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[Intervention Protocol]

Nutrient-enriched formula versus standard formula milk for preterm infants

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To compare the effects of feeding with nutrient-enriched formula versus standard formula on growth and development of preterm infants.

BACKGROUND

Description of the condition

Preterm infants (born before 37 weeks' gestation), especially very preterm infants (born before 32 weeks), have limited nutrient reserves at birth and are subject to physiological and metabolic stresses that increase their nutrient needs. Recommended nutrient requirements for preterm infants based on intrauterine growth studies assume that the optimal rate of postnatal growth should be similar to that of uncompromised foetuses of an equivalent gestational age (Tsang 1993). However, there is evidence that these recommended levels of nutrient input and growth are rarely achieved: Most very preterm infants accumulate substantial energy, protein, mineral, and other nutrient deficits during their initial hospital stay (Embleton 2001; Horbar 2015). By the time they are ready to go home, typically at around 36 to 40 weeks' postmenstrual age, many infants are growth-restricted relative to their term-born peers (Clark 2003; Dusick 2003). Growth deficits, which can persist through childhood and adolescence, are associated with a higher risk of neurodevelopmental impairment and with poorer cognitive and educational outcomes (Hack 1991; Ford 2000; Cooke 2003; Farooqi 2006; Trebar 2007; Bracewell 2008; Leppänen 2014). Preterm infants who have accumulated mineral deficits have higher risks of metabolic bone disease and slower skeletal growth compared with infants born at term. Some uncertainty remains about long-term effects of such deficits on bone mass and health (Fewtrell 2011). Furthermore, there is concern that nutritional deficiency and growth restriction during early infancy may have consequences for long-term metabolic and cardiovascular health (Embleton 2013; Lapillonne 2013).

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Description of the intervention

Human breast milk is the recommended form of enteral nutrition for preterm infants (AAP 2012). When sufficient human breast milk is not available, an artificial formula, either as the sole form of enteral nutrition or as a supplement to human breast milk, may be used as an alternative (Klingenberg 2012). A variety of formulas, typically adapted from cow milk, are available. These vary in energy, protein, and mineral content and can broadly be categorised as follows.

- Standard ('term') formulas based on the composition of mature breast milk; the typical energy content is 67 kCal/100 mL to 70 kCal/100 mL, the concentration of protein is about 1.4 to 1.7 g/100 mL, and the calcium and phosphate content are about 50 mg/100 mL and 30 mg/100 mL, respectively.
- Nutrient-enriched ('preterm') formulas, designed to provide nutrient intakes to match intrauterine accretion rates; these are energy-enriched (typically to about 75 to 80 kCal/100 mL), protein-enriched (2.0 to 2.4 g/100 mL) and variably enriched with minerals, vitamins, electrolytes and trace elements (Hay 2017).

How the intervention might work

Feeding preterm infants with formula enriched with energy, protein, minerals, and other nutrients may be expected to promote nutrient accretion and growth (increase in weight, length, and head circumference). Higher levels of nutrient intake during this critical period may be especially important for infants who are growth-restricted or 'small for gestation' at birth, are unable to consume large quantities of milk, have slow postnatal growth, or have additional nutritional and metabolic requirements (Klein 2002; Agostoni 2010).

Formula with higher nutrient density might, however, interfere with gastric emptying and intestinal peristalsis, or perturb the microbiome, resulting in enteral feed intolerance or increasing the risk of necrotising enterocolitis (Hancock 1984; Siegel 1984; Ramani 2013; Embleton 2017; Shulhan 2017). If nutrient-enriched formula is poorly tolerated, this may reduce intake and any putative benefit for growth and development. Furthermore, concern exists that rapid 'catch-up growth' with accelerated weight gain might be associated with altered fat distribution and related 'programmed' metabolic consequences that increase the long-term risk of insulin resistance and cardiovascular disease (Doyle 2004; Euser 2005; Euser 2008).

