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Functional nutrients in infants born by vaginal delivery or Cesarean section

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Abstract

The development of a proper neonatal microbiota is of great importance, especially for the effects that dysbiosis has in acute and chronic diseases' onset.

The microbiota, particularly the intestinal one, plays a crucial role in maintaining the health of the host, preventing colonization by pathogenic bacteria and significantly influencing the development and maturation of a normal gastrointestinal mucosal immunity.

Several factors may interfere with the physiological development of microbiota, such as diseases during pregnancy, type of delivery, maternal nutrition, type of neonatal feeding, use of antibiotics, exposition to hospital environment (*e.g.*, neonatal intensive care unit) and genetic factors.

Thanks to a proper maternal and neonatal supplementation with specific functional nutrients, it is now possible to correct dysbiosis, thus reducing the risks for the newborn's health.

In this review of the literature, we give an overview of the studies highlighting the composition of the maternal, fetal and neonatal microbiota, the factors potentially responsible for dysbiosis and the use of functional nutrients to prevent diseases' onset.

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Key words: Functional nutrients; probiotics; prebiotics; microbiota; fermented matrix.

Contributions: the authors contributed equally.

Conflict of interests: the authors declare no potential conflict of interests.

Funding: Funded by Merqurio Editore S.r.l., with the unconditional contribution of Nestlè Italiana S.p.A.

Received for publication: 6 November 2017.
Accepted for publication: 19 December 2017.

La Pediatria Medica e Chirurgica 2017; 39:184
doi:10.4081/pmc.2017.184

Introduction

In recent decades, several studies have shown that the increasing incidence of autoimmune, infectious and allergic diseases in pediatric and adult population may be closely related to dysbiosis, which is the alteration of the physiological development of human gut microbiota.

For this reason, the study of microbiota and microbiome has become a priority to clarify the pathogenesis of these diseases, but also to plan a possible therapeutic and preventive intervention.

The microbiota includes all the microorganisms that live in the human body. The human gut, especially the large intestine, has the greatest number of bacteria compared to any other part of the body. It contains about 10^{14} microorganisms, which is ten times the number of human cells.

After initial colonization, the intestinal microbiota composition is unique for each individual, although more than 95% of the bacteria belong to four major phyla: *Firmicutes, Bacteroidetes, Actinobacteria* and *Protecteobacteria.*

The development of this complex microbiota begins at birth and continues over the years. It plays a key role, influencing both intestinal and immune functions, as well as defending the organism from external pathogens. For this reason, any interference with its development can be at the origin of several diseases.

Before going into details of this review, we think it would be useful to provide a small glossary of the most common terms in the field of functional nutrients.

Microbiota is defined as the sum of symbiotic microorganisms, which coexist within the human body without damaging it. On the other hand, the microbiome is the sum of genetic and environmental interactions of all microorganisms in a defined environment, such as the human organism.

Probiotics, according to the universally accepted definition of FAO/WHO, are living organisms that, when administered in an adequate amount, confer a benefit for the host's health. Prebiotic is any substance present in food that is not absorbed in the gut but which selectively stimulates the growth and/or activity of one or a small number of bacteria in the colon. The majority of them are carbohydrates, especially oligosaccharides like fructooligosaccharides (FOS).

The term *symbiotic* is used to indicate products that contain both probiotics and prebiotics; in this case, the combination of the two products is fundamental because each probiotic takes benefits from a specific type of prebiotics.[1]

Recently, a new concept has been introduced: the fermented matrix. This product is obtained following the fermentation process carried out by beneficial bacteria of our organism (probiotics), thus generating metabolites, called postbiotics, capable of performing anti-inflammatory, anti-microbial and anti-oxidant activity.

Maternal microbiota during pregnancy

The number of Cesarean sections (CS) in industrialized countries has dramatically increased in recent decades (from 15% in 1990 to 27% in 2011), and in some countries, it exceeds 50% of total births, when 15% is the estimation of CS strictly needed for maternal and fetal clinical condition.[2]

Several studies have highlighted a correlation between this increase of CS with an even higher incidence of pediatric diseases such as neonatal respiratory distress,[3] respiratory infections by syncytial virus,[4] asthma,[5] and an increased risk of developing celiac disease,[6] diabetes mellitus type 1[7] and obesity.[8]

This correlation could be interpreted by the interruption of maternal bacterial flora transmission to the infant due to the CS delivery. Children born by CS have an altered microbial colonization because, at birth, they are exposed to the maternal skin and environmental microbiota, rather than the vaginal/intestinal maternal microflora.[9]

It has also been shown that during pregnancy maternal vaginal and intestinal microbiota experience several changes, which are crucial for the vertical transmission of the microbes during labor and spontaneous delivery.

