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Review article

## Modern View on the Formation of Intestinal Microbiota in Children of the First Year of Life

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### Abstract

*During pregnancy, the maternal microbiome influences the development of the fetus and generally creates the prerequisites for the formation of the infant microbiome. Currently, the study of external factors on the formation of the microbiome, including the influence of the mother's microbiome on the formation of the infant's microbiome, remains relevant.*

**The purpose of this review:** to provide up-to-date data on the development of the intestinal microbiota of a child at the early stages of its formation and the factors influencing this process.

Research of publications were conducted in search engines as PubMed, eLibrary.ru, Google Scholar. The selection of publications was carried out in accordance with the purpose of the review.

We analyzed current data on the infant gut microbiome and concluded that the infant gut microbiome is affected by maternal age, maternal overweight, obstetric history, gestational age, mode of birth, work performed during pregnancy, place of residence, diet during pregnancy and lactation, illness and antibiotics. All these factors affect the state of the maternal microbiome itself and affect the microbiome of the child through breastfeeding. The intestinal microflora of the newborn is largely dependent on the state of the mother's microbiome, it is mainly through breast milk. The microbes of our body control all life processes, as well as the stability of the internal environment.

**Keywords:** microbiota, caesarean section, breastfeeding, natural childbirth, children.

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## Introduction

In recent years, due to the achievements of medicine, the diseases of mother and child are decreasing, attention is paid to the health of mother and child, a lot of medical work is carried out. The main object requiring serious study of the health of the child and mother is the microbiota, so we pay attention to the study of this topic.

The human microbiota is an evolutionarily formed ecological system of microorganisms that inhabits the open cavities of the body and maintains the biochemical, metabolic, and immunological balance necessary to maintain health [1].

Microbiota is a community of millions and millions of microorganisms living in the human intestine; an internal microbial ecosystem. It is known that the formation of the microbiota begins from the moment of birth of a child and changes throughout life under the influence of the following factors: diet and eating regimen; the presence of diseases; taking medications (for example, antibiotics or hormonal medicines); taking prebiotics / probiotics / synbiotics; lifestyle features.

The human microbiome is a complex organism consisting of 10-100 trillion microbial cells (bacteria, archaea and microbial eukaryotes) and viruses, the genomic catalog of this superorganism consists of 3.3 million genes. The maternal microbiome contributes to the modulation of the fetal immune system starting from the antenatal period [2].

The formation of microbial communities at an early age plays an important role in the immunological, endocrine, metabolic and other pathways of human development. The human microbiome can be considered as a whole separate organ of our body. We acquire it before birth and how it will be depends on many factors, such as the microbial flora of the mother's intestines, the way of birth, nutrition and its frequency, vaccination,

## Search strategy

We searched for sources using the keywords: infant microbiome, intestinal microbiome, children in the scientific databases PubMed, Google Scholar, Web of Science, and Curenica. The depth of the search was 10 years (2012 to 2022). Sources were selected according to the purpose of the literature review. Preference was given to publications in peer-reviewed journals. In the first stage, a general array of articles was selected, from

## Main part

The formation of the intestinal microbiota begins in the intrauterine period and continues for many years postnatally. Research has identified microbial DNA and cellular structures of intestinal bacteria in the placenta and amniotic fluid before birth in the absence of ruptured membranes [8]. Nutrition, maternal lifestyle and the use of anti-bacterial medications during pregnancy play an important role in the formation of the fetal intestinal microbiota.

During childbirth, the mother is the first source of colonization of the gastrointestinal tract of the child, while the natural method of delivery is one of the fundamental factors influencing the formation of the microbiota.

Currently, factors that have been clearly proven to affect the microbiota of the vagina and other parts of pregnant women are diet, antibiotic use, infection and maternal stress. Factors that need to be further studied are immune status, age and genetic background. In

diseases, administration of antibiotics, complementary foods, etc. [3].

It is of obvious interest to determine the significance of maternal health factors in the formation of the level of health of the newborn.

As the maternal body is the environment for fetal development, any deviations in maternal homeostatic parameters have a direct impact, based on the principles of the functional approach of the mother-fetal relationship, the «organ to organ» principle, the concept of histohaematic barriers and the importance of placental function [4].

According to refined calculations, the total mass of the human microbiota is approximately 0.2 kg [5]. The human body contains about  $3.8 \times 10^{13}$  bacteria, which is equal to the number of the body's own cells. Several biotopes with microbial populations are distinguished in the human body [6].

