Factors affecting infant gut microbiota and possible consequences for health

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From once being employed as an extreme measure, to save a fetus on the death of the mother, cesarean section is used more commonly now as a mode of delivery for entirely non-medical reasons (1). A sharp increase in cesarean delivery has been noted in most Western countries during the past decades; in the United States, one-third of all babies is now being delivered by cesarean section (2); in Norway, there has been a sevenfold increase in cesarean rates between the 1970s and 2001 (from 2 to 15%) and the incidence is still increasing (3). Focus so far has mainly been on the short-term health consequences of cesarean delivery, but the long-term effects may be even more important since cesarean delivery may disrupt gut microbiota during early infancy (4). Even if the gut microbiota is normalized with time, the early disruptions may have long-term effects due to the presence of developmental windows that rely on microbial stimulus from the gut, involving development of diverse functions, such as food tolerance, behavior, stress responses, and metabolism (5–8). Given the importance of early gut microbiota composition, it is important to gain knowledge on natural composition and factors altering it (9). However, a major limitation of previous studies is that they are based on infants who have been subject to factors which can have a profound disruptive effect on the natural colonization process (10–12).

In this review we are reporting on previous findings from a Norwegian cohort study, NoMIC is a prospective birth cohort established for the purpose of studying the colonization of infant gut microbiota and subsequent health (13, 14). Participating mothers were recruited at the maternity ward of a county hospital (Sykehuset Østfold) between 2002 and 2005. For every preterm-birth mother enrolled, two mothers of consecutively born term infants were recruited. The children are now aged between 9 and 12 years and have been invited for a clinical examination this year.

Gut microbiota composition was determined using 23 probes targeting 16S rRNA specifically developed for this study (13) as well as using 16S rRNA Illumina amplicon sequencing of feces, at Day 4 and 10, Month 1 and 4, and Year 1 and 2 (15). Extensive information on the use of antibiotics, mode of delivery, maternal diet, birth outcomes, and so on, is available through linkage to pregnancy records, medical birth registry, and repeat questionnaires to the mothers.

We examined the progression of gut microbiota from birth until 2 years. We identified children not subjected to medical interventions (vaginally delivered; term infants; not exposed to antibiotics directly nor through breast milk; breastfed for at least 4 months, exclusively in the first month; no antibiotics to the mother during the last trimester) to describe the gut microbiota composition in children as ‘naturally as possible’.

Then, we calculated the change in weight from birth until 6 months of age to study whether early life gut composition was associated with early growth (14). A child’s growth is expected to follow the percentile according to its birth weight. Mothers extracted information on weight from their ‘baby health visit’ cards, we used the weight closest to 6 months and the World Health Organization’s weight-for-age growth curves.

The results we observed, and which are noted below, have already been published for most parts. A marked progressive change in microbial phyla composition with age was observed. The most marked change was observed in the phylum of Proteobacteria (15). Mode of delivery and antibiotics were among the determinants of decreasing diversity over time (15). Among term infants, only 85 out of 362 (23%) had not been subjected to measures that may alter gut microbiota (13). Even in newborns not subjected to cesarean delivery or antibiotics, Staphylococcus was the most prevalent microbial group detected at 4 days but no longer at 4 months. Escherichia coli was present in 70% of infants at 4 days and was increasing toward 4 months.
At 4 months, different Bifidobacterial groups dominated in these breastfed infants (13). Absence of the probe coding for E. coli during the first month of life was associated with rapid growth during early life while the presence of Bacteroides spp at one month was associated with reduced growth, in males (14).

**Discussion**

Factors that may alter gut microbiota are surprisingly commonly applied (according to the findings in the NoMIC study) as only 23% of term babies had not been subjected to any such measure. Compared to the past century, E. coli is no longer a ubiquitous microbe in newborns. Previously, it was reported as being present in all newborn infants within 4 h after delivery, whereas studies in Sweden have shown that it is steadily less prevalent, especially among cesarean-delivered infants (16–18). We confirm these findings even in newborns not subjected to interventions. Moreover, our study shows that the absence of E. coli may be tied to adverse child health outcomes, since its absence was tied to rapid growth which is an early marker of the risk of obesity in later life. We hypothesize that E. coli may play an important role in very early life, maybe due to cascading events set in motion by the very early colonizers.

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