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REVIEW

Supplementation of prebiotics in infant formula

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Background: In recent years prebiotics have been added to infant formula to make it resemble breast milk more closely and to promote growth and development of beneficial intestinal microbiota. This review aims to present new data on the possible positive effects of prebiotics in infant formula on intestinal microbiota (bifidogenic and lactogenic effect) and on clinical outcomes including growth, infections, and allergies. With that aim, a literature search of the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, Scopus, PubMed/Medline, Web of Science, and Science Direct in the last 10 years (December 2003 to December 2013) was performed.

Results: Altogether 24 relevant studies were identified. It was found that during intervention, prebiotics can elicit a bifidogenic and lactogenic effect. As far as clinical outcomes were concerned, 14 studies investigated the effect of infant formula supplemented with prebiotics on growth and found that there was no difference when compared with non-supplemented infant formula. All available data are insufficient to support prebiotic supplementation in order to reduce risk of allergies and infections.

Conclusion: There is currently no strong evidence to recommend routine supplementation of infant formulas with prebiotics. Further well-designed clinical studies with long-term follow-up are needed.

Keywords: prebiotics, infant formula, growth, allergy, infections, supplementation

Introduction

Prebiotics are defined as non-digestible food ingredients that affect the host by selectively targeting growth and/or the activity of one or more bacteria in the colon that can improve health.[1] Breast-fed infants have an intestinal microbiota dominated by *Bifidobacterium* and *Lactobacilus* and this is quite different from the intestinal microbiota of those fed with a standard infant formula.[2,3] Human milk contains substantial quantities of prebiotics, oligosaccharides which undigested reach the colon and selectively serve as an energy source for desired bacteria, dominantly bifidobacteria.[4]

Intestinal microbiota have been considered an important physiological factor for different functions of the gut; most importantly, development of the immune system.[5] In recent years, attempts have been made to make intestinal microbiota in formula-fed infants similar to those found in breast-fed infants, mostly by adding pro- and prebiotics. Human milk oligosaccharides are structurally very complex, have a huge diversity and currently are not available for commercial use.[4] However, several prebiotics have been developed that have a positive effect on the colonization, growth, survival and function of commensal bacteria. Most commonly used prebiotics in infant formulas

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are a mixture of long-chain galacto-oligosaccharides (GOS) and long-chain fructo-oligosaccharides (FOS), both neutral oligosaccharides with proven prebiotic effect.[6]

This review aimed to present available data on the role of prebiotics in infant formula on growth, infection rate and allergies, and on their influence on intestinal microbiota through the bifidogenic and lactogenic effect.

With that aim we performed a literature search which included The Cochrane CENTRAL, EMBASE, Scopus, PubMed/Medline, Web of Science, and Science Direct over the last 10 years (the period from December 2003 to December 2013). All relevant randomized controlled trials (RCT) were included. No other reports – including case series, retrospective trials, crossover trials and uncontrolled trials – were taken into consideration. We included only the studies which were performed on healthy term infants.

Results

Trial characteristics

The most commonly studied prebiotic was a 9:1 mixture of GOS and FOS, following with GOS, acidic oligosaccharides (AOS), combination of GOS, FOS and AOS, polydextrose (PDX) and GOS, PDX/GOS and lactulose (LOS), oligofructose and inulin. The prebiotic concentration ranged from 0.12 to 0.8 g/100 mL. Sample size of included studies varied from 20 to 1,130 infants and duration of intervention from 15 days to 6 months.

Stool colonization with bifidobacteria (bifidogenic effect)

Twelve of the 24 included studies evaluated the effect of prebiotic supplementation on the bifidobacteria in the stools (Table 1). The majority of published studies[7–14] demonstrated significantly higher levels of bifidobacteria after supplementation, while two trials[15,16] reported a higher count of bifidobacteria; however this was not statistically significant. Salvini et al[17] in their small explorative study (sample size 20) reported a long-lasting bifidogenic effect, which continued even 6 months after intervention was stopped. One study looked at the difference in the stool colonies of bifidobacteria in infants fed on prebiotic-supplemented formula and breast-fed infants and found that formula supplemented

