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Abstract

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THE PRESENT CONCEPTION OF NEONATAL MICROBIOME FORMATION

The neonatal period is critical in the development of the microbiome and the gastrointestinal tract. That is, the microbiome regulates not only the processes that are associated with the basic functions of the gastrointestinal tract, but is associated with the content of vitamins and micronutrients, affects the development of the nervous and endocrine systems of newborns.

Fortunately, microbiome and immunity of pregnant get ready the infant for his inevitable complications. Although preterm birth has been connected with bacterial colonization of the amniotic cavity for many years, the dogma of a sterile intrauterine environment during a normal pregnancy has appeared only recently. Numerous placental microbiome and the occurrence of microorganisms in the amniotic cavity in normal pregnancy was demonstrated by metagenomic sequencing. The occurrence of microorganisms in intestine got from the operating room during resection of intestinal abnormalities immediately after birth and before feeding was also found in neonates born by caesarean section.

In this literature review, we explore the update understanding of microbial colonization of the intestine and foundation of function of the gastrointestinal tract. We discuss how mother's genital and extragenital pathologies, her diet, lifestyle, taking drugs during pregnancy form the microbiome of the fetus and its further development in the neonatal period. Also, equally important for the establishment of the neonatal microbiome are gestational age, mode of delivery, type of feeding and medication, including antibiotics. Therefore, in our opinion, the comparison of microbiota of a full-term newborn in vaginal birth and an infant born prematurely or by cesarean section is clinically significant for physicians in various fields. The study of changes in the microbial composition of the intestine is an important step in the diagnosis of pathological conditions in this period.

Keywords: microbiome, microbiota, newborn, gastrointestinal tract, dysbiosis.

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Резюме

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СУЧАСНЕ УЯВЛЕННЯ ПРО СТАНОВЛЕННЯ МІКРОБІОМУ НОВОНАРОДЖЕНИХ ДІТЕЙ

Період новонародженості є критичним в процесі розвитку мікробіому та шлунково-кишкового тракту у немовлят загалом. Тобто, мікробіом регулює не тільки процеси, які пов'язані з основними функціями шлунково-кишкового тракту, а має зв'язок з вмістом вітамінів, деяких мікронутрієнтів, впливає на розвиток нервової та ендокринної системи новонароджених.

Постнатальна мікробна колонізація є важливою ранньою подією в мутуалізмі господар-мікроб. Дуже добре, що материнські мікробіом та імунітет готують новонародженого малюка до його майбутніх проблем. Хоча передчасні пологи вже багато років пов'язані з мікробною колонізацією амніотичної порожнини та плодових оболонок, догма про стерильне внутрішньоутробне середовище під час нормальної вагітності виникла досить нещодавно. За допомогою метагеномного секвенування було виявлено великий плацентарний мікробіом, наявність мікроорганізмів у амніотичній порожнині у жінок в нормальних термінах вагітності. Також було виявлено у малюків, що були народжені шляхом кесарського розтину, наявність мікроорганізмів у тканинах кишечника, що отримані з операційної під час резекції аномалій кишечника одразу після народження та до початку годування.

В цьому літературному огляді ми досліджуємо сучасне розуміння мікробної колонізації кишечника дітей та становлення функції шлунково-кишкового тракту. Обговорюємо, як генітальна та екстрагенітальна патології матері, її харчування, спосіб життя, прийом лікарських препаратів під час вагітності формують мікробіом плода і його подальший розвиток у періоді новонародженості. Також не менш важливими для формування мікробіому новонароджених є гестаційний вік, спосіб народження, прийом лікарських речовин включаючи антибіотики та спосіб вигодовування. Тому, на нашу думку, порівняння флори дитини, яка народилась доношеною, у вагінальних пологах та дитини, яка була недоношеною, народженою за допомогою кесарського розтину є клінічно значимим для лікарів різних галузей. Дослідження змін у мікробному складі кишечника є важливим кроком у діагностиці патологічних станів у даному періоді та в розвитку дитини протягом всього життя.

