**Table 5.** Intestinal effects of GOS/FOS in term infants.

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| **Reference** | **Prebiotics** | **Dose** | **Objectives** | **Subjects and main features of the trial** | **Outcomes** |
| Moro et al., 2002 [38] | 90% GOS (derived from lactose) and 10% FOS (high-molecular-weight fraction of inulin extracted from chicory root | 0.4 g/100 mL  0.8 g/100 mL | To evaluate the bifidogenic effect of an experimental prebiotic oligosaccharide mixture | Ninety term infants were given two test formulas supplemented with either 0.4 g/dL or with 0.8 g/dL oligosaccharides. In the control formula, maltodextrin was used as placebo. At study day 1 and study day 28, the fecal species, colony forming units (cfu) and pH were measured and stool characteristics, growth, and side effects were recorded | At the end of the 28-day feeding period, the number of Bifidobacteria was significantly increased for both groups receiving supplemented formulas. This effect was dose dependent. The number of Lactobacilli also increased significantly in both groups fed the supplemented formulas but no dose dependence was found. Supplementation had a significant dose-dependent influence on stool consistency. The stool frequency resulted in a significant difference between the placebo group and the group fed the 0.8 g/dL formula at day 28 |
| Moro et al. 2003 [39] | GOS (derived from lactose) and long-chain FOS (derived from chicory) | 0.4 g/100 mL  0.8 g/100 mL | To evaluate dose-related bifidogenic effects of a synergistic mixture of GOS and FOS | A double-blind, randomized, controlled study was performed in 90 full term infants were assigned a standard starting formula supplemented with the prebiotic oligosaccharide mixture or the same starting formula supplemented with maltodextrin (placebo) as the control. On study day 1 and study day 28, fecal flora, stool characteristics (consistency, frequency and pH) were evaluated, and growth and possible side effects (crying, regurgitation and vomiting) were recorded. The results were compared with those of a breastfed group (n=15) | Supplementation of a term formula with a mixture of galacto- and fructo-oligosaccharides has a stimulating effect on the growth of bifidobacteria and lactobacilli in the intestine and results in stool characteristics close to those found in human-milk-fed infants. A dosage of 0.4 g/dL already results in significant effects, but the effects can be enhanced to a level observed in breast-fed infants by increasing the dosage to 0.8 g/dL |
| Knol et al., 2005 [40] | GOS/FOS  (ratio 9:1) | 0.8 g/100 mL | To investigate whether an infant formula supplemented with GOS/FOS is able to establish a bifido-dominant microflora, not only in numbers but also with respect to the metabolic activity in the colon | Randomised, double blind, placebo controlled intervention study. Sixty-eight infants were enrolled and 60 among them completed the study. Infants were fed infant formula with GOS/FOS (OSF group) or control formula (SF group). A breast-fed group was studied in parallel. At study onset and after 4 and 6 weeks, fecal samples were examined for the number of bifidobacteria, pH, short chain fatty acids and lactate | After 6 weeks, the mean proportion of bifidobacteria was significantly higher in the OSF group. Compared with controls, infants in the OSF group had a lower stool mean pH and an increased proportion of acetate and a decreased proportion of propionate. The changes in short chain fatty acids,  lactate and pH in the prebiotic group represent a fermentation profile that is closer to that observed in breast-fed infants compared to infants fed control formula |
| Haarman and Knol, 2005, 2006 [41,42] | GOS/FOS in a 9 to 1 ratio | 0.8 g/100 mL | To study the different *Bifidobacterium* species in infants receiving a standard formula (SF) or a standard formula supplemented with a specific prebiotic GOS/FOS mixture (OSF). | Double blind, placebo controlled multicenter trial with two intervention groups. Fully formula-fed term infants, aged 28 to 90 days: a group that received an infant formula supplemented with GOS/FOS and a group that received a standard infant formula. Within 2 days after study enrollment and at the end of the study period (6 weeks), fecal samples were collected The 5′ nuclease assays were subsequently used to determine the relative amounts of different *Bifidobacterium* species A group of exclusively breast-fed infants was studied in parallel and used as a reference | After a 6-week intervention period, the percentages of bifidobacteria in the BF group and OSF group were significantly higher than in the SF group. Furthermore, there was a significant increase of the percentage of bifidobacteria during the study period in the OSF group. In those infants receiving the prebiotic formula (OSF), the diversity of *Bifidobacterium* species was similar to breast-fed infants |
