



# Neonatal Microbiome- can we Interfere?



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## Abstract

There is increasing body of evidence that microbiome is a major factor determining our health. In growing infants, dysbiosis can lead to susceptibility of infections (especially necrotic enterocolitis), colic and general digestive discomfort. Also, dysbiosis is implicated in lifelong health, by increasing the risk of a wide range of diseases and medical conditions including allergy, autoimmune diseases, cardiovascular and metabolic diseases, digestive disorders, even psychological disorders such as autism, anxiety and depression. Early infancy is an important window for establishing host-microbiome interactions. Intestinal colonization is initiated as early as during fetal life and continues during delivery and early infancy. Among the most important factors that influence early colonisation are the mode of delivery and the gestational age of the newborn. During early infancy, there is a range of other very important factors that are implicated in the development of gut microbiome, such as duration of breastfeeding, infections and antibiotic use, as well as several environmental factors (family size, cultural and geographical influences, early exposure to animals). Better understanding of factors dictating early colonization can point out some possibilities to interfere during that critical period and enable wellbeing throughout the entire life.

**Keywords:** Neonate; Microbiome; Dysbiosis; Mammary glands; Placenta, Amniotic fluid Umbilical cord blood

## Introduction

Microbes, mostly bacteria's, colonize every surface of our body, including the organs that used to be considered sterile such as lungs, placenta and mammary glands. We have tenfold more bacterial cells in our body than our own, which is over 100trillion microbial cells with 8million genes versus our 22000 genes of all body sites, the gut is the most heavily populated and represents the complex and dynamic microbiome community [1-5].

Microbiome is unique for every person, like a finger print. Within the gut of each individual, a group of about 160 bacterial species can be found from a total of approximately 1000 species of known prevalent bacteria [3-6]. Even, identical twins only share 50 to 80 % of the species in the gut microbiome, despite the fact that host genotype plays an important role in determining the bacterial composition in the gut [7-8]. Due to the influence of environmental factors, the composition of gut microbiome varies within the same individual over time, as well. However, despite these changes in microbial composition and interindividual differences, the entire genome of the gut microorganisms is comparable across the human population [3,7].

## Significance of Neonatal Microbiome

The term "microbiome", formerly known as "microbiota", was coined by Joshua Lederberg, an American molecular biologist. This Nobel winner argued that microorganisms inhabiting human body should be included as part of the human genome, because

of their influence on human physiology [9]. And indeed, the gut microbiome has multiple and very important functions that include nutritional, physiological, metabolic and immunological functions [3,10].

According to that, there is increasing body of evidence that microbiome is a major factor determining our health. The association between gut dysbiosis and the development of various disorders has been recognised a long time ago. Even Hippocrates has been quoted as saying "death sits in the bowels" and "bad digestion is the root of all evil" in 400 B.C. and is becoming well established [11]. In growing infants, dysbiosis can lead to susceptibility of infections (especially necrotic enterocolitis), colic and general digestive discomfort. Also, looks like that dysbiosis is implicated in lifelong health, by increasing the risk of a wide range of diseases and medical conditions including allergy, autoimmune diseases, cardiovascular and metabolic diseases, digestive disorders, even psychological disorders such as autism, anxiety and depression [3,12-14].

## Factors affecting Microbiome Composition

Early infancy is an important window for establishing host-microbiome interactions. We should be aware of the fact that intestinal colonization is initiated as early as during fetal life and continues during delivery and early infancy [15]. This period of colonization seems to be crucial for life long health. In addition to host genome, there are several factors that appear to be very

important for affecting infant gut microbiome composition and include: mother to infant vertical transmission during pregnancy, mode of delivery, gestational age, diet, medication use and environment.

At the end of the 19th century, Henry Tissier, pediatrician at the Pasteur institute in Paris, asserted that human babies develop within a sterile environment and that they acquire first bacterial inoculum on their way through the birth canal. For more than a century, the sterile womb hypothesis remained dogma. Any bacterial presence in the uterus was assumed to be dangerous for the fetus. To a certain extent, that was true, since a strong correlation between intrauterine infections and preterm labor has been found, especially when birth occurs before 30 weeks of pregnancy. The possible explanation would be the influence of maternal immune factors on bacterial invasion of the amniotic cavity and the promotion of inflammatory cascade, which can lead to premature labor. As regards healthy, term pregnancies, relatively few studies have examined their uterine microbiome [4,16].