However, the most important biotope of the human body is the intestine, which includes more than 700 genera of bacteria and 2500 different types of microorganisms [7].

The microbiota at an early age is not only the main regulator of infant health, but is also associated with long-term health. Pregnancy and the newborn period is a golden time for the formation of the microbiota of infants, which is influenced by both environmental factors and genetic factors.

**The purpose of this review:** to substantiate the current general information about the state of the issue of the formation and dynamics of the child's microbiome, to provide up-to-date information through a review of the literature on the early development of the microbiome of young children and the factors influencing this process.

which the most relevant ones were filtered according to keywords and context.

Inclusion criteria: Evidence level A, B publications: meta-analyses, systematic reviews, cohort and cross-sectional studies.

Exclusion criteria: summary reports, newspaper articles and expert opinion in the form of short report.

addition to these factors, complications during pregnancy are also important influencing factors. All stages of pregnancy have a significant impact on the formation of the microbiota. It is known that the abundance of many types of microbes changes significantly during pregnancy.

When a full-term baby is born naturally, they swallow small amounts of the mother's vaginal and intestinal microorganisms. Then these are mainly bacteria from the genera *Prevotella*, *Sneathia* and *Lactobacillus*. In the case of a caesarean section delivery, the newborn is initially colonized by the skin microbiome of the mother and medical staff, primarily consisting of bacteria from the genera *Propionibacterium*, *Corynebacterium*, and *Streptococcus* [9,10].

In these infants, a delayed colonization of the intestinal phyla Bacteroidetes and low bacterial diversity have been observed during the first two years of life [11].

However, from four months of age the differences in bacterial diversity with naturally born children begin to fade, and by 12 months of age almost disappear [12].

The intestinal microflora in the first few days of life is heterogeneous and its composition changes very rapidly. During natural birth the infant's digestive tract is intensively colonised by aerobic and facultative anaerobic bacteria: *E. coli* and other enterobacteria, enterococci and staphylococci, which reduce the oxygen concentration in the intestine and thus create conditions for colonisation by obligate anaerobes. From the end of the baby's first week of life the intestinal microbiota begins to be dominated by rigid anaerobes (bifidobacteria, bacteroides and clostridia), which suppress the aerobic flora. The source of bifidobacteria and bacteroides for the baby is usually the maternal intestinal flora [13,14]. There are peculiarities in the formation and composition of the intestinal microbiota of children born by caesarean section. Babies born via caesarean section do not acquire their mother's vaginal and intestinal microflora during birth. Instead, their primary source of microorganisms comes from them the microflora present on the mother's skin, the medical staff, the delivery room, and the hospital wards [11].

In addition, caesarean section is associated with antibiotic therapy for the mother, late onset and often a short period of breastfeeding, which can affect the baby's intestinal microflora [15]. The intestinal microflora of children born by vaginal delivery are usually represented by microorganisms of the genera *Prevotella*, *Sneathia* and *Lactobacillus*, which are part of the maternal vaginal microflora. In children born by caesarean section, the intestinal microbiota is characterised by a lower diversity of bacterial species and a low bifidobacterial and bacteroides content compared with the intestinal microflora of children in vaginal delivery [16].

Various opportunistic microbes (*C. difficile*, *Enterococcus* spp., *Klebsiella* spp., *Streptococcus* spp., *Haemophilus* and *Veillonella*) are more often found in the intestinal microbiota of children born surgically [17,18]. During cesarean section, the formation of intestinal microflora in children takes longer [1]. Thus, natural childbirth or cesarean section is an important factor affecting the formation and composition of the intestinal microflora.

It is now known that the microbiota of the intestine, the most colonized biotope of the human body, largely determines its health, as representatives of the microbiota largely determine the immune response and resistance to pathogens, participate in the metabolism of a wide range of micro and macronutrients [19]. In addition, the intestinal microbiota performs the functions necessary for the vital activity of the organism, including immunomodulatory, detoxification, anticarcinogenic, digestive, colonization resistance, as well as maintaining the biochemical, metabolic and immune balance necessary for maintaining the internal environment and human health in general [20,21].

The nature of breastfeeding plays an important role in the colonisation process of the baby's intestines in the postpartum period. Numerous studies have shown that breast milk has symbiotic properties.