Table 1 Prebiotic-supplemented infant formula and bifidogenic effect

Author	N/age	Duration of intervention	Setting	Prebiotic	Effect
Bakker-Zierikzee et al 2005[15]	34/at birth	4 months	Healthy term infants	GOS/FOS 0.6 g/100 mL	Trend toward higher counts in prebiotic group
Costalos et al 2008[16]	160/<14 days	15 days	Healthy term infants, enrolled ≤14 days	GOS/FOS 0.4 g/100 mL	Trend toward higher counts in prebiotic group
Decsi et al 2005[10]	69/at birth	12 weeks	Healthy term infants	GOS/FOS 0.4 g/100 mL	Increased in prebiotic group
Fanaro et al 2005[11]	31/at birth	6 weeks	Healthy term infants	1. GOS/FOS 0.6 g + AOS 0.2 g/100 mL 2. AOS 0.2 g/100 mL	Increased in prebiotic group
Fanaro et al 2009[13]	159/4–6 months	12 weeks	Healthy infants	GOS 0.5 g/100 mL	Increased in prebiotic group
Moro et al 2003[6]	90/at birth	4 weeks	Healthy term infants	GOS/FOS 0.4 and 0.8 g/100 mL	Increased in prebiotic group
Moro et al 2006[12]	206/at birth	6 months	Term infants at high risk for atopy	GOS/FOS 0.8 g/100 mL	Increased in prebiotic group
Ben et al 2004[8]	147/at birth	6 months	Healthy term infants	GOS 0.24 g/100 mL	Increased in prebiotic group
Ben et al 2008[9]	164/at birth	3 months	Term infants; formula feeding within 4 weeks after birth	GOS 0.24 g/100 mL	Increased in prebiotic group
Salvini et al 2011[17]	20/at birth	6 months	Healthy term infants of HCV-positive mothers	GOS/FOS 0.8 g/100 mL	Long-lasting bifidogenic effect
Scalabrin et al 2012[14]	230/21–30 days	60 days	Healthy term infants	GOS + PDX 0.4 g/100 mL	Increased in prebiotic group
Veerman-Wauters et al 2011[18]	110/<5 days	28 days	Healthy term infants	SYN1 0.4 g/100 mL SYN1 0.8 g/100 mL GOS/FOS 0.8 g/100 mL	SYN1 0.8 and GOS/FOS – comparable to breast-fed infants

Abbreviations: GOS, short-chain galacto-oligosaccharides; FOS, long-chain fructo-oligosaccharides; HCV, hepatitis C virus; PDX, polydextrose; AOS, acidic oligosaccharides; SYN1, Synergy1 (consists of 50:50 oligofructose and long-chain inulin).

Table 2 Prebiotic-supplemented infant formula and lactogenic effect

Author	N/age	Duration of intervention	Setting	Prebiotic	Effect
Fanaro et al 2005[11]	31/at birth	6 weeks	Healthy term infants	1. GOS/FOS 0.6 g + AOS 0.2 g/100 mL 2. AOS 0.2 g/100 mL	Increased in prebiotic group
Moro et al 2006[12]	206/at birth	6 months	Term infants at high risk for atopy	GOS/FOS 0.8 g/100 mL	NS
Ben et al 2008[9]	164/at birth	3 months	Term infants; formula feeding within 4 weeks after birth	GOS 0.24 g/100 mL	Increased in prebiotic group
Salvini et al 2011[17]	20/at birth	6 months	Healthy term infants of HCV-positive mothers	GOS/FOS 0.8 g/100 mL	Long-lasting lactogenic effect

Abbreviations: GOS, short-chain galacto-oligosaccharides; FOS, long-chain fructo-oligosaccharides; AOS, acidic oligosaccharides; NS, not significant; HCV, hepatitis C virus.

with prebiotics has a bifidogenic effect comparable to that of breast milk.[18]

Stool colonization with lactobacilli (lactogenic effect)

As for the lactogenic effect, we identified only four studies that evaluated the prebiotic effect on the counts of lactobacilli colonies (Table 2). All studies presented the data as actual colony counts per gram of stool. Three studies[6,9,18] reported higher levels of lactobacilli in the stool after prebiotic supplementation; in contrast, Moro et al[12] found no difference in colony counts. None of those studies included breast-fed infants.

Growth

Overall 14 studies measured growth as an outcome (Table 3). Growth was validated by body weight, length, and head circumference. In six of the studies,[7–10,19,20] in addition to the prebiotic and control groups, a group of breast-fed infants was included. All identified trials reported no difference in growth among the groups.