| Bakker-Zierikzee et al., 2005 [43] | GOS/FOS  (ratio 9:1) | 0.6 g/100 mL | To compare the effects of infant formula containing a mixture of galacto- and fructo-oligosaccharides or viable *Bifidobacterium animalis* Bb-12 on the composition and metabolic activity of the intestinal microflora. | The prebiotic group (n=19) received regular infant formula supplemented with the mixture of GOS/FOS. The probiotic (Bb-12) group (n=19) received the same formula supplemented with 6.0x1010 viable cells of *B. animalis* per litre. The standard group (n=19) received non-supplemented regular formula. A group of 63 breast-fed infants was included as a reference group. Fecal samples were taken at postnatal day 5 and 10, and week 4, 8, 12 and 16. FISH analysis was performed to detect bifidobacteria, and SCFA, lactate and pH were quantitatively determined | Compared with the groups fed Bb-12 and standard formula, the GOS/FOS formula group showed higher fecal acetate percentage and lactate concentration and lower pH at 16 weeks. Differences in percentage of bifidobacteria between the GOS/FOS, Bb-12 and the standard groups were not statistically significant at 16 weeks |
| Costalos et al., 2008 [44] | GOS/FOS (90% GOS derived from lactose and 10% FOS) | 0.4 g/100 mL | To investigate the growth, acceptability, and stool microbiology of infants fed a starting infant formula containing added prebiotic oligosaccharides. | Prospective, double blind, study in which healthy term bottle-fed infants were enrolled within 0-14 days after birth at term to receive either a prebiotic formula or a standard formula The primary outcome measure of this study was weight gain. Stool samples were taken at inclusion and at the age of 6 weeks. The number of bifidobacteria and clostridia was determined by fluorescent in situ hybridization | Stool frequency was significantly higher in the prebiotic group. Infants in the prebiotic group had also softer stools as compared to the control group. The percentage of fecal clostridia at the completion of the study was significantly lower in the prebiotic group whereas the difference in fecal bifidobacteria did not reach statistical significance |
| Vivatvakin et al., 2010 [46] | 90% GOS and 10% FOS | 0.4 g/100 mL | To determine whether infants fed a whey-predominant formula containing LCPUFA and FOS/GOS exhibit better measurements of gastrointestinal comfort than infants fed a standard starter casein predominant formula | Two hundred and twenty-four infants were enrolled in this single-centre, prospective, double-blind, controlled trial and 169 of these infants completed the study. Healthy, full-term infants (n=144) were randomly assigned to receive exclusively either experimental or control formula from 30 days to 4 months of age. A group of exclusively breast-fed infants served as reference (n=80). Parents recorded frequency and physical characteristics of infants’ stool, frequency of regurgitation, vomiting, crying and colic. At 2-months, gastric emptying (ultrasound) and intestinal transit time (H2 breath test) were measured, and stool samples collected for bacterial analysis | No statistically significant differences were detected compared with the control group as regards gastric empting. Compared to the control (n=69), fewer of the experimental group (n=67) had hard stools and more had soft stools. Also compared to the control, the experimental group’s stool microbiota composition (mean % bifidobacteria: 78.1 (experimental, n=17), 63.7 (control, n=16), 74.3 (breastfed, n=20)), gastric transit times (59.6 (experimental, n=53), 61.4 (control, n=62), 55.9 (breast-fed, n=67) minutes) and intestinal transit times were closer to that of the breast-fed group. Growth parameter values were similar for all groups |
| Veereman-Wauters et al., 2011 [47] | 50 oligofructose:50 FOS);  GOS:FOS (90:10) | 0.4 g/dL or 0.8 g/dL (50 oligofructose:50 FOS);  0.8 g/100 mL, (GOS:FOS) | To assess the physiological and bifidogenic effects of galactooligosaccharides (GOS), oligofructose, and long-chain inulin (fructooligosaccharides, FOS) in formula | Randomized controlled trial involving 110 healthy neonates. A breast-fed group was included for comparison. Outcome parameters were weight, length, intake, stool characteristics, crying, regurgitation, vomiting, adverse events, and fecal bacterial population counts | In the SYN1 0.8 g/dL and GOS:FOS groups, *Bifidobacterium* counts were significantly higher at D14 and 28 compared with D3 and were comparable with the breast-fed group. Stool consistency and bacterial composition of infants taking SYN1 0.8 g/dL or GOS:FOS-supplemented formula were closer to the breast-fed pattern |
| Salvini et al., 2011 [48] | GOS/FOS  (ratio 9:1) | 0.8 g/100 mL | To evaluate the influence of a prebiotic mixture administered from the first day of life on the development of intestinal microbiota in formula-fed infants | Double-blind, randomized, placebo-controlled, explorative study, 20 newborns of hepatitis C virus-infected mothers who decided not to breast feed due to their concerns regarding their plasma viral load were randomly assigned to either a formula with the specific prebiotic mixture or a formula containing the same amount of maltodextrin (placebo). Clinical examination including anthropometric measurements, microbiological analysis of fecal samples, and blood leukocyte population analysis were performed at birth and 3, 6, and 12 months of age | Prebiotic supplementation resulted in more fecal bifidobacteria and lactobacilli compared with the placebo group. There was no influence of the different diets on anthropometric data or the measured immunological variables |