It has been observed that there is a reduced vaginal bacterial diversity in pregnant women compared to non-pregnant women, with a predominance of *Lactobacilli, Clostridiales, Bacteroidales* and *Actinomycetales*. Also, at later gestational ages, there is a higher concentration of some species of *Lactobacillus* such as *L. iners, L. crispatus, L. jensenii and L. johnsonii.*[10]

Another study has shown that from the first to the third trimester of pregnancy there is a reduction in pro-inflammatory microorganisms of the *Proteobacteria* species, including the family of *Enterobacteriaceae* and the genus *Streptococcus*, while there is an increase in anti-inflammatory bacteria, such as *Faecalibacterium prausnitzii.*[11]

All these changes are not influenced by pre-pregnancy weight, gestational diabetes, diet and antibiotics administration, demonstrating that they are physiological changes related to pregnancy itself and regulated by the maternal endocrine and immune system.

These changes in the maternal microbiota are part of an adaptive response that promotes the health of the fetus and proper colonization at birth before exposing the baby to environmental microorganisms.

The growing presence of *Lactobacilli* during pregnancy allows maintaining a low pH in the vaginal environment, thus limiting bacterial diversity, reducing the incidence of bacterial vaginosis[12] and preventing the pathogens rise to the uterus, where they may infect amniotic fluid, placenta and foetus.[13,14]

Animal studies have shown that changes in the maternal gut microbiota can promote the growth of the mice. Probably, these microorganisms are able to accumulate energy for both maternal and fetal growth. Moreover, their transfer at birth helps the infant in the first hours of life, which is characterized by high energy expenditure.

The intrauterine environment has always been considered sterile, but recent evidence has shown the presence of microorganisms in amniotic fluid, cord blood, amniotic membrane and placenta of healthy neonates born through both CS and vaginally.[15-17]

Animal studies also found that administration of *Enterococcus faecium*-labelled strains to pregnant mice leads to the presence of these strains in amniotic fluid and fetal gut.[18]

These preliminary data need to be confirmed with further research, as the mechanisms behind the transfer of these bacteria from mother to fetus are not entirely clear. However, it seems that the microorganisms found in the amniotic fluid and in the umbilical cord come from the maternal gastrointestinal tract.

The most likely hypothesis is that maternal dendritic cells cross the paracellular space of the intestinal epithelium and take bacteria from the maternal intestinal lumen. Then, through lymphocytes, intestinal microorganisms of microbiota reach the circulatory and lymphatic system, other mucous surfaces such respiratory and genitourinary tract, salivary, lacrimal and mammary glands and the placental barrier.[19]

It has also been demonstrated that the administration of probiotics during pregnancy is capable of modifying the expression of Toll-like receptor (TLR) genes in placenta and meconium of neonates.[20]

These data seem to conclude that there is also a specific placental microbiota, which is the result of the interaction between maternal microorganisms coming from different parts of the body. These microorganisms are modified by pregnancy, antibiotic use and probiotic administration, and are able to begin the process of colonization of the fetus that will be completed after birth and with feeding.[21]

Development of neonatal microbiota

In addition to this intrauterine exposure, the major bacterial colonization of the neonates occurs at birth when they are exposed to the fecal, vaginal and skin maternal microbiota.[22]

During vaginal delivery, anaerobic strains such as *Escherichia coli, Staphylococcus* and *Streptococcus,* colonize the infant's gut and create the optimal environment for *Bacteroides* and *Bifidobacterium* species growth.

Microbiological differences between neonates born by spontaneous vaginal delivery or CS (especially with intact membranes) are relevant: in neonates undergoing CS, there is only an early colonization with bacteria which are located on the mother's skin (*e.g.*, *Staphylococcus*, *Corynebacterium*, *Propionibacterium*), while *Bacteroides* and *Bifidobacterium* are found later. Moreover, high concentrations of *Clostridium difficile* were observed.[23]

Nowadays, we do not know exactly how long these differences of microbiota last, but there are evidence showing up to 7 years of life.[24]

However, a recent review[25] showed significant differences until 3-6 months of life, while in the following period they are substantially reduced. Hence, the role of delivery modality seems to decrease after this age.

Particularly, in neonates born by Cesarean section, there are plenty of phylum *Firmicute* (especially *Clostridium* and *Lactobacilli*),[26] while there are a small amount and diversity of phylum such as *Actinobacteria* and *Bacteroidetes*, especially *Bifidobacterium* and *Bacteroides* strains, which are very frequent in vaginally delivered neonates.

Beyond the type of delivery, another crucial determinant in the development of the microbiota is the type of feeding: in particular, human milk, with its probiotic and prebiotic concentration, is able to continue the transfer of micro-organisms from mother to child started in the uterus.

Moreover, it is likely that with exclusive breastfeeding infants born by Cesarean section can benefit from a microbiota which is very similar to those of infants born by vaginal delivery.

