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Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD004862.

DOI: 10.1002/14651858.CD004862.pub2.

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[Intervention Review]

Nutrient-enriched formula milk versus human breast milk for preterm infants following hospital discharge

Ginny Henderson², Tom Fahey³, William McGuire¹

¹Department of Paediatrics and Child Health, Australian National University Medical School, Canberra, Australia. ²School of Nursing and Midwifery, Griffith University, South Brisbane, Australia. ³Department of Family Medicine and General Practice, Royal College of Surgeons in Ireland Medical School, Dublin, Ireland

Contact address: William McGuire, Department of Paediatrics and Child Health, Australian National University Medical School, Canberra Hospital Campus, Canberra, ACT 2606, Australia. william.mcguire@act.gov.au.

Editorial group: Cochrane Neonatal Group.

Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.

Review content assessed as up-to-date: 12 July 2007.

Citation: Henderson G, Fahey T, McGuire W. Nutrient-enriched formula milk versus human breast milk for preterm infants following hospital discharge. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD004862. DOI: 10.1002/14651858.CD004862.pub2.

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ABSTRACT

Background

Preterm infants are often growth-restricted at hospital discharge. Feeding infants after hospital discharge with nutrient-enriched formula milk instead of human breast milk might facilitate “catch-up” growth and improve development.

Objectives

To determine the effect of feeding nutrient-enriched formula compared with human breast milk on growth and development of preterm infants following hospital discharge.

Search methods

The standard search strategy of the Cochrane Neonatal Review Group was used. This included searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2007), MEDLINE (1966 - May 2007), EMBASE (1980 - May 2007), CINAHL (1982 - May 2007), conference proceedings, and previous reviews.

Selection criteria

Randomised or quasi-randomised controlled trials that compared feeding preterm infants following hospital discharge with nutrient-enriched formula compared with human breast milk.

Data collection and analysis

The standard methods of the Cochrane Neonatal Review Group were used, with separate evaluation of trial quality and data extraction by two review authors.

Main results

No eligible trials were identified.

Authors' conclusions

There are no data from randomised controlled trials to determine whether feeding preterm infants following hospital discharge with nutrient-enriched formula milk versus human breast milk affects growth and development. Mothers who wish to breast feed, and their health care advisors, would require very clear evidence that feeding with a nutrient-enriched formula milk had major advantages for their infants before electing not to feed (or to reduce feeding) with maternal breast milk. If evidence from trials that compared feeding preterm infants following hospital discharge with nutrient-enriched versus standard formula milk demonstrated an effect on growth or development, then this might strengthen the case for undertaking trials of nutrient-enriched formula milk versus human breast milk.

PLAIN LANGUAGE SUMMARY

Nutrient-enriched formula milk versus human breast milk for preterm infants following hospital discharge

Preterm infants are often much smaller than term infants by the time that they are discharged home from hospital. This review sought evidence that feeding these infants with nutrient-enriched formula milk rather than breast milk would increase growth rates and benefit development. No trials of this intervention were found. Whether undertaking such trials would be acceptable to mothers of preterm infants is not known.

BACKGROUND

Most preterm infants accumulate significant energy, protein, mineral, and other nutrient deficits by the time of discharge from hospital (Embleton 2001; Lucas 1984; Clark 2003). Although demand-fed preterm infants consume greater volumes of milk than term infants following hospital discharge, growth deficits persist throughout infancy and beyond (Lucas 1992; Morley 2000; Ford 2000). Poor postnatal growth in preterm infants, especially of the head, is associated with an increased risk of neurodevelopmental impairment in later childhood, as well as with poorer cognitive and educational outcomes (Hack 1991; Cooke 2003). Preterm infants who have accumulated deficits in calcium and phosphate by the time of hospital discharge are at increased risk of poor bone mineralisation, metabolic bone disease, and slower skeletal growth compared to infants born at term (Rigo 2000). There has also been concern that nutritional deficiency and growth restriction, both in utero and in early infancy, may have consequences for long-term cardiovascular health (Barker 2002).