| Holscher et al., 2012 [45] | GOS/FOS  (ratio 9:1) | 0.4 g/100 mL | Assess gastrointestinal tolerance and fecal microbiota, pH, and short-chain fatty acid (SCFA) concentrations of infants consuming formula with prebiotics | Randomized, controlled, double-blind, prospective clinical trial. Full-term formula-fed infants were studied to a breastfed comparison group (BF). At the baseline visit, 50 breastfed (BF) infants were enrolled, and 89 formula-fed infants were randomized to consume a partially hydrolyzed whey formula with (PRE) (43 infants) or without (CON) GOS/FOS (46 infants). Stool samples from 102 infants were analyzed. Fecal bacteria, pH, and SCFA were assessed at baseline, 3 weeks, and 6 weeks. Caregivers of patients recorded stool characteristics and behavior for 2 days before the 3- and 6-week visits | Feces from infants fed PRE had a higher absolute number and proportion of bifidobacteria than CON-fed infants and did not differ from BF. BF had a higher proportion of bifidobacteria than CON and lower number of *Clostridium difficile* than FF. Feces from formula-fed infants had higher concentrations of acetate, butyrate, propionate, and total SCFAs than BF; however, fecal pH was lower in PRE and BF than CON. Prebiotic supplementation did not alter stool patterns, tolerance, or growth. BF had more frequent stools that were yellow and more often liquid than FF |
| Dasopoulou et al.,2015 [50] | GOS/FOS | 0.8 g/100 mL | To test if prebiotics could alter motilin and gastrin secretion and reduce lipids in healthy preterms | A total of 167 newborns were randomized to either a prebiotics enriched formula containing dietary oligosaccharides or a common preterm formula. Day 1 and 16 basal motilin, gastrin concentrations, and lipids were evaluated together with growth parameters, gastric residue, bowel habits,and feeding tolerance. Adverse events including necrotizing enterocolitis (NEC) and septicemia were also recorded | Mean motilin increase and day 16 mean values were greater for the intervention, compared with the control group, while gastrin remained high in both groups. Mean cholesterol and low density lipoprotein (LDL) increase were significantly greater in the control, compared with the intervention group. Day 16 LDL levels were significantly higher in the control group. Mean weight was increased in the control group, while gastric residue was less and stool frequency was increased in the intervention group. NEC and septicemia were not statistically different between groups |
| Huet et al., 2016 [53] | GOS/FOS  (ratio 9:1) | 0.8 g/100 mL | To assess the safety and tolerance of the combination of partly fermented infant milk formulae and scGOS/lcFOS in healthy term infants | Four hundred thirty-two infants were enrolled before 28 days of age and followed up to 17 weeks of age and assigned to 1 of the 4 groups: (i) formula with scGOS/lcFOS, (ii) scGOS/lcFOS cFOS/lfermented formulae (FERM), (iii) scGOS/lcFOS + 50% FERM, or (iv) 50% fermented formula (50% FERM). Primary outcome was daily weight gain during intervention (equivalence criterion: difference in daily weight gain ≤3 g/day). Infants' anthropometrics, formula intake, number, and type of (serious) adverse events (AEs) were monitored monthly. Stool samples were collected at baseline and after 17 weeks for analysis of physiological and microbiological parameters | Equivalence of weight gain per day was demonstrated in both the intention-to-treat and per-protocol population, with a mean weight gain (SD) of 29.7 (6.1), 28.2 (4.8), 28.5 (5.0), and 28.7 (5.9) g/day for the groups i to iv respectively. No differences were observed in other growth parameters, formula intake, and the number or severity of AEs. In all scGOS/lcFOS-containing formulae, a beneficial effect of scGOS/lcFOS was observed, indicated by the lower pH, lower *Clostridium difficile* levels, and higher secretory immunoglobulin A levels |
| Szajewska et al., 2017 [49] | GOS/FOS  (ratio 9:1) | 0.54/0.061 g/100 mL | To evaluate the effects of consumption of infant formula supplemented with prebiotics (GOS/FOS) compared with synbiotics (FOS/GOS and *Lactobacillus paracasei* ssp. *paracasei* strain F19) | 182 full-term infants who were weaned completely from breast milk to infant formula at 28 d of age were randomly assigned to receive prebiotic- or synbiotic-supplemented, otherwise identical, IF until 6 mo of age (intervention period). A total of 146 (80%) infants were included in the intention-to-treat analysis at 6 mo | Anthropometric parameters were similar in the two groups during the intervention and follow-up period until 12 months of age. No statistical significance difference was found between the formula-fed groups in infant growth, or the occurrence of serious adverse events |
| Vandenplas et al., 2017 [54] | GOS/FOS  (ratio 9:1) | 0.8 g/100 mL | To examine the effects on gastrointestinal tolerance of an infant formula combining specific fermented formula (FERM) with (scGOS/lcFOS) | This prospective, double-blind, randomised, controlled trial comprised 432 healthy, term infants aged 0-28 days whose parents decided to not start, or discontinued, breastfeeding. Infant formula with scGOS/lcFOS+50%FERM, scGOS/lcFOS+15%FERM, 50%FERM and scGOS/lcFOS were tested. Parents recorded gastrointestinal symptoms, crying, sleeping and stool characteristics each month until the infants were 17 weeks | All the formulas were well tolerated. At four weeks, the overall incidence of infantile colic was significantly lower with scGOS/lcFOS+50%FERM than scGOS/lcFOS or 50%FERM |