Ключові слова: мікробіом, мікробіота, новонародженість, шлунково-кишковий тракт, дисбіоз.

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Introduction

The microbiome at this stage of medical development is a relatively new organ. There are billions of microorganisms in the human body, the cooperated activities of which are very significant for normal functions of organism. Such microbial association is located in the intestinal tract, where they together form the intestinal microbiome. Is there a fundamental variation between the terms of "microbiota" and "microbiome"? A microbiota is a cooperation of organisms present within a microbial association in human host. The human gastrointestinal microbiota composes of root and transitional microorganisms. A microbiome is a common microbial community and their genetic material, incorporating commensals and pathogenic microorganisms.

Decide the issue of how often gastrointestinal dysbiosis find in early life means an understanding of the "normal" neonatal microbiota which

disappointingly is need [59]. For a long time, it was reported that a neonate was born sterile, and the intestinal microbiota and other organs was full formed after birth, but many investigators now disclaim these theories about the "sterile womb" paradigm. A growing body of explorer fact has left data of finding germs in the amniotic fluid, placenta and umbilical cord in healthy full-term pregnancies [24]. Furthermore, the detection of differences in the intestinal microbiome of the newborns is a very important theme, because the microbial communities of the intestine changes in alter pathological conditions of infants. Analyses have linked certain qualities of the microbiome, such as decreased variations of numerous compositions, to intestinal disorders infants or disease states that are manifested at later stages of life like as asthma, inflammatory bowel disease, and metabolic disorders. Thus, a number of studies have reported how the early human gut microbial community can affect risk factors touch on adult health features [5].

The purpose of this literature review is to compare different opinions of scientists, selection of articles and analysis of opinions that refute the data on colonization by microorganisms after birth.

Materials and methods. 65 research articles were processed with the selection of the most relevant information about formation of the infant microbiome.

Literature review

Microorganisms and pregnancy

Many scientists believed that the development and growth of the fetus is possible only in sterile conditions. In contrast to the theory of "sterile uterus", there is information that intrauterine contact with microbes can occur [3]. Researchers by using molecular diagnostic methods have identified few non-pathogenic bacteria in the placenta and amniotic fluid of healthy children [34]. Comparing microbial associations in the placenta, amniotic fluid, meconium with meconium in infants born by caesarean section, the similarity of the microbial composition was determined by half [35].

Microbial variations have recently been found in intestinal specimens obtained directly from surgery for congenital bowel defects immediately after birth and before breastfeeding in neonates born by caesarean section [10]. This determines the possible colonization of the intestines of the child even before his birth.

There are studies that report that the upward movement of bacteria to the placenta through the vagina is not the only way to colonize the placenta, scientists suggest hematogenous spread of bacteria from the oral cavity [2]. Some of the scientists' conclusions are that the microbiome of the placenta has a low mass and small number of bacteria, is also most similar to the microbiota of the oral cavity, and is more different from the microbiota of feces and vaginal associations [4]. It is worth noting that uterine cells and other reproductive tissues show similar taxa in their low biomass microbiota [13]. Placental cells that are implanted at the same locus have a similar microbial composition [3].

Nutrition for pregnant women and the microbiome

It has long been recognized that the maternal diet during pregnancy has an impact on the formation and development of the microbiome of newborns [37]. Pregnant women who eat foods with a high fat index have low bacteroid levels [12]. Bacteroids are essential for the normal development of immunity in the intestines [15]. Scientists report that a high fat diet during pregnancy in Japanese monkeys while breastfeeding caused dysbiosis in the microbiome of infants, and these microbial changes were later discovered in young macaques. In a future life, the previously occurring microbiome dysbiosis could not be cured with a low-fat diet. The microbiome of mothers who ate high-fiber foods correlated with higher levels of short-chain fatty acids in infant mice [12].

Long-term changes in the microbiome of newborns are associated with excessive fat intake by pregnant women [41]. Researchers believe that the detection of Helicobacter pylori in offspring is associated with increased dietary intake of animal fats, which may affect the composition of the gut microbiome [23]. There may be a link between the changing composition of the gut microbiota and the decline in Bacteroides in people who over-consume animal fats [41].

