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First year of life: the *Golden Age* of gut microbiota

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Abstract. During the first year of life, development and balance of newborn gut microbiota are strongly influenced by external factors such as delivery mode, breastfeeding, duration of pregnancy, mother diet and lifestyle, siblings and pets, environment, and antibiotics administration. Gut microbiota colonization starts with facultative anaerobes and continues with the establishment of anaerobic genera of which *Bifidobacteria* are the *gold standard* of a healthy gut neonatal microbiota. Scientific literature traditionally describes the fetus as sterile in the womb and identifies the membranes rupture as the beginning of microbial colonization. Vaginal delivery is an important source for the onset of infant colonization which will then continue with the transfer of a new selection of intestinal bacteria with breastfeeding. During cesarean delivery a direct contact of the mouth of newborn with the vaginal and intestinal microbiota is absent, and environmental bacteria play an important role for infants intestinal colonization. Nature has ensured that newborns receive other specific maternal bacteria, through a subsequent method of transfer: breastfeeding. We present a brief and comprehensive state-of-the-art in order to encourage natural childbirth and breastfeeding whenever possible and discuss innovative directions for develop new *ad hoc* personalized treatments in order to restore physiological microbiota.

Keywords: gut microbiota, newborn microbiota, bifidobacteria, breastfeeding, vaginal delivery, cesarean delivery.

INTRODUCTION

The intestinal microbiota is essential for the development and maturation of the immune, metabolic, and cognitive systems. According to current knowledge, it is crucial to ensure its balance in the first year of life in order to guarantee a well-being even in adulthood. In full-term infants, natural delivery and breastfeeding represent the most important drivers for the early composition of the intestinal microbiota, but the overall composition of neonatal gut microbiota is influenced by additional factors such as mother's diet and lifestyle, siblings, pets, environment, and antibiotics administration (Yasmin F. et al., 2017; Stewart C.J. et al., 2018) (Figure 1).

