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Gut microbiota profiles associated with caesarean section influence the effects of a synbiotic infant formula early in life – data of a current randomized trial

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Microbial colonization of the gastrointestinal tract after birth is an essential event, which influences infant health with life-long consequences. Birth via Caesarean section (CS) modulates the early gut microbiota, which is associated with an increased risk of developing infectious and allergic diseases.[1,2] Therefore, it is important to develop approaches to support the early microbial ecosystem.

Human milk (HM) is the gold standard for infant nutrition. Due to its prebiotic and probiotic components, it is the major extrinsic factor influencing the dynamics of microbial communities in the gut of newborns and infants. HM contains bacteria that are important in seeding the infant's intestine, especially in CS-infants lacking distinct bacteria resulting in a naturally different ecosystem profile.[3]

If breastfeeding is not possible, infant formula should ideally support similar development of the intestinal ecosystem. Hence, the supplementation of infant formula with bacterial isolates from HM is a sound approach to positively modulate colonization in early life. *L. fermentum* CECT5716 is one such HM-isolated bacterium, for which probiotic properties and safety were proven in two infant cohorts with intervention periods of up to one year and follow-up until the age of 3 years.[4–6]

The aim of the present study was to assess the effects of a synbiotic intervention formula with *L. fermentum* CECT5716 and galactooligosaccharides (GOS) on the fecal microbiota (high-throughput 16S rRNA amplicon sequencing) and milieu parameters (i.e. pH, humidity, IgA, calprotectin, short-chain fatty acids) in formula-fed infants. Therefore, a multicentre, randomized, controlled, double-blind intervention trial was conducted enrolling 540 infants, including measurements at the age of 4, 12, and 24 months.

At month 4, significant effects of the synbiotic intervention formula (IF) compared to control formula (CF) without synbiotics were visible. These included higher occurrence of *Bifidobacterium* spp. and *Lactobacillaceae* in the IF group.

The IF formula also induced changes in fecal milieu parameters shown by lower fecal pH and lower concentrations of butyrate in the IF and HM group (reference group), compared to the CF group.

De-novo clustering of the bacterial communities at 4 months of age revealed that the phylogenetic profiles of infants receiving IF were closer to profiles of infants fed HM (reference group), compared to infants fed CF. Two distinctly separated clusters (C1 and C2) of the fecal microbiota were observed. Of note, HM-feeding was equally represented in the two clusters. Calculating similarities to reference HM profiles, showed that the effect of IF was driven primarily by infants with the natural microbiota profile C2. Interestingly, the C2 cluster was associated with a statistically significant higher prevalence of CS infants.

In the present study, synbiotic intervention influenced the gut microbiota and milieu parameters during early life to resemble some major characteristics found in breastfed infants (higher relative abundances of bifidobacteria, lower richness, lower fecal pH and butyrate concentration). These effects are depended on the natural ecosystem profile of the infants which is influenced by variable factors (e.g. mode of birth). Further analysis of clinical parameters are needed to test the potential for disease prevention (e.g., diarrhea or respiratory tract infections) – especially in infants with a disadvantageous microbial profile as often found in CS-infants, as they might benefit most of the synbiotic intervention.

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Why do infants born by caesarean section have an unfavourable gut microbiota and why should we change that?

Vaginal birth is a natural and physiological process. However, in certain conditions, a caesarean section (CS) may be required to protect the woman and the baby's health. Since 1985, the World Health Organization (WHO) has considered the ideal rate for CS births to be between 10 to 15 %. According to new research from the WHO, the CS use continues to rise globally, now accounting for more than 1 in 5 (21 %) of all childbirths.[1] This number is set to continue increasing over the coming decade, with nearly a third (29 %) of all births likely to take place by CS by 2030. At the moment, CS now outnumber vaginal deliveries in five countries (Dominican Republic, Brazil, Cyprus, Egypt and Turkey).

Despite CS delivery can be a life-saving intervention when medically indicated, this procedure can lead to short-term and long-term health effects for children with the absence of transmission from maternal microbiota to the newborn. The microbial population of neonates born vaginally resembles the maternal vagina and perianal microbes, while CS-delivered neonates predominantly acquire bacteria derived from the maternal skin and the surrounding environment.[1] Maternal microbiota exerts a significant effect on the neonatal microbiome and contributes to regulating the development of offspring immunity, metabolism, brain function, and behavior. These advantageous effects of maternal microbiota can be vertically transmitted to offspring through vaginal delivery.

Mode of delivery has also been associated with differences in the infant microbiome. CS delivery is one of the strongest disrupting factors of the normal colonization process and a risk factor for disorders in later life.[3] In addition to the lack of exposure to vaginal microbiota, it is likely that indication for CS delivery, intrapartum antibiotic administration, differences in breastfeeding behaviors, maternal diseases, and gestational age are associated with alterations in the infant microbiome. It has been suggested that these differences are attributable to the "bacterial baptism" of vaginal birth, which is bypassed in cesarean deliveries, and that the abnormal establishment of the early-life microbiome is the mediator of later-life adverse outcomes observed in CS infants.

