in the companion review of "formula milk versus donor breast milk" (Quigley 2007)
9 July 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

William McGuire (WM) and Mary Anthony developed the protocol and undertook the original review in 2000. Ginny Henderson and WM updated the review in 2003 and 2007. Jennifer Brown and Verena Walsh updated the review in 2019.

DECLARATIONS OF INTEREST

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In order 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, Dr. Mohan Pammi, was the Sign-off Editor for this review. A Senior Editor from the Cochrane Children and Families Network, Robert Boyle, assessed and signed off on this Cochrane Review.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

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

INDEX TERMS

Medical Subject Headings (MeSH)

*Enteral Nutrition; *Infant Food; *Infant, Low Birth Weight; *Infant, Premature; *Milk, Human; Growth

MeSH check words

Humans; Infant, Newborn