There is an opportunity for continued nutritional intervention during the post-hospital discharge period of early infancy (Cooke 2000; Griffin 2002). Nutritional supplementation during this period may be of particular importance for infants with on-going additional metabolic requirements, for example due, to chronic lung disease. Several strategies for increasing nutrient delivery for preterm infants following hospital discharge are available. The effect of multicomponent, nutrient fortification of human breast milk for preterm infants following discharge is addressed in an-

other Cochrane review (McGuire 2007a). The purpose of this review is to determine whether there is any evidence that feeding preterm or low birth weight infants after hospital discharge with a nutrient-enriched formula milk versus human breast milk improves growth and development.

A variety of nutrient-enriched formulae, mainly modified cow milk, are available (Fewtrell 1999). These vary in energy, protein and mineral content and can be categorised broadly as:

1. Preterm formula; energy (about 80 kcal/100 ml) and protein (about 2.0 - 2.4 grams/100ml) -enriched, and variably enriched with minerals, vitamins, and trace elements to support intra-uterine nutrient accretion rates. These milks are often used for nutrition of preterm infants prior to hospital discharge.
2. Post-discharge formula; specifically designed for formula-fed preterm infants following discharge from hospital. These are less nutrient dense compared with preterm formulae, but are energy- (about 72- 74 kcal/100 ml) and protein- (about 1.8 grams/ 100ml) enriched, and variably enriched with minerals, vitamins, and trace elements compared to human breast milk.

Feeding with nutrient-enriched formula milk might be expected to increase nutrient delivery compared to feeding with human breast milk (Gross 1980). However, there are putative non-nutrient benefits of feeding with human milk for mothers and preterm infants. For example, the delivery of immunoglobulins, growth factors, and other immunological mediators to the immature gut mucosa may help with postnatal adaptation, improve feed toler-

ance, and prevent infection (WHO 2001). Feeding with nutrient-enriched formula may also be associated with other adverse effects such as reduced gastric motility and emptying (Hancock 1984; Siegel 1984). Nutrient-enriched formula milk may, therefore, be more poorly tolerated by reducing nutrient delivery and, potentially, removing any benefits for growth and development.

OBJECTIVES

To determine whether feeding preterm infants following hospital discharge with nutrient-enriched formula milk versus human breast milk affects growth and development. Separate comparisons of feeding with nutrient-enriched formula milk versus human breast milk in infants fed formula milk as a sole diet, and as supplement to maternal breast milk were planned.

The following sub-group analyses were pre-specified:

1. Infants of very low birth weight (less than 1.5 kilograms) or who are very preterm at birth (less than 32 weeks)
2. Infants who remain small for gestational age (less than 10th percentile for weight) at hospital discharge
3. Infants with chronic lung disease requiring home supplemental oxygen therapy
4. Trials comparing feeding with nutrient-enriched formula milk versus donated expressed breast milk
5. Trials comparing feeding with nutrient-enriched formula milk versus expressed breast milk fortified with one or more the following components: protein, fat, carbohydrate, or minerals (calcium and/or phosphate)
6. Trials in which infants receive “preterm” formula (energy content between greater than 75 Kcal/100ml and protein content at least 2.0 grams/100ml) versus human breast milk
7. Trials in which infants receive “post-discharge” formula (energy content between 72 and 75 Kcal/100ml and protein content at least 1.6 grams/100ml, but less than 2.0 grams/100ml) versus human breast milk

METHODS

Criteria for considering studies for this review

Types of studies

Controlled trials using random or quasi-random patient allocation. Unpublished studies and studies published only as abstracts

were to be included if assessment of study quality was possible and if other criteria for inclusion were fulfilled.

Types of participants

Preterm infants (less than 37 weeks' gestation) and low birth weight infants (less than 2.5 kilograms) following discharge from hospital.

Types of interventions

Feeding with nutrient-enriched [at least 72 kcal/100 ml and at least 1.6 grams/100ml protein] formula milk versus feeding with human breast milk (either maternal breast milk or donor breast milk). Formula milk may additionally have been enriched with minerals, vitamins and trace elements. The formula milks may have been fed either as sole diet or as a supplement to human milk. No restrictions to the pre-hospital discharge feeding regimes were specified *a priori*. The intervention may have begun up to one week prior to planned discharge from hospital and should have continued for at least two weeks to allow measurable effects on growth. Infants in the groups within each study should have received similar care other than the type of milk. For example, there should not be any within-study differences in the prescription of target levels of volume of intake, or advice or support for demand feeding.