Table 3 Prebiotic-supplemented infant formula and growth

Author	N/age	Duration of intervention	Setting	Prebiotic	Effect
Moro et al 2003[6]	90/at birth	4 weeks	Healthy term infants	GOS/FOS 0.4 and 0.8 g/100 mL	NS
Moro et al 2006[12]	206/at birth	6 months	Term infants at high risk for atopy	GOS/FOS 0.8 g/100 mL	NS
Ben et al 2004[8]	147/at birth	6 months	Healthy term infants	GOS 0.24 g/100 mL	NS
Ben et al 2008[9]	164/at birth	3 months	Term infants; formula feeding within 4 weeks after birth	GOS 0.24 g/100 mL	NS
Costalos et al 2008[16]	160/<14 days	15 days	Healthy term infants, enrolled ≤14 days	GOS/FOS 0.4 g/100 mL	NS
Fanaro et al 2005[11]	31/at birth	6 weeks	Healthy term infants	1. GOS/FOS 0.6 g + AOS 0.2 g/100 mL 2. AOS 0.2 g/100 mL	NS
Ziegler et al 2007[28]	226/<14 days	120 days	Healthy term infants	1. PDX + GOS 0.4 g/100 mL 2. PDX + GOS + LOS 0.8 g/100 mL	NS
Bettler et al 2006[29]	297/at birth	12 weeks	Healthy term infants	FOS 0.3 and 0.15 g/100 mL	NS
Decsi et al 2005[10]	69/at birth	12 weeks	Healthy term infants	GOS/FOS 0.4 g/100 mL	NS
Alliet et al 2007[7]	225/at birth	6 months	Healthy term infants	GOS/FOS 0.6 g/100 mL	NS
Piemontese et al 2011[20]	830/<8 weeks	1 year	Healthy term infants	GOS/FOS 0.68 g/100 mL + AOS 0.12 g/100 mL	NS
Brunser et al 2006[19]	91/3.5 months old	13 weeks	Healthy term infants	FOS 0.2 g/100 mL	NS
Ribeiro et al 2012[30]	133/9–48 months	108 days	Healthy term infants	PDX/GOS 0.5 g/100 mL	NS
Ashley et al 2012[31]	419/12–16 days	120 days	Healthy term infants	1. PDX/GOS 0.4 g/100 mL 2. GOS 0.4 g/100 mL	NS

Abbreviations: GOS, short-chain galacto-oligosaccharides; FOS, long-chain fructo-oligosaccharides; PDX, polydextrose; LOS, lactulose; NS, not significant; AOS, acidic oligosaccharides.

Table 4 Prebiotic-supplemented infant formula and atopic dermatitis

Author	N/age	Duration of intervention	Setting	Prebiotic	Effect
Moro et al 2006[12]	206/at birth	6 months	Term infants at high risk for atopy	Extensively hydrolyzed whey formula + GOS/FOS 0.8 g/100 mL	↓ AD
Ziegler et al 2007[28]	226/<14 days	120 days	Healthy term infants	1. PDX + GOS 0.4 g/100 mL 2. PDX + GOS + LOS 0.8 g/100 mL	NS
Arslanoglu et al 2008[22]	259/<6 months	6 months	Term infants at high risk for atopy	Extensively hydrolyzed whey formula + GOS/FOS 0.8 g/100 mL	2 years follow-up (134 children finished follow-up) ↓ AD 5 years follow-up (92 children finished follow-up): NS AD
Gruber et al 2010[21]	1,130/<8 weeks	1 year	Healthy term infants	Regular formula + GOS/FOS 0.68 g + AOS 0.12 g/100 mL	↓ AD

Abbreviations: AD, atopic dermatitis; GOS, short-chain galacto-oligosaccharides; FOS, long-chain fructo-oligosaccharides; PDX, polydextrose; LOS, lactulose; AOS, acidic oligosaccharides; NS, not significant.

Allergy

Results are summarized in the Table 4. Two studies[12,21] found a positive effect on the reduction of the risk for atopic dermatitis; however the children included in one study were infants with high risk of atopy[12] and in the other study, only healthy full-term infants were included.[21] Arslanoglu et al[22] showed a protective effect of prebiotic supplementation on allergies in a follow-up period of 2 years; however, that effect was not seen after 5 years of follow-up.[23] Moreover, both studies had a high dropout rate which should be taken into consideration when interpreting the results.

Respiratory and gastrointestinal infections

Results of the trials investigating the role of prebiotics on infection prevention are summarized in Tables 5 and 6. Arslanoglu et al[24] reported fewer episodes of physician-diagnosed overall and upper respiratory tract infections and fewer antibiotic prescriptions. Bruzzese et al[25] reported a lower incidence of gastroenteritis in the supplemented group. On the other hand, the study by van Stuijvenberg et al[26] found a non-significant difference in the number of fever episodes.

Discussion

Currently available data show that prebiotic supplementation of infant formula can yield bifidogenic and lactogenic effects similar to those found in breast-fed babies. That trend was reported by all studies using the prebiotic mixture GOS/FOS. On the other hand, acidic oligosaccharides failed to yield the same effect when used alone, but when used in combination with the GOS/FOS mixture, an effect was observed.[11] As far as concentration is concerned, both effects have been