If breastfeeding can not be started and maintained, it is possible to administer human bank milk as an alternative to formula milk. The problem arises during the pasteurization, because this process, besides destroying pathogenic microorganisms, also kills

useful bacteria. On the other hand, this process does not alter prebiotic concentrations such as long-chain polyunsaturated fatty acids and oligosaccharides, which can promote the growth of *Bifidobacterium* species in the neonatal gut.[27] When human milk is not available, it is possible to use formula milk enriched with prebiotics, probiotics and, more recently, fermented matrix.

In addition to the type of delivery, the use of antibiotics and the type of feeding may determine a sub-optimal composition of the neonatal microbiota, as well as the presence of an altered maternal vaginal or intestinal microflora (*e.g.*, overweighted or obese women[28]). Moreover, some diseases correlated with pregnancy, such as diabetes[29] or eczema,[30] could transfer to the infant the typical microbiota of the diseases themselves.

Possible interventions to modify microbiota

There is strong evidence about therapeutic and preventive effects of functional nutrients supplementation, like probiotics, prebiotics, synbiotics and fermented matrix. Several studies have attempted to better clarify the possible effects of these products administration during pregnancy on the maternal microbiota and the newborn.

For example, an Italian study has shown that supplementing women during pregnancy and breastfeeding with a mixture of probiotic strains (VSL # 3) causes an increase in bifidobacteria and lactobacilli in colostrum and mature milk, positively influencing the microbiota of human milk.[31]

These positive effects were more evident in women who had vaginal delivery than in those undergoing a Cesarean section. In addition, in a recent review, Thum and colleagues[32] reported that maternal supplementation during pregnancy with probiotics, prebiotics and synbiotics had several positive effects (*e.g.*, prevention of atopic diseases, improvements in glucose homeostasis, reduction of gestational diabetes and immune and inflammatory diseases, increase in the concentration of available folate).

Although high heterogeneity between studies, it seems evident that there are convincing data about the supplementation with functional nutrients in neonates and infants. In this field, literature provides abundance of conclusive data, supported by international pediatric scientific societies. For example, there are promising results regarding probiotic supplementation in the treatment of acute gastroenteritis,[33] antibiotic-associated diarrhea,[34] but also in the prevention of atopic diseases[35] and necrotizing enterocolitis of premature infants.[36-37]

In addition, some evidence is available on the use of formula milk supplemented with functional nutrients such as prebiotics. For example, several researches have shown that the use of formulas specifically supplemented with prebiotics, improves stool consistency when compared to infants fed with standard formulas.[38] Moreover, genetic sequence studies have demonstrated the role of prebiotics (especially oligosaccharides) in modifying the intestinal microbiota similarly to what happens in breast-fed infants.[39]

However, there is increasing interest in the possible use of fermented matrix as a supplement for formula milk. The available results are encouraging, especially considering the benefits of this type of administration, which avoids exposure of the newborn to living microorganisms such as probiotics.

In 2015 a review including five randomized controlled trials in which a fermented formula milk was compared with standard formula milk showed no additional beneficial effects from the use of fermented milk, although the authors did not exclude benefits in term of gastro-intestinal symptoms.[40]

However, a recent multicenter, randomized, double-blind, placebo-controlled study revealed that the administration of fermented skim milk with *Lactobacillus paracasei CBA L74* could prevent common respiratory and intestinal infections in preschool-age children (12-48 months of life).[41] Further research is needed to demonstrate the capacity of this fermented matrix to modify the neonatal microbiota, but the available data would seem to confirm its role.[42]

In addition to maternal or neonatal supplementation with these functional nutrients, other methods have also been experimented to achieve effective microbiota modification. In particular, a pilot study has shown that contact in the first 2 minutes of life of the mouth, face and body of the baby with a sterile gauze previously incubated in the vagina of healthy women a few hours before CS, was effective in restoring a microbiota similar to that of a vaginally born baby.[43] These results are intriguing, but the small number of subjects involved in the study and the short follow-up of the patients need to be confirmed by larger well-designed studies.

Conclusions

Given these data, in order to guarantee the development of a neonatal intestinal microbiota as physiological as possible, the following conclusions can be drawn: i) try to limit CS to those strictly necessary for maternal-fetal medical problems; ii) according to severity of clinical conditions, try to reduce prescription of pre and intrapartum antibiotic therapy and administration to neonates; iii) promote exclusive breastfeeding, also in neonates born by Cesarean section, since it has proven to be capable of restoring almost total physiological gut microbiota. When breastfeeding is not possible, the use of human bank milk or formula milk added with prebiotics, probiotics and fermented matrix is recommended; iv) prescribe specific functional nutrients following international guidelines. Each functional nutrient has its own characteristics, and it is effective in preventing or curing a specific disease.

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