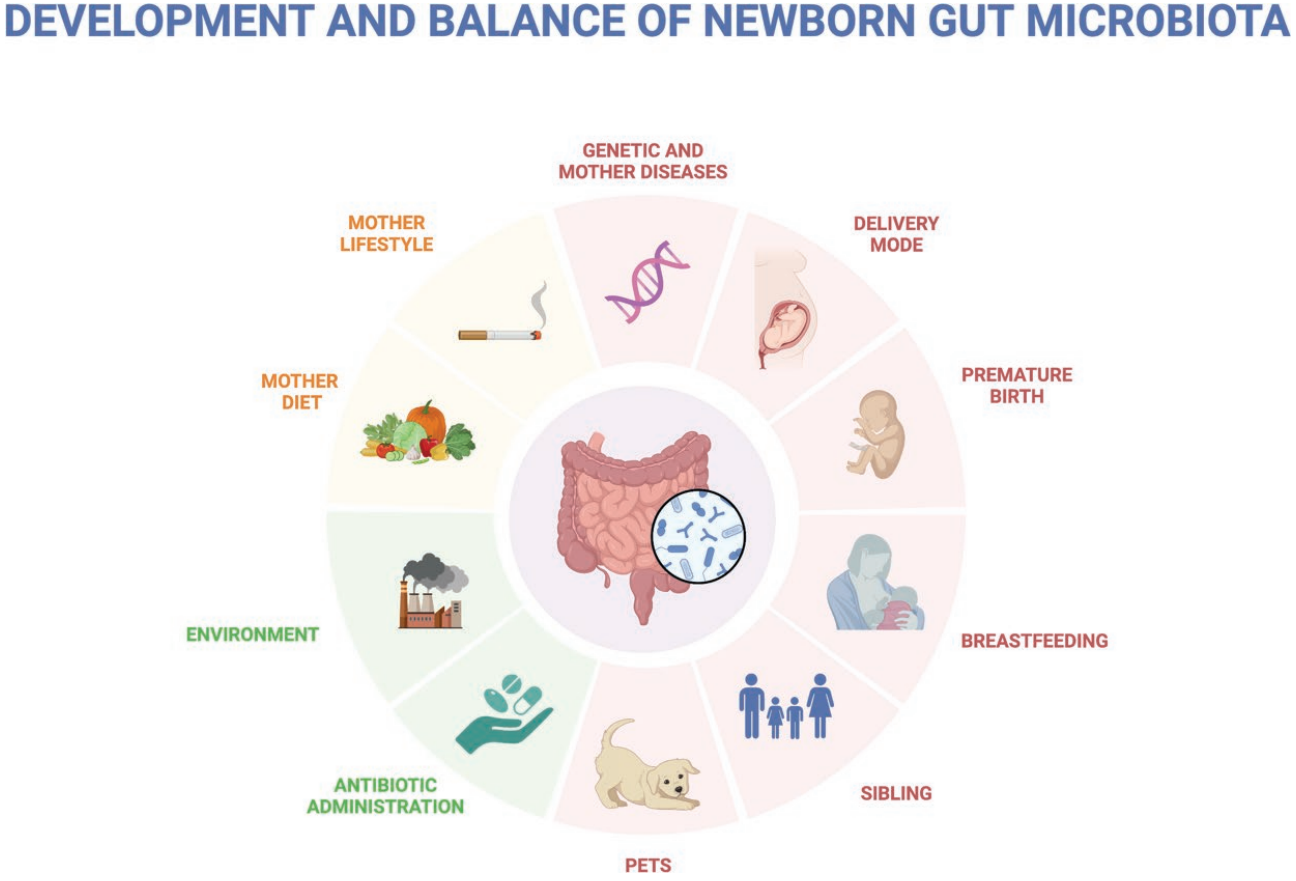

Figure 1. Determinants of development and balance of newborn gut microbiota. Created with BioRender.com.

Natural birth provides a greater bacterial richness and variety with a clear overlap with the maternal microbial profile. An interesting systematic analysis showed significant domain of *Bifidobacterium* and *Bacteroides* in naturally delivered compared with cesarean section delivered newborn, colonized by *Clostridium* and *Lactobacillus* (Rutayisire E. et al., 2016). *Bifidobacteria* are also transmitted to infants with breastfeeding. Thus, children born by cesarean section and/or not breastfed, commonly develop a bifidobacterial dysbiosis. Tojo R. et al. showed that neonatal bifidobacterial dysbiosis, as well as in adulthood, correlates and increases the risk of atopy, allergy, irritable bowel syndrome, inflammatory bowel disease, celiac disease, and obesity (Tojo R. et al., 2014).

An "upstream" hypothesis suggests that fetus already encounters initial microbial colonization at intrauterine level (Collado M.C. et al., 2016).

What's new? Interesting novel studies highlight how the evolution has been able to ensure the microbes transfer from mother to child. Vatanen T. et al. discovered that maternal gut microbioma influence the infant microbioma through mobile genetic elements from the late pregnancy (Vatanen T. et al., 2022). Bogaert T. et al. suggest the presence of auxiliary routes of mother-to-infant microbial seeding (Bogaert T. et al., 2023).

NATURAL DELIVERY: THE *GOLDEN WAY*

Over the last twenty years, elective or emergency cesarean delivery (CD) increased worldwide (Arboleya S. et al., 2018). This delivery mode, undoubtedly mandatory in most cases, led to alterations of newborn intestinal microbial profile, lacking the classical vaginal microbiota transmission route. In addition, antibiotic prophylaxis, following CD, directly impacts, on the newborn intestinal microbiota.

In physiological conditions, in pregnant women intestinal microbiota undergoes a process of bacterial inflammatory drift resulting in an increase of *Proteobacteria* and a decrease of butyrate-producing species, in order to increase the supply an adequate maternal fat reserve for breastfeeding.

Infant intestinal microbiota composition is mostly derived from different maternal body districts: intestine (22.1%), vagina (16.3%), oral cavity (7.2%), and skin (5%) (Cardelli E. et al., 2021). Vaginal delivery (VD), as compared to CD, confers different and more stable microbial colonization, containing mainly *Lactobacilli*, *Prevotella* and *Bifidobacteria*. Childs from CD, on the contrary, acquire a microbiota similar to the skin microbiota, with a greater expression of *Clostridium*, *Staphylococcus* and *Enterococcus* (Figure 2). This results in a delayed colonization of *Lactobacilli*, *Bifidobacterium* and *Bacteroides* and a consequent reduction of Th1 lymphocytes or *Bacteroides*-dependent cytokines during the first two years of life (Jakobsson H.E. et al., 2014).