Why it is important to do this review

Given that early enteral nutrition strategies may affect growth and development in preterm infants, and that uncertainty exists about the balance between possible benefits and harms, this Cochrane Review aims to detect, appraise, and synthesise evidence from randomised controlled trials (RCTs) to inform policy, practice, and research.

This review will focus on the effect of feeding preterm infants with nutrient-enriched formula versus standard formula during the initial hospitalisation after birth. Related Cochrane Reviews have assessed the effect of feeding preterm infants with nutrient-enriched formula versus standard formula after discharge from hospital (Young 2016), and of multi-nutrient fortification of human milk for feeding preterm infants (Brown 2016).

OBJECTIVES

To compare the effects of feeding with nutrient-enriched formula versus standard formula on growth and development of preterm infants.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or quasi-RCTs.

Types of participants

Preterm infants (less than 37 weeks' gestation at birth) fed formula (exclusively or as a supplement to human breast milk) during birth hospitalisation.

Types of interventions

- Nutrient-enriched formula: both energy content > 72 kcal/100 mL and protein content > 1.7 g/100 mL

versus

- Standard formula: both energy content ≤ 72 kcal/100 mL and protein content ≤ 1.7 g/100 mL

The formula could be fed as the sole diet or as a supplement to human breast milk. Infants in trial groups should have received similar care other than the type of formula. The intervention should have been intended to continue for at least two weeks to allow measurable effects on growth.

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Types of outcome measures

Primary outcomes

Growth

- Time to regain birth weight and subsequent rates of weight gain, linear growth, head growth, or skinfold thickness growth up to six months post-term.
- Long-term growth: weight, height, or head circumference (or proportion of infants who remain below the 10th percentile for the index population's distribution, or both), assessed at intervals from six months post-term.

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 Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) main domains (cognitive, motor, language).
- Cognitive and educational outcomes in children aged at or more than five years old.

Necrotising enterocolitis

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

- Duration of birth hospitalisation (days).
- Feed intolerance during the trial intervention period that results in cessation in enteral feeding for > 4 hours.
- All-cause mortality before hospital discharge.
- Measures of body composition (lean/fat mass) and growth parameters including z-score of weight, length, and head circumference, skinfold thickness, body mass index, and proportion of infants who remain < 10th percentile for the index population distribution of weight, length, or head circumference at 44 weeks' postmenstrual age and beyond.
- Measures of bone mineralisation, such as serum alkaline phosphatase level, or bone mineral content assessed by dual energy x-ray absorptiometry (DEXA) at 44 weeks' postmenstrual age and beyond.
- Measures of long-term metabolic or cardiovascular health, including insulin resistance, obesity, diabetes, and hypertension.

Search methods for identification of studies

We will use the standard search strategy of Cochrane Neonatal.

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL, 2018, current issue), Ovid MEDLINE (1946 to date), OVID Embase (1974 to date), OVID Maternity & Infant Care Database (1971 to date), and the Cumulative Index to Nursing and Allied Health Literature (1982 to date) using a combination of text words and MeSH terms described in Appendix 1. We will limit the search outputs with the relevant search filters for clinical trials as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We will not apply any language restrictions.

We will search ClinicalTrials.gov (http://clinicaltrials.gov/), the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/ictrp/en/), and national trial registries (such as www.anzctr.org.au/) for completed or ongoing trials. We will pilot test the proposed search terms to ensure capture of known trials.

Searching other resources

We will examine the references provided in studies identified as potentially relevant. We will search the abstracts from annual meetings of the Pediatric Academic Societies (1993 to 2018), the European Society for Pediatric Research (1995 to 2018), the UK Royal College of Paediatrics and Child Health (2000 to 2018), and the Perinatal Society of Australia and New Zealand (2000 to 2018). We will considered trials reported only as abstracts to be eligible if sufficient information is available from the report, or from contact with study authors, to fulfil the inclusion criteria.

Data collection and analysis

We will use the standard methods of Cochrane Neonatal.