The formation of atopic and autoimmune diseases in children may be the result of variations in commensal associations [15]. Increased levels of staphylococci and lactobacilli and decreased levels of bifidobacteria in breast milk were found in obese women compared with women with normal BMI [1].

Variations in the placental microbiome are possibly associated with pathologies such as maternal stress and gestational diabetes, newborn weight, and preterm birth [36]. The placental microbiome of preterm infants' changes with weight gain during pregnancy [37]. It is possible that this bacterial community can mediate and alter

the development of the fetus under the influence of the state of health of the pregnant woman.

Mode of delivery

It is very interesting that there is a connection between the mode of delivery and the formation of the microbiome in later life. A naturally born infant is believed to have a relationship with the mother's natural fluids, such as vaginal mucus and feces, and is likely to have a microbiome community similar to these fluids after birth. A baby born by caesarean section is not associated with the vaginal microbiota, so microbial colonization is similar to the mother's skin and the environment.

Laboratory studies and culture and molecular methods including high-throughput sequencing and metagenomic studies have been performed that detailed changes in the composition of the gastrointestinal tract microbiota in these newborns [25, 26].

Scientists have determined that proteobacteria are the main fillers that appear within several days of life, and actinobacteria are found in the feces of newborns born by caesarean section, 1-2 weeks after birth [27]. Newborns born by caesarean section have more complications from the intestinal microbiota and are less colonized by microbes such as Bifidobacterium and Bacteroides, while Clostridium sensu stricto and Clostridium difficile are colonized more often [26, 27]. The variable composition of the microbiota of newborns during home and hospital births has been documented [60].

Caesarean section during labor involves the use of antibiotics, possibly altering the quality of microbial colonization in infants [17]. There is speculation that caesarean section surgery may also alter the maturation of the microbiota in newborns while taking antibiotics. Using the microbiota maturation model described above, the researchers found that newborns born after cesarean section and vaginal delivery showed the same level of microbiota maturation during the first half of life. Subsequently, microbiota maturation declined in neonates born after caesarean section, with relative maturity declining compared to naturally born neonates for the remainder of the study period [25].

Gestational age

It is a well-known fact that premature birth affects the functional state and development of babies. The link between microbiome development and the gestational age of an infant does exist.

Several researchers have reported changes in the composition of the gut microbiota of preterm and full-term infants. For example, traditional culture of portions of meconium from 21 healthy full-term newborns, obtained within 2 hours after birth and before feeding, revealed different groups of microorganisms [18]. The most frequently found genus was Enterococcus, followed by Staphylococcus. It is quite interesting to compare the microbiome between meconium samples and sequential fecal samples from newborns. When meconium excreted from 14 preterm infants was evaluated and prospectively compared with postpartum feces, the meconium microbiota was significantly different from the fecal microbiota obtained during the first week of life [19]. Bacilli and other Firmicutes were the main groups of microorganisms found in meconium, while Proteobacteria predominated in feces. Cultural studies have shown that staphylococci were abundant in meconium, while enterococci, along with Escherichia, Klebsiella and Serratia, were more in feces. A more severe form of prematurity is detected with a high content of microbiota in meconium and a microbial association found in amniotic fluid, and with a high ratio of pro-inflammatory cytokines [20].

Very premature newborns are a new generation because they are in the hospital for a long time, often receive antibiotics and have an immature innate and adaptive immune system [59]. In very preterm infants, changes in major components of the gut microbiota are postmenstrual age and age in weeks [64, 65].

Feeding

The human gut microbiome controls many interactions that affect the health of the host later in life. Microbes colonize the intestines of babies immediately after birth. The creation and development of this early gut microbiome is thought to be related to components present in human milk.

Feeding type is another major factor, possibly determining early microbial colonization and controlling the infant's gut microbiota and gastrointestinal function. Differences in the microbial associations of the intestines in breastfed and bottle-fed newborns have long been known [29], while infants receiving breast milk have a higher level of bifidobacteria. Breastfeeding promotes the formation of a set of nutrients, microbial and antimicrobial substances, which creates the phenomenon of "milk-oriented microbiota". Breast milk is also composed of breast milk oligosaccharides, which can regulate the

growth and function of congenital intestinal microorganisms.