In the vaginal area, *Lactobacilli* produce lactic acid from glucose derived by glycogen catabolism, an essential function for the pH maintenance of pH to avoid infections; furthermore, through the α-galactosidase, are able to catabolize milk lactose. *Lactobacilli* also stimulate pulmonary growth and alveolarization process in the lungs of newborns and exert a protective effect, probably due to their anti-inflammatory and immunostimulatory properties, with a reduced incidence of inflammatory airways diseases (Stokholm J. et al., 2020; Cardelli E. et al., 2021). In addition, during VD, contractions and oxygen hypoxia promote the development of stress hormones such as catecholamine and cortisol. Cortisol increase at birth is a predictor of hypothalamic-pituitary-adrenal axis activation of the immune system, lung, and organ maturation and neurogenesis. In contrast, in CD the use of synthetic oxytocin, antibiotics correlates with higher global DNA methylation in cord blood derived leukocytes, which could be involved in T-helper type 1 and 2 T-helper cells imbalance, leading to an increased risk of immune diseases (Cho C.E. and Norman M., 2013).

HUMAN MILK: THE *WHITE GOLD*

Differences in gut microbial composition between breast-fed and formula-fed infants are well-established. Mammary glands are colonized by fecal bacteria through the entero-mammary circulation and thus release "contaminated milk". Indeed, maternal intestine, mammary gland and milk show the same strains that are then traced in newborn intestine. Specifically, breastfeeding has been associated with the presence of *Bifidobacterium* and *Lactobacillus* present in breast milk and *Staphylococcus* present on the skin surrounding the nipple (Stewart C.J. et al., 2018) (Figure 2).

Since the maternal microbiota shapes the antibody "repertoire" of breast milk, breastfeeding contributes to the transfer of immune memory from the mother to the child. Once infants begin weaning, the protective effects of milk disappear (Ganal-Vonarburg S.C. et al., 2020).

Exclusive breast-fed newborns present an eubiosis characterized by a lower biodiversity, primary focused on *Bifidobacteria*, by a slower microbiota maturation and progressive diversification until weaning. On the contrary, formula-fed newborn are exposed to different substances that promote different patterns of intestinal microbial colonization and resulting in an anticipated divergence towards the typical adult composition (Figure 2). Both formula-fed and mixed-fed infants microbiota are characterized by an anticipated decrease in *Bifidobacteria*, with a consequent immune immaturity that has both immediate and delayed effects.

A study by Stewart C.J. et al. showed a clear increase of *Bifidobacteria* in early stages of life associated with breastfeeding, while its interruption leads to an anticipated decrease of *Bifidobacteria* and therefore to immune immaturity (Stewart C.J. et al., 2018). To note, *Bifidobacteria* are capable to metabolize Human Milk Oligosaccharides (HMO), and to produce aromatic lactic acids, bacterial post-biotic metabolites able to strengthen the intestinal barrier, protect against infection, influence the host's metabolism, and modulate immune function (Laursen M.F. et al., 2021).

It is important to emphasize that milk microbiome is far from stable: a maternal wrong diet can decrease the benefits and/or cause newborn dysbiosis resulting in gastrointestinal and metabolic disorders. For example, varying the glycemic index or the energy source influences the composition of the HMO and, consequently, the bacterial strains involved in their metabolism. Therefore, it is crucial to consider the dynamics and possible factors influencing milk microbiome, in order to safeguard the newborn health (Seferovic M.D. et al., 2020).

In summary, breast milk can act as a dynamic "incubator" that enriches, protects, and transports specific bacteria in the newborn intestinal tract. Exclusivity, duration, and modality (directly or using breast pump) of breastfeeding shape infants gut microbiota and its overall composition (Moossavi S. et al., 2019; Fehr K. et al., 2020).

