Prebiotic supplementation of formula in preterm neonates: a systematic review and meta-analysis of randomised controlled trials

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CRD summary
The authors concluded that prebiotic supplemented formula for pre-term infants increased stool colony counts of bifidobacteria and lactobacilli without adversely affecting weight gain, but due to limited evidence it could not be recommended as routine. This was a generally well-conducted review, but given the small number of trials and significant heterogeneity, the reliability of the authors’ conclusions is unclear.

Authors’ objectives
To assess the efficacy and safety of prebiotic oligosaccharide supplementation of formula in improving clinical outcomes in pre-term neonates.

Searching
Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL were searched for articles in any language. Search dates varied across sources spanning 1966 to June 2008. Search terms were reported. Bibliographies of identified articles and key reviews were handsearched. The proceedings of the Pediatric Academic Society Meetings and the Pediatric Gastroenterology conferences were searched in July and November 2007. [A: Google and Quil.com were also searched and experts contacted for unpublished data.]

Study selection
Randomised controlled trials (RCT) or quasi-randomised studies of galacto-oligosaccharide and/or fructo-oligosaccharide supplemented formula compared with placebo or unsupplemented formula, continued for at least two weeks, in neonates with gestation less than or equal to 37 weeks at birth, were eligible for inclusion. Randomisation and supplementation had to commence before the corrected gestational age of 40 weeks. Trials were excluded if they compared a combination of prebiotics and probiotics with controls, or if the formula differed in composition between the intervention and the control groups. Primary outcomes eligible for inclusion were incidence of stage two (or above) necrotising enterocolitis, blood culture positive sepsis and weight gain. Secondary outcomes were gut colonisation with enteric pathogenic bacteria, physical characteristics of the stool, stool viscosity, gastrointestinal transit time and feed tolerance.

Included studies were of fructo-oligosaccharide 0.4g daily or galacto-oligosaccharide and fructo-oligosaccharide 0.8g to 1g daily compared with maltodextrin as placebo, supplemented for between 14 and 30 days, in pre-term infants with gestation at birth ranging from 24 weeks to less than 36 weeks.

Two reviewers independently selected the studies for review, with disagreements resolved through discussion with a third reviewer.

Assessment of study quality
The methodological quality of the included trials was assessed using the Jadad scale, which assessed randomisation, blinding and withdrawal or drop-outs, giving a maximum score of 5. Trials with a score of 3 points or above were considered to be good quality.

Two reviewers independently selected the studies for review, with disagreements resolved through discussion with a third reviewer.

Data extraction
For continuous outcomes, the mean and standard deviation of intervention and control groups were extracted and used to calculate the mean difference with 95% confidence intervals (CI). Authors were contacted for additional data.
Two reviewers independently extracted the data, with disagreements resolved through discussion with a third reviewer.

**Methods of synthesis**
Weighted mean differences with 95% CI were calculated using both fixed and random effects models. Statistical heterogeneity was calculated using the $I^2$ statistic. Some outcomes were reported in a narrative synthesis.

**Results of the review**
Four RCTs were included for the review (n=126 infants). Three trials scored 5 points on the Jadad scale, one trial scored 2 points. The sample sizes ranged from 20 to 56 pre-term infants.

**Primary outcomes:** There was no significant difference in weight gain between intervention and control groups (WMD -1.60 g/day, 95% CI -3.76 to 0.57; three RCTs; n=106 infants). There was evidence of moderate to high statistical heterogeneity ($I^2=50.5\%$). Two trials (n=40 infants) reported no incidence of necrotising enterocolitis in any infants enrolled, but the trials were underpowered to assessed the impact of prebiotics on necrotising enterocolitis. No trials assessed the incidence of sepsis.

**Secondary outcomes:** Prebiotic supplementation was associated with a significant increase in bifidobacterial counts (WMD 0.53, 95% CI 0.33 to 0.73; two RCTs, n=86 infants), but there was significant statistical heterogeneity ($I^2=87.2\%$). Meta-analyses were not conducted for any other outcomes. Two trials (n=86 infants) reported that infants receiving prebiotic supplementation had lower colony counts of pathogenic bacteria and had more frequent softer stools compared to controls. One RCT (n=20 infants) reported that infants receiving prebiotic supplemented formula had stools with lower viscosity ($p=0.006$) and more acidity ($p=0.001$). Two RCTs reported no difference between intervention and control groups in the incidence of symptoms of intolerance (n=86 infants) or in gastrointestinal transit time (n=40 infants).

**Authors' conclusions**
Prebiotic supplemented formula for pre-term infants increased stool colony counts of bifidobacteria and lactobacilli without adversely affecting weight gain. However, the available evidence was limited and oligosaccharide supplementation could not be recommended as routine.

**CRD commentary**
The review addressed a clear question and inclusion criteria were well-defined. Several relevant databases were searched for articles in any language, so the risk of language bias was minimised. Some attempts were made to identify unpublished data, minimising the risk of publication bias. Appropriate steps were taken at all stages of the review process to minimise reviewer error and bias. A suitable validity assessment was carried out and the quality of the included trials was generally high. Maltodextrin was used as a comparator, as it was the only agent available that simulated the active pre/probiotic agent, but the absence of a true placebo limited the conclusions that could be drawn. Pooling of results was hampered by the small number and sample sizes of available trials and high levels of statistical heterogeneity between trials; the synthesis may have been better treated wholly as a narrative synthesis. This was a generally well-conducted review, but given the small number of available studies and the high levels of statistical heterogeneity, the reliability of the authors' conclusions is unclear.

**Implications of the review for practice and research**
**Practice:** The authors stated that oligosaccharide supplementation could not be recommended as routine in formula fed pre-term infants.

**Research:** The authors stated that further large scale well-designed RCTs are needed investigating the impact of prebiotic supplementation in preterm neonates on necrotising enterocolitis, sepsis and weight gain with long term follow up. Further research is also needed into oligosaccharide supplementation in pre-term breast-fed infants whose mothers are low or non-secretors of prebiotic oligosaccharides.

**Funding**
Bibliographic details

PubMedID
19359074

DOI
10.1016/j.clnu.2009.03.008

Original Paper URL
http://www.journals.elsevierhealth.com/periodicals/yclnu/article/S0261-5614(09)00070-3/abstract

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Bifidobacterium /growth & development; Enterocolitis, Necrotizing /epidemiology /prevention & control; Feces /microbiology; Gastrointestinal Transit /drug effects; Humans; Infant Formula; Infant, Newborn; Infant, Premature /growth & development; Lactobacillus /growth & development; Oligosaccharides /administration & dosage /adverse effects; Probiotics /administration & dosage /adverse effects; Randomized Controlled Trials as Topic; Sepsis /epidemiology /prevention & control; Weight Gain

AccessionNumber
12009107014

Date bibliographic record published
23/09/2009

Date abstract record published
11/11/2009

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.