Transcriptome analysis of intestinal epithelial cells showed that the type of feeding of the newborn also affects the expression of the host genes, while breastfeeding enhances the transcription of genes that correlate with the immune and metabolic systems [30].

Bottle-fed newborns are exposed to carbohydrates, bacteria and micronutrients that cause other types of microbial colonization of the intestine. In this sense, several studies have shown that feces from breastfed newborns contain higher levels of bifidobacteria and lactobacilli and lower levels of potential pathogens than formula-fed infants, the latter being associated with a more diverse gut microbiota that is common: Staphylococci, Bacteroides, Clostridia, Enterococci, Enterobacteria and Atopobium sp. [31]. In addition, formula-fed infants appear to have a more similar composition to the microbiota of an adult [30].

Milk also consists of urea and oxalate, the two final ingredients of human metabolic activity. Why would nature add such indigestible molecules to babies' diets? There are innate microorganisms that can use these molecules, such as carbon, nitrogen, or other energy resources [16]. Variations in glycans found in breast milk can alter the gut microbiota of the newborn and the microbial community of breast milk, in particular strains of Bifidobacterium [39]. The level of development of sensory and motor states of the brain in newborns with strict lactation is indescribable. Ultimately, understanding this period, the activity of milk glycans and other substances, and their chosen microorganisms, will be critical to understanding human development [16]. The researchers also show a dose-dependent correlation between the neonatal gut microbiome community and the amount of daily breastfeeding [14].

In addition, formula-fed infants show slight variation and abundance of microbes even after the first year of life (12–24 months) [25]. Epidemiological evidence further supports the innate role of breastfeeding in neonatal health. Formula feeding is associated with a higher risk of developing various inflammatory and immune-mediated disorders [42, 40]. In addition, breastfeeding protects against wheezing during the first year of life among newborns born to women with bronchial asthma [40]. Other variations in the influence of the microbiome during neonatal development include vitamin production during postnatal development [16].

Continuing a high-fat diet during the postpartum period could potentially affect the breast milk microbiome, further exacerbating the dysbiosis that occurs in the early gut microbiome when a newborn is breastfed. Although previous studies have reported that the macronutrient mix (such as fatty acids) in human milk is up to a certain level dependent on the mother's diet, how the diet affects the microbial community in human milk is unknown. Given the overall importance of breast milk for newborn health and its potential role in microbial transfer, further research is needed to close these knowledge gaps [41].

The role of the microbiome after birth

It is well known that the formation of a newborn's microbiome is a period with potential long-term consequences for the baby's health and disruptions in the future life [1]. Gut microbial association may be affected by pH, oxygen / redox levels, nutrients, water, temperature, and other environmental conditions [6].

The method of profiling the intestinal microbiome of newborns immediately after birth and up to 24 months suggests that the birth method can cause intestinal dysbiosis in newborns. In a study of 43 pairs of mothers and newborns, newborns born by caesarean section showed variations in microbial communities immediately after birth. However, after 30 days, the variation in the microbial composition of newborns born by cesarean section decreased compared to those in newborns born via vaginal delivery. In recent studies, mode of delivery has been associated with changes in the microbial communities of the nostrils, skin and mouth immediately after birth, but not with changes in neonatal meconium [25].

Influence of antibiotics

It is well known that antibiotic therapy is one of the early stressors for the gut microbiome of newborns. Antibiotic therapy for pregnant women caused changes in both microbial communities of the neonatal gut [44]. Antibiotic drugs reduced the composition of the microbiota immediately after birth, but increased the level of growth within 12 months [25].

