Prebiotic supplementation in full-term neonates: a systematic review of randomized controlled trials

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CRD summary
This review concluded that prebiotic supplemented formula milk was well tolerated by full-term infants. It increased stool colony counts of bifidobacteria and lactobacilli, and resulted in stools comparable to breast-fed infants, without affecting weight gain. The overall finding, that routine supplementation should not be recommended without further research, reflected the evidence and should be considered to be reliable.

Authors' objectives
To review the efficacy and safety of prebiotic supplementation in full-term neonates.

Searching
The following databases were searched to May 2008: PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and CINAHL. Search terms were reported. Proceedings of paediatric academic society meetings and paediatric gastroenterology conferences were handsearched. Reference lists and review papers were searched for relevant citations. No language restrictions were applied.

Study selection
Randomised and quasi-randomised controlled trials of full-term neonates, randomised within 28 days of birth that compared formula milk supplemented with prebiotics versus placebo or un-supplemented formula milk, were eligible for inclusion in the review. Supplementation was required to begin within 28 days from birth and continue for at least two weeks. At least one of the following outcome measures had to be reported: stool characteristics, stool colony count of bifidobacteria and lactobacilli, stool colonisation with enteric pathogenic bacteria, weight gain during first year of life, or symptoms of intolerance. Trials that compared a combination of prebiotics and probiotics versus controls, and trials where the intervention formula differed from the control formula were excluded.

Over half of included trials assessed milk supplemented with galactose oligosaccharide-fructose oligosaccharide; the remaining trials compared milk supplemented with galactose oligosaccharides, fructose oligosaccharides, galactose oligosaccharide-fructose oligosaccharide plus acidic oligosaccharide, or a combination of polydextrose, galactose oligosaccharide and lactulose. The concentration of the prebiotics ranged from 0.15 to 0.8g/dL. Control groups received placebo or un-supplemented formula; some trials also included a reference group of breast-fed infants. The duration of supplementation ranged from two weeks to six months. Outcomes reported by the individual trials varied considerably.

Studies were independently selected by two reviewers; any differences were resolved by discussion with a third reviewer.

Assessment of study quality
Validity was assessed using a published scale (Jadad) which rated trials on a 5 point scale according to blinding, randomisation and loss to follow-up.

Trials were independently assessed by two reviewers; any differences were resolved by discussion with a third reviewer.

Data extraction
Data were independently extracted by two reviewers; any differences were resolved by discussion with a third reviewer. Authors were contacted for further data or information where required.

Methods of synthesis
Fixed-effect models were used to calculate weighted mean differences (WMDs) and 95% confidence intervals (CI) for the main outcomes. Random-effects models were used to cross-check these results. Heterogeneity was assessed using the I² statistic. Publication bias was explored using funnel plots.
Results of the review
Eleven RCTs were included in the review (n=1,459 infants); nine were rated as being of good quality (scoring 3 or more out of 5). Sample size ranged from 34 to 297 infants. There was no indication of publication bias.

**Stool colonisation with bifidobacteria and/or lactobacilli:** Nine trials evaluated this outcome, but meta-analysis was not possible due to significant heterogeneity in the methods used to measure and report colony counts. Six trials reported significantly higher levels of bifidobacteria following prebiotic supplementation; the remaining three trials found no significant differences. Two of three trials reporting on lactobacilli counts reported higher levels in the supplemented group.

**Stool colonisation with pathogenic bacteria:** Six trials reported mixed results on this outcome, but no meta-analysis was possible.

**Stool pH:** Eight trials reported on this outcome. Six trials were pooled in a meta-analysis and found a significant reduction in stool pH for children receiving prebiotic supplementation (WMD -0.65, 95% CI -0.76 to -0.54). Significant heterogeneity was noted for this outcome ($I^2=81\%$).

**Stool consistency:** Five trials that assessed this outcome, reported that stools were softer in the prebiotic-supplemented group.

**Stool frequency:** Three trials reported a higher frequency of stools in prebiotic-supplemented infants.

**Physical growth in first year of life:** Nine trials reported this outcome. The four trials that were pooled showed that infants receiving supplemented milk formula had better weight gain (WMD 1.07g, 95% CI 0.14 to 1.99).

**Tolerance:** Seven of eight trials that reported various indicators of tolerance found that prebiotic supplementation was well tolerated. Symptoms evaluated included excessive irritability, crying, regurgitation and vomiting. The one trial that reported some problems with tolerance assessed two different strengths of two different prebiotics; more tolerance problems appeared to occur in the higher strength supplementation group.

Authors’ conclusions
Prebiotic supplemented formula milk was well tolerated by full-term infants. It increased stool colony counts of bifidobacteria and lactobacilli, and resulted in stools comparable to breast-fed infants, without affecting weight gain. Larger trials with long term follow-up are required before routine supplementation can be recommended.

CRD commentary
This review addressed a clear question with appropriate inclusion criteria and fairly comprehensive searches. Appropriate measures were taken to reduce reviewer error and bias throughout.

Trials were assessed for quality. A description of the trials, in terms of interventions, outcomes, and quality assessment, were provided in tables. Meta-analysis appeared to have been used cautiously where there was sufficient homogeneity in study design between primary trials; however, it was not always clear why a narrative approach was adopted for some outcomes. Although statistical heterogeneity was identified for one set of pooled results, it was not explored further. Some of the conclusions appeared to be fairly strong, despite being based on small numbers of trials and few meta-analyses. However, the overall finding that routine supplementation should not be recommended without further research, reflected the evidence and should be considered to be reliable.

Implications of the review for practice and research
**Practice:** The authors recommended that routine supplementation with oligosaccharides should not be considered without further research and consideration of cost.

**Research:** The authors recommend that large population-based trials, with long-term follow-up into adulthood, are required to demonstrate if the short-term benefits related to improved general health.

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