Probiotic and preterm infant gut study

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Probiotic supplementation in preterm infants improves gut microbiome

Probiotics can improve the microbiome in preterm infants, according to the results of a significant new study published in *Cell Reports Medicine* ([1]).

The research demonstrated that specific strains of probiotic *Bifidobacterium* and *Lactobacillus* bacteria given to preterm infants together with breast milk assisted in developing microbial populations and a gastrointestinal environment more closely resembling infants born at full-term.

The gut microbiome plays a crucial role in the development of the immune system, particularly during infancy and childhood. Several factors, including mode of delivery, diet, environment and use of antibiotics, can significantly impact the gut microbiome, and have a profound impact on childhood development and health ([2]).

Preterm infants (< 37 weeks gestation) account for 1 in 9 births globally ([3]). These infants are more likely to have disrupted gut microbiota due to Caesarean delivery, repeated antibiotic exposure and extended stays in neonatal intensive care units (NICUs). The altered gut microbial ecosystem can increase the risk of serious morbidity, including necrotising enterocolitis (NEC) ([4]) and late-onset sepsis (LOS) ([5]). It can also lead to chronic health conditions in childhood and later life, such as asthma, allergies, obesity, diabetes, and inflammatory bowel disease ([6],[7],[8]). Accordingly, there is great interest in finding interventions, such as probiotics, to assist preterm infants in establishing a ‘normal’ microbiome.

A recent clinical audit showed that routine probiotic supplementation in an NICU was associated with a halving in the rates of NEC (from 7.5% to 3.1%) and LOS (from 22.6% to 11.5%) when comparing the 5 years before and 5 years after the initiation of routine probiotic use with a

combined *Bifidobacterium* and *Lactobacillus* supplement ([9]).

However, despite the positive outcomes obtained in previous systematic reviews and meta-analyses, a 2018 survey of all 58 tertiary-level NICUs in the UK found only 10 NICUs (17%) were routinely using probiotics, primarily due to the lack of extensive, long-term studies into the benefits of probiotic supplementation and health ([10]).

To address these research gaps, researchers carried out a prospective observational study, comparing 101 NICU infants orally supplemented with specific strains of *Bifidobacterium bifidum* and *Lactobacillus acidophilus* with 133 infants in other NICUs that were not providing probiotic supplementation ([1]).

The multi-centre study involved collecting samples from infants matched by sex, age, and delivery method across the two groups. Faecal samples were collected from the infants over their first 100 days of life and analysed for bacterial composition and bacterial metabolites, including short chain fatty acids (SCFAs).

The results showed distinct differences in the microbiota profiles between the two groups. The supplemented infants had microbiota dominated by *Bifidobacterium*, while the un-supplemented infants contained a range of potentially pathogenic bacteria including *Staphylococcus, Escherichia*, and *Klebsiella*. These results suggest that oral probiotic supplementation can effectively displace these pathogens.

Diet is a significant driver of microbiota diversity, and there is a strong relationship between breast milk and *Bifidobacterium* abundance. The oligosaccharides in human breast milk act as prebiotics, allowing *Bifidobacterium* to grow ([11]). However, in the current study, although both groups of preterm infants received high rates of breast milk, via maternal or donor milk, the low abundance of *Bifidobacterium* found in control infants indicated breast milk consumption alone was not sufficient to encourage high levels of *Bifidobacterium* without probiotic supplementation ([1]).

The analysis of faecal samples showed lower levels of human milk oligosaccharides (HMO) excreted by the supplemented infants but higher levels of HMO metabolites including acetate and lactate ([1]). Acetate is a SCFA that has beneficial health effects by enhancing defence functions in host epithelial cells, including natural killer cells and T regulatory cell function ([12],[13]). Lactate can regulate critical functions of several key players of the immune system such as macrophages and dendritic cells and can modulate inflammatory activation of epithelial cells ([14]). These metabolites create an acidic environment that may be less favourable for pathogenic bacteria ([1]).

The current study is the most extensive longitudinal observational study to date, combining multiple analytical methods to examine the beneficial impact of probiotic supplementation on the microbiota of preterm infants. The findings can be used to guide future randomised controlled trials and assist healthcare professionals in implementing targeted probiotic supplementation in a high-risk population.

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