During breastfeeding the intestinal microbiota is mainly composed of lactic acid bacteria such as *Lactobacillus*, *Leuconostoc*, *Streptococcus*, *Enterococcus*, *Lactococcus* and *Weissella*, as well as some beneficial *Bifidobacterium* species [22,23]. Some

studies have shown that anaerobic flora, *Bacteroides* and *Clostridium*, dominate the microbiota in children receiving formula milk [24].

Most modern milk formulas are enriched with oligosaccharides, which should theoretically promote the development of the bacteria type *Bifidobacterium*. However, changes in the composition of the colonic microbiota in formula-fed children are characterised by an overdevelopment of bacteroides and clostridia and an increase in the proportion of opportunistic bacterial species, such as *Escherichia coli*, *Clostridium difficile* [25,26].

It is possible that the effect of breast milk on the formation of the infant's colon microbiota is not only due to oligosaccharides. In addition to these, breast milk contains Ig A and IgG immunoglobulins, the antimicrobial substances lysozyme and lactoferrin, interleukin-10, and lymphocytes, which modulate the child's immune system and influence the composition of microorganisms that take root in the gastrointestinal tract [27,28]. The addition of pasteurized human milk to the diet of formula-fed infants is known to promote the formation of a microbiota similar to that of breastfed infants [26].

According to some studies, in the first year of life, the infant microbiota is characterised by relatively low microbial diversity. Gradually, depending on the type of diet and the breadth of contact with the environment (presence of animals in the home, number of siblings, hygienic conditions, use of antibiotics), the taxonomic diversity of the colon microbiota enriches considerably [29,30].

According to researchers, after the introduction of complementary foods into the child's diet, in addition to the activation of the growth of polysaccharide-fermenting bacteria, there is a significant change in the microbial community of the colon, characterized by a decrease in the proportion of *Bifidobacterium* (*Bacteroidetes* or *Firmicutes*) [31,32].

To this day, it has been established that the normal intestinal microbiota has the following functions: prevention of colonisation of the digestive tract by pathogenic microorganisms (direct competition with pathogenic bacteria for nutrient substrate and habitat); participation in the regulation of gastrointestinal motility; formation of local and systemic immunity (as antigen); and formation of food tolerance; non-digestible endogenous and exogenous detoxification of substrates and metabolites; intestinal microbiota absorb toxic substances and destroy them with intestinal contents or use them for their own needs; takes part in cholesterol metabolism in the enterohepatic circulation of bile acids; participates in the synthesis of vitamins B, K, biologically active substances, etc. *Bifidobacteria* synthesize B vitamins and play a role in vitamin C and D metabolism, while vitamin K production is performed by microorganisms of the bacteroidetes group [33].

Family members and close relatives (siblings) have also been described as important environmental factors that may influence the colonisation pattern of the infant intestinal microbiota, but so far there is no conclusive evidence for the influence of birth parity, the sex of the children, remains to be established.

According to a cohort study in the Netherlands, it has been shown that 1-month-old infants, along with older siblings, have more bifidobacteria in the intestinal microbiota than infants without siblings [34].

In this case study, it was also reported that the proportion of bacteria not related to *Escherichia coli* increased in infants without older siblings.

A recent study with a Danish cohort has shown that the presence of older siblings is associated with increased microbial diversity and intestinal biodiversity in early childhood, while the presence of pets has little effect on the intestinal microbiota.

Geographic location may also influence the microbiota, as differences in the microbiota appear to be related to diet and lifestyle in a particular area. In addition, different ethno-geographical populations have different regional diets and cultural practices. For example, the microbiota of children living in rural Africa differs from the microbiota of children living in urban areas of Italy [35]. At the same time, several other studies have investigated microbial diversity and composition on geographical influences related to ethnicity or diet [34].

In general, home structure and family environment (rural or urban) appear to influence colonisation of the intestinal microbiota after birth, although more research is needed to identify specific contributing factors.

## Conclusions

Thus, the development of the infant intestinal microbiota begins during the period of intrauterine development. The qualitative and quantitative parameters of the intestinal microbiota of the newborn are influenced by a number of exogenous and endogenous factors, including nutritional and environmental characteristics, primarily related to the maternal body.

The formation of the intestinal microbiota in infants and children in the first year of life is also influenced by the mode of delivery - natural childbirth or caesarean section, and the nature of breastfeeding - breastfeeding or artificial feeding. Despite the considerable amount of information in this area, the interpretation of the results obtained in many studies is ambiguous among the authors. This is due, in particular, to different ways of identifying microorganisms, the lack of clear recommendations for the study of the

The intestinal microbiota mainly consists of six microbial species, including Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Tenericutes and Fusobacteria. Interestingly, the dominant species found in the adult microbiota are Firmicutes and Bacteroidetes, which together may account for up to 90% of the total gut microbiota [35, 36].