Table 5 Prebiotic-supplemented infant formula and respiratory tract infections

Author	N/age	Setting	Prebiotic	Effect
Arslanoglu et al 2007[24]	259/<6 months	Term infants with a parental history of atopy	GOS/FOS 0.8 g/100 mL	No significant difference in the incidence of respiratory tract infections Lower incidence of recurrent upper respiratory infections No difference in prescribed antibiotics
Arslanoglu et al 2008[22]	259/<6 months	Term infants with a parental history of atopy	GOS/FOS 0.8 g/100 mL	Two years follow-up (134 children finished follow-up): lower number of upper respiratory tract infections Lower number of prescribed antibiotics
Bruzzese et al 2009[25]	342/15–120 days	Healthy term infants	GOS/FOS 0.4 g/100 mL	No significant difference in the incidence
van Stuijvenberg et al 2011[26]	830/<8 weeks	Healthy term infants	GOS/FOS 0.68 g + AOS 0.12 g/100 mL	No significant difference in the incidence No difference in prescribed antibiotics
Ribeiro et al 2012[30]	133/9–48 months	Healthy term infants	PDX/GOS 0.5 g/100 mL	No significant difference in the incidence Lower number of prescribed antibiotics

Abbreviations: GOS, short-chain galacto-oligosaccharides; FOS, long-chain fructo-oligosaccharides; PDX, polydextrose; AOS, acidic oligosaccharides.

Table 6 Prebiotic-supplemented formula and gastrointestinal infection

Author	N/age	Duration of intervention or follow-up	Setting	Prebiotic	Effect
Arslanoglu et al 2007[24]	259/<6 months	6 months	Term infants with a parental history of atopy	GOS/FOS 0.8 g/100 mL	NS
Arslanoglu et al 2008[22]	259/<6 months	6 months	Term infants with a parental history of atopy	GOS/FOS 0.8 g/100 mL	2 years follow-up (134 children finished follow-up): NS
Ribeiro et al 2012[30]	133/9–48 months	108 days	Healthy term infants	PDX/GOS 0.5 g/100 mL	NS
Bruzzesse et al 2009[25]	342/15–120 days	1 year	Healthy term infants	GOS/FOS 0.4 g/100 mL	Lower number of gastrointestinal infections
van Stuijvenberg et al 2011[26]	830/<8 weeks	1 year	Healthy term infants	GOS/FOS 0.68 g + AOS 0.12 g/100 mL	NS

Abbreviations: GOS, short-chain galacto-oligosaccharides; FOS, long-chain fructo-oligosaccharides; PDX, polydextrose; AOS, acidic oligosaccharides; NS, not significant.

achieved with the concentration recommended by the Scientific Committee on Food of the European Commission (ie, lower than 8 g/100 mL of milk).[27]

However, although presented studies proved that prebiotics have a bifidogenic and lactogenic effect, their clinical relevance still remains unknown. Moreover, we are not aware whether or not that effect on intestinal microbiota early in life could be long-lasting or whether it could also have clinical relevance later in life. Currently available data assessed only short-term clinical effects including growth, allergy and infection rate. As far as growth was concerned, none of the studies showed a significant difference between the supplemented and non-supplemented group.[6–12,16,19,20,28–31] However, several limitations should be considered: first of all, the role model for ideal infant growth is not the formula-fed but the breast-fed infant; moreover, none of those studies assessed long-term prebiotic effect on infant growth.

There is some evidence that a prebiotic supplementation may prevent eczema.[12,21] However, the evidence is weak; moreover, studies which measured long-lasting effect had very high dropout during the follow-up.[22,23] It is still unclear whether the use of prebiotics should be restricted only to infants at high risk of allergy or whether they should also be used in low-risk populations. For the evidence-based recommendation on the use of prebiotics in infant formula for allergy prevention, we need more well-performed randomized controlled trials with long-term follow-up.

The role of prebiotics in the prevention of respiratory and gastrointestinal infections is still controversial; the number of well-designed clinical trials is limited. Regarding the effect on upper respiratory tract infections, the data is not unequivocal; there are two studies both on the same cohort, one during the use of prebiotics and the other during the follow-up.[22,24] Both studies found a decreased incidence of respiratory tract infections. However, the follow-up study had a very high drop-out rate and, furthermore, intention-to-treat analysis was not performed.[22] In these two studies the significant difference in the number of gastrointestinal infections was not observed. Because there is no clear evidence, further recommendation of the role of prebiotics in the prevention of infections could not be given.

The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition published a Position Paper in 2011 on the role of supplementation of infant formula with pro- and prebiotics in different clinical outcomes.[32] The overall recommendation of that systematic review was that there was not enough evidence to recommend routine supplementation of infant formula with pro- and prebiotics. However, it was also clearly stated that supplementation does not raise safety concerns regarding side effects and infants' growth.

Conclusion

Currently available evidence failed to find positive effect of prebiotics in infant formula on growth and any other studied clinical outcome in healthy term infants. It has been found that prebiotics, during administration, can modify intestinal microbiota; however, clinical relevance still remains questionable. Certainly, well-designed, prospective, long-term studies are needed in order to provide the best possible alternative for infants who cannot be breast-fed.

Disclosure

The authors report no conflicts of interest in this work.

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