Types of outcome measures

Primary:

1. Long-term growth: Proportion of infants who remain below the tenth percentile for the index population's distribution of weight, height, or head circumference when assessed at 6 - 12 months corrected age, or at 12 - 18 months corrected age, and beyond.
2. Neurodevelopmental outcomes at greater than, or equal to, 12 months of age (corrected for preterm birth) measured using validated assessment tools such as Bayley Scales of Infant Development, and classifications of disability, including auditory and visual disability. Severe neurodevelopmental disability will be defined as any one or combination of the following: non-ambulant cerebral palsy, developmental delay (developmental quotient less than 70), auditory and visual impairment.

Secondary:

1. Growth during the trial period: Weight gain (grams per day, or grams per kilogram per day), linear growth (millimetres per week), head growth (millimetres per week), skinfold thickness growth (millimetres per week).
2. Cognitive and educational outcomes at aged more than five years old: Intelligence quotient and/or indices of educational achievement measured using a validated assessment tool (including school examination results).

3. Measures of bone mineralisation such as serum alkaline phosphatase level, or bone mineral content assessed by dual energy x-ray absorptiometry at the end of the trial period.

4. Feed intolerance such as vomiting or diarrhoea that results in the infant requiring treatment for dehydration (for example, oral rehydration solution, or hospital admission, or intravenous rehydration).

5. Rickets on long term follow-up: Radiological evidence of osteopaenia, metaphyseal cupping or splaying, or fractures. We will not pre-specify a minimum duration of follow up.

6. Body mass index on long-term follow-up (a minimum duration of follow up was not pre-specified).

7. Blood pressure on long term-follow up (a minimum duration of follow up was not pre-specified).

Search methods for identification of studies

The standard search strategy of the Cochrane Neonatal Review Group was used. This consisted of searches of the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2007), MEDLINE (1966 - May 2007), and EMBASE (1980 - May 2007), and CINAHL (1982 - May 2007). The electronic search used the following text words and MeSH terms: [Infant, Newborn OR Infant, Premature OR Infant, Low Birth Weight OR infan* OR neonat*] AND "Infant-Nutrition"/all subheadings OR Milk, Human OR milk OR breast OR fortif* OR supplement*]. The search outputs were limited with the relevant search filters for clinical trials. No language restriction was applied. References in previous reviews and studies were examined. Abstracts presented at the Society for Pediatric Research, European Society for Pediatric Research, the North American Society of Pediatric Gastroenterology and Nutrition, and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition between 1990 and 2006/7 were searched. 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. The UK National Research Register (<http://www.nrr.nhs.uk>), and Current Controlled Trials (<http://www.controlled-trials.com>) websites were searched for completed or ongoing trials.

Data collection and analysis

1. The title and abstract of all studies identified by the above search strategy were screened and the full articles for all potentially relevant trials obtained. The full text of any potentially eligible reports was re-assessed and those studies that did not meet all of the inclusion criteria were excluded. Any disagreements were discussed until consensus was achieved.

2. We planned to use the criteria and standard methods of the Cochrane Neonatal Review Group were used to assess the methodological quality of the trials in terms of allocation concealment,

blinding of parents, carers, and assessors to the intervention, and completeness of assessment in all randomised individuals.

3. We planned to use a data collection form was used to extract relevant information. If data from the trial reports were insufficient, the trialists were contacted for further information.

4. We planned to present outcomes for categorical data were presented as relative risk, risk difference, and number needed to treat. For continuous data, the weighted mean difference (with respective 95% confidence intervals) was presented.

5. We planned to estimate the treatment effects of individual trials and heterogeneity between trial results was examined by inspecting the forest plots and quantifying the impact of heterogeneity in meta-analyses using a measure of the degree of inconsistency in the studies' results (I-squared statistic). If statistical heterogeneity was detected, the possible causes (for example, differences in study quality, participants, intervention regimens, or outcome assessments) were explored using post-hoc sub-group analyses. A fixed effects model was planned for meta-analyses.