However, the dogma of sterile fetal life has recently been challenged [16,17]. Indeed, the presence of microbe's traces have been found in placenta, amniotic fluid and umbilical cord blood of term infants without any indication of inflammation. Meconium is not sterile either, since it harbors its own microbiome, only less diverse than adults one (4-5,17,18). During pregnancy, future mother's body undergoes many adaptation changes of virtually all organs, affecting in the same time her oral, urinary tract, vaginal and mammal microbiome, resulting in dramatic remodeling and reduction of microbial diversity in the gut [19,20]. The study of Jimenez, on mice, has shown the transfer of maternal gut bacteria to fetus in mammals, but the exact origin, timing, as well as the significance of intrauterine microbe transfer, is still not clear [17,19].

Among the most important factors that influence early colonization are the mode of delivery and the gestational age of the newborn. On their way through the birth canal, virginally born newborns form microbiome similar to mother's vaginal and fecal bacteria composition, in contrast to those born by cesarean section whose microbiome resemble bacteria from mother's skin and hospital environment. In addition, prophylactic antibiotic therapy prior cesarean section, which is standard care and part of the guidelines in many countries, also has important role in altering the microbiome of these infants. We should mention here, that cesarean born babies, among all of these, have delayed and less probability of being breastfed. So, in comparison to virginally born, infants delivered by cesarean section have lower total bacterial count and less diversity of bacteria with higher levels of *Staphylococcus*, *Corynebacterium* and low or absent *Bifidobacterium*. Eventually, these babies "catch-up" the diversity and stability of the microbial composition of vaginal birth babies, but still retain a fact that they had aberrant patterns of colonization during one critical period for immune and metabolic development [3,13,14,18].

There is a significant difference between microbiome of healthy term and premature newborns. Microbiome of preterm infants is characterized by delayed colonization, lower diversity with lower proportion of beneficial *Bifidobacteria* and increased susceptibility to colonization with pathogenic microbes. In addition to immature gut structure and function, premature infants are under severe risk of delayed and aberrant colonization, taking in consideration factors such as aseptic environment of the intensive care unit, frequent use of total parenteral nutrition with delayed enteral feeding, as well as frequent prenatal and postnatal antibiotic administration [3,13,18,21].

Mode of early nutrition also plays a very important role in gut colonization [3,13,18]. By the end of the first week of life, in a gut of healthy term babies predominate beneficial *Bifidobacteria* and *Lactobacillus*, while in formula fed infants prevalent flora is more like adult one, with abundance of potentially pathogenic bacteria (18). Human milk is rich in prebiotics and probiotics, both very beneficial for the gut. Prebiotics of human milk, soluble, non-digestible carbohydrate molecules, selectively stimulate the growth of gut bacteria, particularly *Bifidobacteria*, and can bind pathogens, preventing their adhesion to the mucosal surface. They are present in 10 to 100fold the concentration of oligosaccharides found in cow's milk [22]. Also, 2 to 18 species from the total of over 200 different species of bacteria could be isolated from human milk [23]. For the newborn, human milk presents a rich source of beneficial bacteria's that significantly contribute to the composition of healthy gut microbiome [3,18]. It is also important to note that the composition of breast milk depends on the health of the mother, her immunologic, metabolic and nutritional status and diet, socioeconomic status, stress, antibiotic use, as well as her own microbiome [5].

After birth, during early infancy, there is a range of other very important factors that are implicated in the development of gut microbiome. In addition to the duration of breastfeeding, infections and antibiotic use, several environmental factors (including family size, cultural and geographical influences, early exposure to animals) significantly contribute to microbiome composing [13,14,24].

There is a strong association between microbiome disturbances and antibiotic use, both prenatally and postnatally. The exact influence of antibiotic treatment is difficult to predict due of the differences in antibiotic specificity, dosage, administration route and length of treatment. However, studies have shown that about one third of bacterial species may be disrupted, without recovery of the microbiome composition within 4 weeks and only partial recovery within 8 weeks [3,25-27]. Even a course, as short as 48 hours, of parenteral use of ampicillin and gentamicin appears to cause significant reduction of *Bifidobacterium* and *Lactobacillus* species and allows an overgrowth of other species such as *Proteobacteria* in term newborn [27]. So, early empiric use of antibiotics can cause sustained suppression of microbial diversity and increase the risk of rebound pathogenic overgrowth. Delayed and disrupted gut colonization can also be the result of

perinatal antibiotic treatment, especially in premature infants [3,28].

It became clear that the environment, in which newborn and young infant grow, also represents a significant factor influencing microbiome development. Numerous epidemiological studies have shown that children who grow up on traditional farms and had an early-life contact with farm animals are protected from asthma, hay fever and allergic sensitization [24,29-30].

### Conclusion

The influence of the microbiome composition on lifelong health, starting from the very beginning of life, became obvious. This should encourage further research in the field of early colonization and all involved factors. Better understanding of factors dictating early colonization can point out some possibilities to interfere during that critical period and enable wellbeing throughout the entire life.

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