The intestinal microbiome is important for promoting overall health because it supports the digestive system, immunity and metabolism and also influences intestinal-brain interaction processes. The maternal microbiota is transmitted vertically to the newborn. The method of birth, gestational age at birth, method of feeding and maternal factors determine the colonisation of the infant's microbiota. The microbiota in early life is crucial for brain development and immune system formation in the offspring, which affects both infant and long-term health. Therefore, from the course of pregnancy until birth, it is important to make sensible interventions to regulate the maternal or offspring's microbiota for the health of the offspring.

digestive tract microbiota of infants in the first year of life, taking into account the multifactorial system of human microbiota formation. Consequently, the development of microbiota research and research approaches remains an actual problem for the medical industry.

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## Нәрестелердегі микробиотаның қалыптасуы мен динамикасы мәселесінің қазіргі жағдайы

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## Түйіндіме

Жүктілік кезінде ана микробиомасы ұрықтың дамуына әсер етеді және жалпы нәресте микробиомасының қалыптасуына алғышарттарды жасайды. Қазіргі уақытта микробиоманың қалыптасуына сыртқы факторларды, соның ішінде нәресте микробиомасының қалыптасуына ана микробиомасының әсерін зерттеу өзекті болып қала береді.

**Шолудың мақсаты:** бала ішек микробиомасының қалыптасуының және дамуының алғашқы кезеңдеріне әсер ететін факторлар туралы заманауи мәліметтер беру.

Зерттеу жарияланымдары PubMed, eLibrary.ru, Google Scholar іздеу жүйелерінде іздестірілді. Басылымдарды іріктеу шолу мақсатына сәйкес жүргізілді.

Нәресте ішек микробиомасы туралы ағымдағы деректерді талдадық және нәресте ішек микробиомасына ананың жасы, ананың артық салмағы, акушерлік анамнез, жүктілік мерзімі, босану жолы, ананың жүктілік кезіндегі атқарған жұмысы, тұрғылықты жері, жүктілік кезіндегі және емізу кезіндегі тамақтануы, ауырған аурулары және қабылдаған препараттары әсер етеді деген қорытындыға келдік. Осы факторлардың барлығы ананың микробиомасына және де емшек емізу арқылы баланың микробиомасына әсер етеді. Жаңа туған нәрестенің ішек микрофлорасы көбінесе ананың микробиомасының күйіне байланысты, ол негізінен емшек сүтімен өтеді. Біздің денеміздің микробтары барлық өмірлік процестерді, сондай-ақ ішкі ортаның тұрақтылығын бақылайды.

**Түйін сөздер:** микробиота, кесарь тілігі, емшек сүтімен емізу, табиғи жолмен босану, балалар.

## Современный взгляд на формирование кишечной микробиоты у детей первого года жизни

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## **Резюме**

*Во время беременности материнская микробиома влияет на развитие плода и в целом создает предпосылки для формирования микробиома младенца. В настоящее время остаются актуальными изучение внешних факторов на формирование микробиома, в том числе влияния микробиома матери на формирование микробиома младенца.*

**Цель настоящего обзора:** *предоставить современные данные о развитии микробиоты кишечника ребенка на ранних стадиях его формирования и факторах, влияющих на этот процесс.*

*Проведен поиск научных публикаций в поисковых системах PubMed, eLibrary.ru, Google Scholar. Отбор публикаций осуществлялся в соответствии с целью обзора.*

*Мы проанализировали современные данные о микробиоме кишечника младенцев и пришли к выводу, что на микробиом кишечника ребенка влияют возраст матери, избыточный вес матери, акушерский анамнез, гестационный возраст, способ рождения, работа, которую он выполнял во время беременности, место жительства, его диета во время беременности и кормления грудью, болезни и прием антибиотиков. Все эти факторы отражаются на состоянии собственно материнского микробиома и влияют на микробиом ребенка посредством грудного вскармливания. Микрофлора кишечника новорожденного во многом зависит от состояния микробиомы мать, она в основном через грудное молоко. Микробы нашего организма контролируют все процессы жизнь, а также стабильность внутренней среды.*

**Ключевые слова:** *микробиота, кесарево сечение, грудное вскармливание, естественные роды, детский возраст.*