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Selection of studies

We will screen the title and abstract of all studies identified by the above search strategy and two review authors (VW and JVEB) will independently assess the full articles for all potentially relevant trials. We will discuss any disagreements until consensus is achieved. We will exclude studies that do not meet all of the inclusion criteria and will list all studies excluded after full-text assessment and their reason for exclusion in a 'Characteristics of excluded studies' table. We will illustrate the study selection process in a PRISMA diagram.

Data extraction and management

Two review authors (VW and JVEB) will independently extract data using a form to aid extraction of information on design, methodology, participants, interventions, outcomes, and treatment effects from each included study. We will discuss any disagreements until we reach a consensus.

Assessment of risk of bias in included studies

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

- 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.

See Appendix 2 for a description of each domain.
We will resolve disagreements by discussion or by consulting a third review author (WM or NDE). We will not exclude trials on the basis of risk of bias, but we will conduct sensitivity analyses if applicable to explore the consequences of synthesising evidence of variable quality.

Measures of treatment effect

We will analyses the treatment effects in the individual trials and will report risk ratio (RR) and risk difference (RD) values for dichotomous data and mean difference (MD) values for continuous data, with respective 95% confidence intervals (CI). We will determine the number needed to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH) for analyses with a statistically significant difference in the RD.

Unit of analysis issues

The unit of analysis will be the participating infant.

Dealing with missing data

Where data are missing without explanation, and cannot be derived as described, we will approach the analysis as follows.

- We will contact the original study investigators to request the missing data.
- Where possible, we will impute missing standard deviations (SDs) using the coefficient of variation (CV) or calculate from other available statistics including standard errors, confidence intervals, t values, and P values.
- If the data are assumed to be missing at random, we will analyse the data without imputing any missing values.
- If this cannot be assumed then we will impute the missing outcomes with replacement values assuming all to have a poor outcome and conduct sensitivity analyses to assess any changes in the direction or magnitude of effect resulting from data imputation.

Assessment of heterogeneity

Two review authors (NDE and WM) will assess clinical heterogeneity, and will conduct a meta-analysis only when both review authors agree that study participants, interventions, and outcomes are sufficiently similar.
We will examine the treatment effects of individual trials and heterogeneity between trial results by inspecting the forest plots. We will 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 detect high levels of heterogeneity (I^2 statistic > 75%), we will explore the possible sources (for example, differences in study design, participants, interventions or completeness of outcome assessments).

Assessment of reporting biases

If we include more than 10 trials in a meta-analysis, we will examine a funnel plot for asymmetry.

Data synthesis

We will use the fixed-effect model in Review Manager 5 (RevMan 5) for meta-analyses to estimate the typical RR, RD, or MD with 95% CIs (RevMan 2014). Where substantial heterogeneity exists, we will examine the potential causes in subgroup and sensitivity analyses.

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Summary of findings and certainty of evidence

We will assess the certainty of the body of evidence for the main comparisons at the outcomes level using the GRADE approach (Schünemann 2013; see Appendix 3). Two review authors (VW and JVEB) will independently assess the certainty of the evidence for outcomes identified as critical or important for clinical decision-making: growth, development, and necrotising enterocolitis. We will consider evidence from RCTs as high-certainty evidence but will downgrade the certainty of the evidence by one level for serious (or two levels for very serious) limitations based upon: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We will use the GRADEpro Guideline Development Tool (GDT) to create a 'Summary of findings' table to report the certainty of the evidence (GRADEpro GDT 2015).

Subgroup analysis and investigation of heterogeneity

Where data are available, we will undertake the following subgroup analyses.

- Trials in which infants received formula only versus those where formula could be given as a supplement to breast milk.
- Extremely preterm (< 28 weeks' gestation) infants versus infants born at 29 to 36 weeks' gestation.
- Infants with birth weight < 10th percentile for reference population ('small for gestation') versus infants with birth weight ≥ 10th percentile ('appropriate for gestation').