It was found that postnatal antibiotic therapy, intended in the first 3–9 months, changed the number of ruminococci and clostridial. In addition, antibiotic courses in the first 6–12 months of life were correlated with low biomass of the neonatal microbiota [25]. This means that antibiotics can

stop the development of microbial communities that can induce neonates to develop microbiome-related disorders later in childhood [37]. Recent studies have suggested that antibiotic-induced neonatal dysbiosis may lead to many late childhood disorders such as obesity, bronchial asthma, and inflammatory bowel disease [45].

In addition to antibiotics [49], other drugs commonly prescribed to mothers and / or newborns that affect the gut microflora, such as acid blockers [61], selective serotonin reuptake inhibitors, metformin, and laxatives [62, 63].

Effect of prebiotics on microbiome

In addition, the effects of probiotics on childhood disorders include effects on allergies, obesity, gastrointestinal infections, or colic [57]. However, the combination of bifidobacteria with Streptococcus thermophilus has been shown to be useful in the prevention and treatment of antibiotic-associated diarrhea in children [58].

In addition, the findings of a randomized controlled trial demonstrated that oral synbiotics for premature infants altered the gut microbiota and reduced the risk of atopic disease [21], while reducing fussing and crying [22].

The use of prebiotics in infant formula is already a common cause in infant feeding systems. There is no clarity regarding functional fluctuations between the effects of different types of prebiotics, a combination of different prebiotics, or even synbiotics. Usually, the effect of prebiotics is measured as the increase in bifidobacteria in the gut microbiome of newborns [5].

Birth asphyxia and gut

With birth asphyxia, the fetus wants to preserve more vital organs, such as the brain, myocardium and adrenal glands, by reducing blood flow to the kidneys or intestines [8]. Perinatal asphyxia caused by hypoxia-ischemia of the fetus, which leads to damage to the gastrointestinal tract and causes intestinal motility disorders and the appearance of necrotic enterocolitis (NEC). Models of artificial intestinal hypoxia-ischemia in adult animals have shown that inflammation is a fundamental factor in intestinal damage. Global hypoxia-ischemia has caused inflammation of the intestines and defects of the intestinal nervous system, which may be associated with postpartum complications such as food intolerance, changes in the gastrointestinal tract and NEC [9].

Calprotectin levels and microbiome

Scientists have found that there is a link between Crohn's disease (CD), calprotectin levels, and variation in gut microbial associations. Variations in alpha diversity were found between controls and apparently healthy patients. The authors also demonstrated an increase in Enterococcus and a decrease in Bifidobacterium, Ruminococcus Roseburia, Veillonellaceae, Gemmiger and Faecalibacterium. Moreover, variations in the alpha and beta discordance associated with calprotectin were found. In patients with calprotectin <100 μg/g versus those with calprotectin> 100 μg/g, CD activity had changes in the gut microbiome. The results of this study are a decrease in variation and dysbiosis at the earliest stage of CR. Changes in microbial communities and low numbers of bifidobacteria may hint at the usefulness of drugs for modifying microbes [7].

Atopic and allergic diseases

According to the "hygiene hypothesis", the occurrence of eczema and bronchial asthma contributes to a decrease in the number of contacts with microorganisms in childhood [1]. Changes in the maternal fetal microbiome contributed more to the development of asthma [37]. Subsequent offspring of mice were protected from allergic airway disorders by creating a maternal microbiome when feeding pregnant mice acetate or high fiber [50]. It is also possible that high acetate levels in pregnant women were associated with a reduction in hospital visits with symptoms of cough or wheezing in their children up to 12 months [50].

The occurrence of intestinal [51, 52] or respiratory [53] dysbacteriosis at an early age is associated with atopic disorders and bronchial asthma in the future. Studies in this area of study reveal only correlative evidence of a link between dysbacteriosis at an early age and bronchial asthma. But other authors [52] report preliminary evidence of a causal relationship associated with early life, dysbacteriosis, and immune system development in the context of asthma. In this study, inoculation of previously microbial-free mice with 4 strains of bacteria reduced in newborns at high risk for asthma reduced allergic airway inflammation [52].