Accumulating evidence has shown that the gut microbiota plays a fundamental role in the health and disease by assisting in the synthesis and absorption of nutrients, strengthening gut integrity, protecting against enteropathogens, modulating the immune system, and exerting control over the gut–brain axis.[4]

Accordingly, perturbations influenced by any detrimental factors in early life may cause adversely long-lasting consequences for host health, ranging from gastrointestinal diseases, such as inflammatory bowel disease and irritable bowel syndrome, immune reactivity and immunopathology to allergies, including asthma, food allergy, and atopic dermatitis.[5]

Recent data revaled that CS delivery infants have also been reported to posses increased burden of respiratory infections in childhood in addition to gastrointestinal infections.[6] The correlation between CS delivery and these increased infection risks may be interpreted by the subsequent disturbance in immune response regulation after the absence of contact with maternal vaginal microbes at birth.

Probiotic, prebiotic or synbiotic supplementation may lead to beneficial gut microbiota in CS delivered infants, closer to that in vaginally delivered newborns, particularly Bifidobacterium colonization.[7] This beneficial effect is achieved when the intervention begins soon after birth. Changes in the infant microbial ecosystem due to the interventions seem to continue after the end of the intervention in most of the studies.[7] More clinical studies are needed to elucidate the most effective strains and its doses, and also the optimal synbiotic combinations for achieving the favourable gut microbiota colonization of CS delivered newborns.

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Beneficial effects of the administration of *L. fermentum* CECT 5716 to infants delivered by cesarean section

Cesarean section (CS) disrupts the natural microbiota colonisation process in infants, which might compromise immune system maturation, leading to a higher risk of infections. Vaginal delivery (VD) allows contact of the neonate with the vaginal and enteric microbiota of the mother and therefore influences infants' gut colonization. CS disrupts this natural colonization process, promoting a significantly different microbiota compared to that in VD infants. Specifically, the microbiota of VD infants is characterised by microbes including *Limosilactobacillus, Prevotella, Bacteroides, Escherichia/Shigella, Bifidobacterium* spp. and other members of the former genus *Lactobacillus.*[1]
In contrast, *Staphylococcus, Streptococcus, Corynebacterium, Veillonella* and *Propionibacterium* spp. dominate in the microbiome of CS delivered infants[2,3] and delay the expected normal intestinal colonization. Moreover, lower amounts of total intestinal bacteria and lower diversity have been observed in CS infants.[4–6]

Breastfeeding seems to counteract the deleterious effect of CS on the microbiota However, women who deliver babies by CS are less likely to breastfeed or delay breastfeeding initiation.[7] When breastfeeding is not possible or insufficient, a feasible strategy would be to introduce bacteria naturally present in human milk into infant formulae.

Limosilactobacillus (L.) fermentum CECT 5716, previously named *Lactobacillus fermentum* CECT 5716 [1], is a probiotic strain originally isolated from human milk.[8] Three randomized clinical trials performed in infants demonstrated the safety of the probiotic strain as well as its usefulness for preventing community-acquired infections, such as gastrointestinal and respiratory infections.[9–11] Briefly, the three studies were double-blind, randomized, controlled trials and included healthy infants exclusively fed formula, with an inclusion age ranging from one month[10,11] to six months.[9] In all the studies, *Limosilactobacillus fermentum* CECT5716 was administered in a powdered infant formula. The three studies involved both VD- and CS-born infants. The CS rates in the studies were 31 % in Maldonado et al. (2019)[11], 43 % in Gil-Campos et al.[10] and 44 % in Maldonado et al. (2012)[9].

We have analysed the effect of *L. fermentum* CECT 5716 consumption on the incidence of gastrointestinal and respiratory infections in the CS subgroup of the three study trials. Therefore, data on CS-born infants in the three aforementioned clinical trials were extracted separately, and the obtained results were pooled in a meta-analysis. The occurrence of gastrointestinal and respiratory infections was described for each study using the incidence rate (IR) and the incidence rate ratio (IRR) with the 95 % CI and p value for the IRR in each clinical trial. A Poisson regression model was applied to adjust the number of events by sex, age at intervention entry, and whether infants were breastfed before the intervention.

Analysis of data from CS infants showed that the incidence of gastrointestinal infections was reduced by the consumption of *L. fermentum* CECT 5716, reaching significance in two of the three RCTs analyzed separately. Furthermore, pooled results from the 173 CS infants showed a significant reduction of 73 % in the incidence of gastrointestinal infections in CS-born children receiving *L. fermentum* CECT 5716 in comparison to infants receiving the control formula (n = 173, IRR: 0.27, p = 0.0002). Analysis of the incidence of respiratory infections (RI) showed no significant reduction by *L. fermentum* CECT 5716 in CS-delivered infants, although a decreasing trend of these types of infections was observed. The pooled results showed a 14 % reduction in the incidence of respiratory infections in CS-born infants receiving the probiotic, although the difference was not statistically significant (n=173, IRR: 0.86, p= 0.25).

In conclusion, the administration of *L. fermentum* CECT 5716 to CS-born infants protects them from gastrointestinal infections by reducing the risk of this type of infection by up to 73 % in this population. The protective effect of this probiotic has been extensively demonstrated in several clinical trials, but the results of the present study suggest that it could be even more relevant in the case of CS-born infants, a population at higher risk for all types of clinical infections.

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