Sensitivity analysis

We will undertake sensitivity analyses to determine if the findings are affected by including only studies of adequate methodology (low risk of bias), defined as adequate randomisation and allocation concealment, blinding of intervention and measurement, and less than 10% loss to follow-up.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Electronic search strategy

Indicative strategy developed and tested for Ovid MEDLINE®

To be adapted for Embase, Maternity & Infant Care Database (MIDIRS), and CINAHL Plus
1 exp Infant, Newborn/
2 Premature Birth/
3 (neonat$ or neo nat$).ti,ab.
4 (newborn$ or new born$ or newly born$).ti,ab.
5 (preterm or preterms or pre term or pre terms).ti,ab.
6 (preemie$ or premie or premies).ti,ab.
7 (prematur$ adj3 (birth$ or born or deliver$)).ti,ab.
8 (low adj3 (birthweight$ or birth weight$)).ti,ab.
9 (lbw or vlbw or elbw).ti,ab.
10 infan$.ti,ab.
11 (baby or babies).ti,ab.
12 or/1-11
13 Infant Formula/
14 (infant$ adj2 formula$).ti,ab.
15 (enrich$ adj2 formula$).ti,ab.
16 (supplement$ adj2 formula$).ti,ab.
17 (fortif$ adj2 formula$).ti,ab.
18 ((nutrient$ or micronutrient$) adj2 formula$).ti,ab.
19 (energy adj2 formula$).ti,ab.
20 (protein$ adj2 formula$).ti,ab.
21 (pediatric adj2 formula$).ti,ab.
22 (paediatric adj2 formula$).ti,ab.
23 ((baby or babies) adj2 formula$).ti,ab.
24 (formula$ adj2 milk).ti,ab.
25 ((preterm or pre-term or premature) adj2 formula$).ti,ab.

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26 (low birthweight adj2 formula$).ti,ab.
27 (low birth-weight adj2 formula$).ti,ab.
28 ((lbw or vlbw or elbw) adj2 formula$).ti,ab.
29 ((term or standard) adj formula$).ti,ab.
30 or/13-29
31 Nutriprem.ti,ab.
32 Enfamil premature.ti,ab.
33 Similac special care.ti,ab.
34 Aptamil preterm.ti,ab.
35 Good Start premature.ti,ab.
36 Preemie SMA.ti,ab.
37 or/31-36
38 30 or 37
39 12 and 38
40 randomized controlled trial.pt.
41 controlled clinical trial.pt.
42 randomized.ab.
43 placebo.ab.
44 drug therapy.fs.
45 randomly.ab.
46 trial.ab.
47 groups.ab.
48 or/40-47
49 exp animals/ not humans/
50 48 not 49
51 39 and 50

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 will categorise the method used to generate the allocation sequence as follows.

- 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).
- Unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?
For each included study, we will categorise the method used to conceal the allocation sequence as follows.

- 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).
- 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 will categorise the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorise the methods as follows.

- Low risk, high risk, or unclear risk for participants.
- 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 will categorise the methods used to blind outcome assessment. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorise the methods as:

- Low risk for outcome assessors.

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

- Low risk (< 20% missing data).
- High risk (≥ 20% missing data).
- Unclear risk.

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

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

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

- Low risk.
- High risk.
- Unclear risk.

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

Appendix 3. GRADE

The GRADE approach generates an assessment of the certainty of a body of evidence to 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 of effect.

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WHAT'S NEW

Date	Event	Description
17 April 2019	New citation required and major changes	Protocol re-written by new author team.

HISTORY

Protocol first published: Issue 2, 2003

Date	Event	Description
20 March 2019	Amended	Protocol re-written by new author team to update and supersede Simmer 2003.

CONTRIBUTIONS OF AUTHORS

All authors contributed to developing and writing the protocol, and approved the final protocol version.

DECLARATIONS OF INTEREST

Nicholas Embleton has conducted research with support from manufacturers of infant formula including Nestec SA (Switzerland), Wyeth UK, and Nutricia UK but did not receive any payment, support, or benefit in kind for contribution to this review.

VW has no conflicts of interest.

JB has no conflicts of interest.

LA has no conflicts of interest.

WM has no conflicts of interest.

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