There are studies that confirm the link between the development of food allergies and the microbiome. The researchers showed that high food sensitization in 12-month-old children showed a decrease in microbial changes by 3 months of age and an increase in the number of Enterobacteriaceae and Bacteroidaceae in the period 3–12 months [54]. Changes in the intestinal microbiome at the age of 3–6 months may also be associated with the development of milk allergy up

to 8 years [55]. Recent studies of the microbiome and the development of allergies and bronchial asthma have identified a period of 1 day to 12 months as a window of development for this disease. This immune hypersensitivity is manifested in later childhood, despite the temporary characteristics of microbial dysbacteriosis [37].

Risk of necrotizing enterocolitis development

In addition to the risks associated with preterm birth, preterm infants have severe dysbiosis in children [37]. In fact, the gut microbiota community of preterm infants is associated with a high risk of necrotizing enterocolitis (NEC) or sepsis [28]. By analyzing the 16S ribosomal RNA gene sequence data, the researchers found different numbers of proteobacteria, phyricumative, and bacteroidal bacteria, which contributed to the emergence of NEC [46]. Gut dysbiosis has similar differences in bacterial taxa and has been shown to cause NEC in a study of 122 very low birth weight infants [47]. An increase in proteobacteria along with an increase in the activity of enterocytic Toll-like receptors 4 in these neonates with NEC suggests a hyper-firing response to dysbiosis [48]. However, a recent study was conducted in which scientists found uropathogenic colonization of E coli as a significant risk marker for NEC [48]. This confirms the role of antibiotic-induced dysbiosis in children with NEC, which may increase the sensitivity of the neonatal gut microbiome prior to invasion by pathogens [37]. Because of the apparent link between microbial dysbiosis and NEC, biologics in preterm infants are becoming an important research tool for the prevention and treatment of NEC [49]. Several studies have shown that empiric antibiotic treatment of preterm infants for more than 4 days increases the risk of further developing NEC [43].

Nervous system formation

Some scientists believe that the behavioral activity and mental activity of mice is influenced by the composition of the intestinal microbiota. This effect is mediated by the so-called brain-intestinal axis. It is believed that the established neural circuits connect the brain and intestines [33, 37]. There are more facts about changes in intestinal microbial associations and early anxiety reactions in children. Therefore, signals to the brain from the intestinal microbiome are sent by the vagus nerve [32]. The function of the gut is in part that the brain sees neurotransmitters. In addition, the release of certain substances by microbial associations affects the transmission of nerve impulses across synaptic membranes and affects the coordination of movements and the emergence of behavior similar to anxiety in older children. This means that the process of microbial colonization of the intestinal tract is established genetically and affects the development of anxiety and motor activity in children [33].

Stress in women during pregnancy has influenced the formation of more anxious behavior in adults [36]. There is evidence that some changes in the composition of the placental microbiota were caused by maternal stress during pregnancy [36]. This means that microbial associations are partly related to the effects of maternal stress on changes in children's behavior in future life [37].

Conclusions

Therefore, the assumptions of scientists about the intrauterine effects of microorganisms on the fetus, the formation of intestinal microbiome before birth are preliminary, more accurate research is needed in this area. From researchers reports it was found that the intestinal microbiome of the newborn is affected by different factors, such as maternal nutrition during pregnancy and a high in fat diet, gestational age, mode of delivery - vaginal or cesarean section, type of feeding – breastfeeding, formula-feeding or combinations of it.

However, the formation of the microbiome of the intestinal tract continues after the birth. The effect of antibiotics on the composition of the microbiota, inhibiting the development of microorganisms is well known. Some medications also have an effect on intestinal microbial associations, such as laxatives, proton pump inhibitors, metformin, and selective serotonin reuptake inhibitors. Probiotics had a positive effect on the diversity of microorganisms, increasing the number of Bifidobacteria. Birth asphyxia was a factor of hypoxic-ischemic condition and was associated with the development of intestinal dysmotility and NEC, which had a possible effect on the formation of the intestinal microbiome.

Changes in the composition of the gut microbiota may be related to the development of pathologies in later childhood, such as allergic and atopic diseases, including bronchial asthma and food intolerance, stress and anxiety.

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The authors declare no conflict of interest.

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