RESULTS

Description of studies

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

No studies that fulfilled the eligibility criteria were found. Two studies that appeared to be relevant, but on review of the full text were found not to be randomised controlled trials, were excluded ([Abrams 1988](#); [Wauben 1998](#) see table: Characteristics of excluded studies).

Risk of bias in included studies

No eligible trials were found.

Effects of interventions

No eligible trials were found.

DISCUSSION

No randomised controlled trials of nutrient-enriched formula milk versus human breast milk for feeding preterm infants following hospital discharge were identified. This is likely to be due to reluctance of researchers to assess an intervention that results in young infants stopping (or at least reducing) breast-feeding, especially when this is contrary to the mother's initial choice to establish breast-feeding. If nutrient input during the period of early

infancy following hospital discharge is important in determining long-term growth and developmental outcomes, it may be that the benefits of higher nutrient input outweigh the disadvantages of formula feeding. However, systematic review of trials of nutrient-enriched formula versus standard term formula (which contains about the same level of energy, protein and other nutrients as human breast milk) did not find any clinically important effects on growth or development (McGuire 2007b). A possible explanation for this apparent paradox is that ad libitum fed infants adjust their intake to the energy content of the formula and consume lower volumes of nutrient-enriched formula than standard term formula. Therefore, it is plausible that feeding infants ad libitum with nutrient-enriched formula rather than human breast milk would not result in higher levels of nutrient intake.

It may be appropriate to focus research efforts on the subgroup of preterm infants who are not able to feed ad libitum following hospital discharge and who have extra metabolic demands, for example, because of growth-restriction or chronic lung disease. It would be important to determine the acceptability to mothers and health care advisors of undertaking trials of feeding with nutrient-enriched formula, perhaps as a supplement to human breast milk, in this population. Multicomponent fortification of human breast milk may be a preferable strategy for increasing nutrient input for mothers who have established breast-feeding (McGuire 2007a).

Finally, considerable uncertainty exists with regard to the effect of growth status during fetal life and early infancy on long term health. A recent systematic appraisal of observational studies did not find evidence to support a strong association between fetal

growth and cardiovascular health in later life (Huxley 2002). Similarly, although rapid “catch-up” growth has been proposed as a potential contributor to a “metabolic syndrome” that results in long term adverse cardiovascular outcomes, current evidence suggests that any contribution of diet in early infancy to long-term outcomes of preterm infants is likely to be very small (discussed by Greer 2007).

AUTHORS' CONCLUSIONS

Implications for practice

There are no data from randomised controlled trials to determine whether feeding preterm infants following hospital discharge with nutrient-enriched formula milk versus human breast milk affects growth and development. Mothers who wish to breast feed, and their health care advisors, would require very clear evidence that feeding with a nutrient-enriched formula milk had major advantages for their infants before electing not to feed (or to reduce feeding) with maternal breast milk.

Implications for research

If evidence from trials that compared feeding preterm infants following hospital discharge with nutrient-enriched versus standard formula milk demonstrated a clinically important effect on growth or development, then this would strengthen the case for undertaking trials of nutrient-enriched formula milk versus human breast milk.

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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
Abrams 1988	Post-discharge feeding regimens were not randomly allocated.
Wauben 1998	Post-discharge feeding regimens were not randomly allocated.

DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 12 July 2007.

Date	Event	Description
22 August 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 4, 2007

Date	Event	Description
13 July 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

William McGuire and Tom Fahey developed the protocol. Ginny Henderson and William McGuire undertook the electronic and hand searches, screened the title and abstract of all studies identified, and the full text of potentially relevant reports, and completed the final review.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Tayside Institute of Child Health, Ninewells Hospital and Medical School, Dundee, UK.
- Tayside Institute for General Practice, Ninewells Hospital and Medical School, Dundee, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant Formula; *Milk, Human; Infant, Low Birth Weight [*growth & development]; Infant, Newborn; Infant, Premature [*growth & development]; Patient Discharge

MeSH check words

Humans