CONCLUSION

Pregnant women should be properly informed by medical staff about the actual consequences of VD or

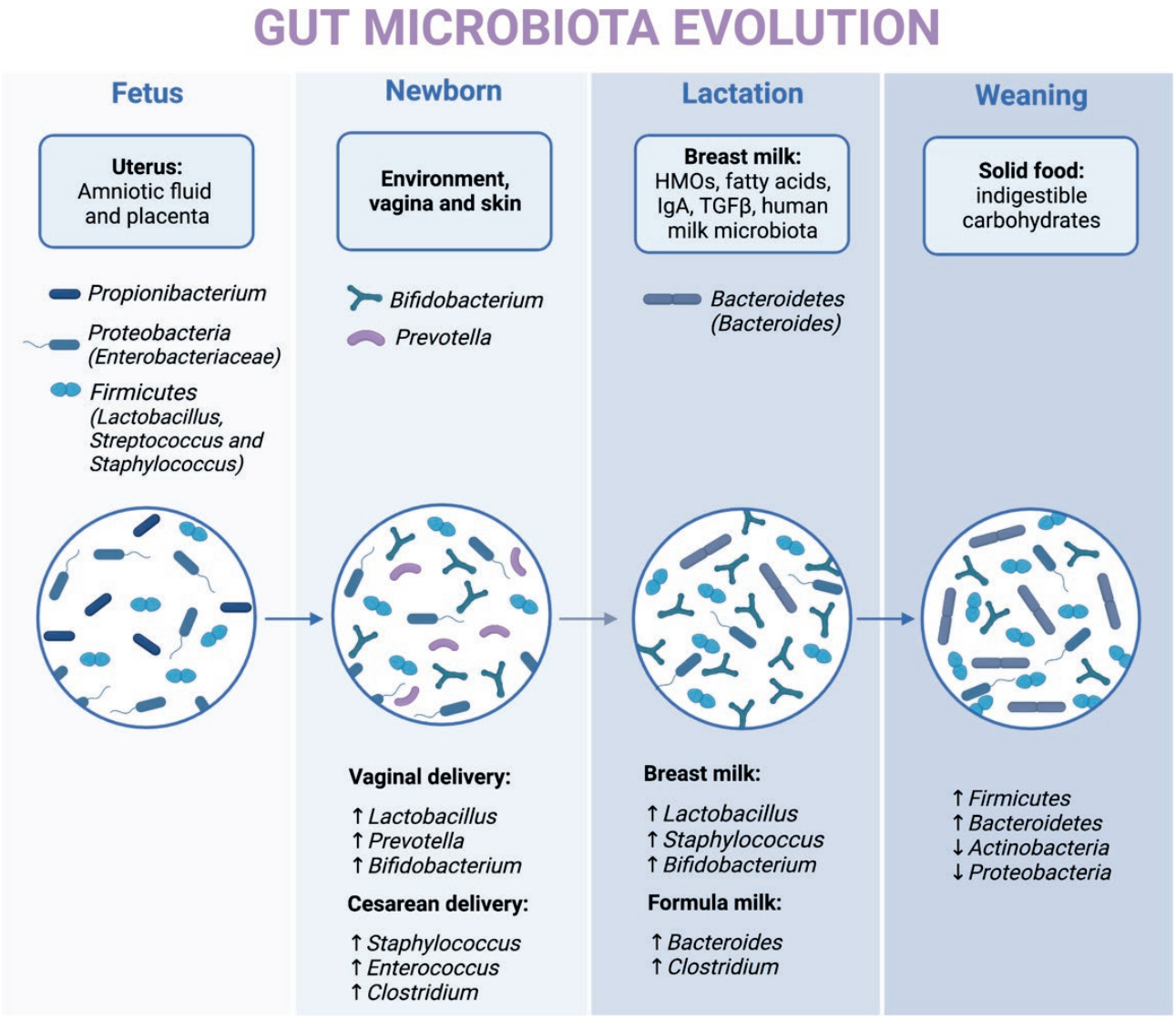

Figure 2. Development of gut microbiota in human infant. Diversity of gut microbiota increases with age. Arrow represents an increase/decrease. Created with BioRender.com.

CD delivery modes on child health, limiting CD to peculiar conditions.

Breastfeeding becomes even more important after CD, since newborn do not inherit maternal vaginal and intestinal microbiota.

Currently, it is possible genetically identify bacterial microbiota in maternal feces and breast milk and transfer specific selected strains to newborn to help developing a physiological microbiota.

It will be crucial to determine the best way to transfer mother microbiota to her caesarean-born children, through vaginal seeding or fecal microbiota transplantation, as well as to develop a universal cocktail of bacteria to reproduce the healthy microbiota (Mueller N.T. et al., 2019; Korpela K. et al., 2020).

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