Gut Microbiota in Developing Neonates

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The first 1,000 days of human life represents a crucial period in early development when organs and tissues are rapidly developing. This period offers a critical window for influencing long term health via optimum nutrition, be it *in utero* during pregnancy and following childbirth. Starting from birth, a diverse and complex microbial ecosystem begins to develop in the infant gastrointestinal tract, a process which undoubtedly influences health and disease status – not just in early life but more likely throughout life.

The population of bacteria on babies at the time of birth reportedly resembles mother's vaginal microbiota if the baby is born vaginally or that of maternal skin, if born by Cesarean section (C-section).[1] In addition to delivery mode, factors reported to influence the development of the infant gut microbiome include: gestational age, host genetics, feeding regimen, and perinatal antibiotic usage. Thus, the microbiota of full-term vaginally-born, exclusively human milk-fed infants, with no previous exposure to antibiotics, can be considered the "gold standard" of gut microbiota in early life. The gut microbiota composition is initially known to be in a state of flux and consequently stabilizes by 2-3 years of age, to more closely resemble that of an adult.

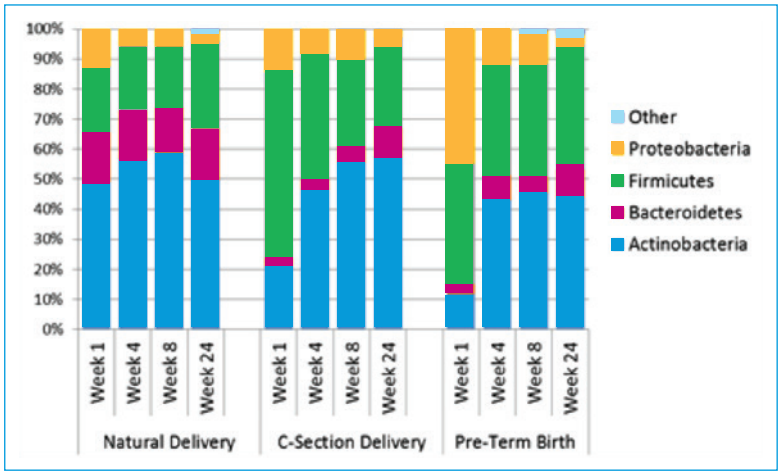

Fig 1. INFANTMET Microbiota to Week 24.[2]

In the INFANTMET study, we compared gut microbiota development of full term and preterm (<35 weeks gestation) infants that were either spontaneous vaginally delivered or delivered by C-section. These babies were followed from birth to two years of age, in initially breastfed infants (n = 199). We have recently reported on the microbiome development in this cohort during the first 24 weeks of age (Fig 1),[2] and confirmed that mode of delivery and gestational age at birth both have significant effects on early neonatal microbiota development.

Vaginally-delivered infants had a more diverse microbiota at just one week of age, which remained relatively stable over the first six months compared to infants born by C-section, whose initial microbiota was very different with lower Actinobacteria and Bacteroidetes at one week of age. Indeed, there was relatively little change in the microbiota composition of vaginally-delivered infants throughout the first 24 weeks of life. In contrast, it took eight weeks for infants born by C-section to develop a similar composition to the former group. At 24 weeks, all infants whether preterm or full-term and born vaginally or by

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C-section had similar though distinct gut microbiota compositions. *Bifidobacterium* was found to be a major component of the infant gut throughout this period and represented up to 50% of entire fecal microbiota. Interestingly, prolonged breastfeeding (> 4 months) was found to impact the gut microbiota of C-section-delivered but not vaginally-delivered infants.

An interesting outcome of the INFANTMET study concerned 10 twin sets contained within the sample population. We found that twins' microbiota were more similar to one another than to random infants, reflecting the influence of host genetics and environment on early microbiota composition.[2] Indeed, in a separate study, we reported on the microbiota composition of monozygotic twins within a dichorionic triplet set.[3]

Dichorionic triplets pose a unique informative study design as they contain monozygotic twins and a naturally-occurring fraternal triplet as control with similar pre- and postnatal environmental factors. By one month of age, the gut microbiota was observed to be dominated by bifidobacteria in all three babies with a lower level of diversity at the genus level observed in the fraternal twin and greater similarity between the monozygotic twin pair. The colonization pattern converged by 2 and 3 months of age and while at 12 months microbial diversity was increased in all three infants, there appeared to be no greater similarity in the microbiota profile of the monozygotic twins versus the fraternal control. Principal coordinate analysis (PCoA) of the microbiota composition showed that the monozygotic twins grouped together compared to the fraternal triplet at months 1 and 2. However, at 3 months and particularly by 12 months of age, the microbiota composition appeared equally dissimilar among all three. It is tempting to suggest from this observation that host genetics plays a role in shaping the microbiota at a very early stage of development, the long term health implications of which are unknown.

It is our belief that interference with the natural development of the infant microbiota as a result of C-section delivery mode, preterm birth and early antibiotic exposure has long term implications for microbial diversity/stability and consequent health. A number of disease states are reportedly associated with lower intestinal microbial biodiversity,[4] indicating that C-section combined with aseptic conditions and antibiotic treatment, although often necessary for treating/preventing infection, may not be the optimum start in early life.

The preschool years (1–5 years of age) is a time of rapid and dramatic postnatal brain development and neural plasticity, and thus of fundamental acquisition of cognitive development (i.e., working memory, attention and inhibitory control). Ensuring optimal nutrition during this period is essential for long term health into adulthood, but currently little is known about how early the gut microbiome is positively manipulated through nutrition. However, understanding the optimal nutritional regimen required for the beneficial development of the gut microbiome composition/functionality is an appealing strategy to promote health and reduce disease risk.

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While human milk is the optimum first food for microbiome development following birth, alternative feeding regimens, based on infant formula require further research to develop and confirm the efficacy of microbiome-modulating ingredients, including prebiotics and probiotics, to mirror the benefits of human milk.

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