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Research Article

# Intestinal Microbiome Activity and Formation in Children Born from Mothers with Gestational Diabetes Mellitus

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## Abstract

**Relevance:** According to modern studies, a set of microbiocenosis represents the human microbiome. They have shown some factors to shape the architecture and functionality of microorganisms. Human gut microbiome influences on the pathological processes not only in the digestive tract but also in other organs.

**Objective:** To determine a correlation between intestinal microbiota violations and its functional activity in children born from mothers with gestational diabetes by studying their intestinal microecology to predict health status of the cohort.

**Materials and Methods:** We studied the changes in intestinal microbiocenosis in 60 infants aged 1 - 28 days, including 22 infants by healthy mothers (control group, CG) and 38 infants by mothers with diabetes (GDM). We studied the species composition of the gut microbiocenosis by fecal ngs sequencing and functional state of the microbiocenosis by short-chain fatty acid (SCFA) concentrations using gas-liquid chromatography of acidified fecal supernatant. To quantify the biodiversity of the microbial community, we calculated Shannon index using the formula:

$$H = -\sum_{i=1}^{n} p_i log_2 p_i; \text{ where } p_i = \frac{x_i}{\sum_{i=1}^{n} x_i}$$

corresponds to the number of microbial species in the intestinal microbial community. Statistical analysis was performed with Statistica 8.0 and MS Office Excel 2010.

**Results:** The species diversity increases and different classes of isolated bacteria correlate strongly to form microbiome in infants from mothers with gestational diabetes mellitus. The functional activity of the neonatal microbiota is related directly to the intensity of bacterial colonization. Significant biodiversity and interspecies bacterial symbiosis develop compensatory mechanisms in the colon to allow for the coexistence of the microorganism and the microbial community.

***Keywords:*** *Gut Microbiome; Gestational Diabetes Mellitus; Children*

## Abbreviations

CG: Control Group; GDM: Gestational Diabetes Mellitus; SCFA: Short-Chain Fatty Acids; SI: Structural Index

## Introduction

Currently, metabolic disorders involve an increasing percentage of both adults and children. Among them, gestational diabetes mellitus (GDM) became a "tsunami" of the 21st century, affecting not only the pregnant woman but also the formation and development of the fetus in utero and the child after birth, leading to delayed dysfunctional processes and chronic diseases in adulthood [1]. Metabolic disorders in the human body can be associated not only with the peculiarities of interaction between genotype and environmental factors but also with violations of the intestinal microbiome [2]. A set of diverse microbial communities represents the human microbiome. It influences vital processes in the body and performs digestive, energetic, biosynthetic, morphokinetic, immunomodulatory, and protective functions. Each microbial community has a specific metabolic activity, depending on the predominance of certain types of bacteria, which affects various systems of the body, including the "gut-fatty tissue" axis and others [3].

The metabolic activity of the microbiome is determined by the amount and ratio of concentrations of short-chain fatty acids (SCFA): oily, acetic, propionic, valerian, capronic, and their isomers [4]. In the symbiosis of indigenous microbiota with the microorganism, the ratio of these metabolites remains constant within a small concentration interval. To assess the ratio of functional activity of anaerobic indigenous microflora to the total metabolic activity of microorganisms of the microbial-tissue complex of the colon, the structural index (SI) is determined. SI characterizes the structure of the microbiome and is the ratio of the sum of concentrations of propionic, butyric, valerian, capronic acids and their isomers to the concentration of acetic acid [5].

The modern technology identified the difference between the microbial clusters of children and adults. Recent studies have advanced the theory of intrauterine seeding from placenta, i.e. the lack of sterility of amniotic fluid, placenta, umbilical cord blood, and meconium [6]. Also, of normal microflora forms in the newborn in sequential phases: first, the intestine is populated by aerobes, then facultative anaerobic bacteria predominate, eventually creating favorable conditions for obligate anaerobes. The outcome is the formation of a bacterial biofilm [7]. Thus, if the microbiocenosis of the mother during pregnancy is disturbed, her newborn will probably have a dysbiotic microbial community from an early stage. Therefore, the study of the state of the intestinal microbiota in newborns from mothers with GDM is of particular interest.

## Materials and Methods

We studied the changes in intestinal microbiocenosis in 60 infants aged 1 - 28 days, including 22 infants by healthy mothers (control group, CG) and 38 infants by mothers with diabetes (GDM). We studied the species composition of the gut microbiocenosis by fecal ngs sequencing and functional state of the microbiocenosis by short-chain fatty acid (SCFA) concentrations using gas-liquid chromatography of acidified fecal supernatant. To quantify the biodiversity of the microbial community, we calculated Shannon index using the formula:

$$H = -\sum_{i=1}^{n} p_i log_2 p_i; \text{ where } p_i = \frac{x_i}{\sum_{i=1}^{n} x_i}$$

corresponds to the number of microbial species in the intestinal microbial community. Statistical analysis was performed with Statistica 8.0 and MS Office Excel 2010.

## Results and Discussion

We evaluated SCFA concentrations and their estimated indices in the studied groups (Table 1). A significant difference was found between gut microbiota functional activity indices in control and GDM groups in valerian and isocapronic acids concentration. Valerian acid is a «heavy" SCFA. It stimulates colon motility with a weak spasmolytic effect. Isocapronic acid is a product of protein processing by the intestinal microbiota and shows an increase in proteolytic activity in the lumen of the large intestine. When entering the blood, it is toxic to the nervous tissue of the macroorganism (Table 1).

| SCFA component | GDM | Control | Reference values | Significance, p* |
|---|---|---|---|---|
| **Absolute values** | | | | |
| Acetic, mmol/g | 48.32 [30.9 - 125.9] | 47.59 [17.4 - 73.6] | 50.21 [32.67 - 76.09] | 0.29 |
| Propionic, mmol/g | 3.84 [1.4 - 18.2] | 3.15 [1.3 - 7.9] | 5.95 [2.86 - 13.05] | 0.35 |
| isobutyric, mmol/g | 0.57 [0.2 - 1.6] | 0.61 [0.3 - 1] | 0.54 [0.24 - 1.24] | 0.93 |
| Butyric, mmol/g | 1.96 [0.6 - 6.3] | 1.86 [0.5 - 3.4] | 3.92 [1.99 - 7.46] | 0.38 |
| Isovalerian, mmol/g | 0.63 [0.2 - 1.2] | 0.66 [0.3 - 0.9] | 0.44 [0.18 - 0.76] | 0.82 |
| Valerian, mmol/g | 0.13 [0.1 - 1] | 0.28 [0.1 - 0.5] | 0.2 [0.08 - 0.39] | 0.05 |
| Isocapronic, mmol/g | 0.07 [0 - 0.1] | 0.03 [0 - 0.1] | 0.01 [0.01 - 0.02] | 0.04 |
| Capronic, mmol/g | 0.07 [0 - 0.3] | 0.07 [0 - 0.1] | 0.02 [0.01 - 0.21] | 0.76 |
| **Calculation indices** | | | | |
| Total concentration of SCFA, mmol/g | 54.37 [34.2 - 151.5] | 53.76 [21.5 - 92.6] | 67.3 [43.7 - 101.6] | 0.23 |
| Structural index, units | 0.17 [0.1 - 0.3] | 0.23 [0.2 - 0.3] | 0.29 [0.17 - 0.43] | 0.62 |
| Iso - acid index, units | 0.52 [0.4 - 0.9] | 0.68 [0.4 - 0.9] | 0.25 [0.13 - 0.47] | 0.68 |
| **Acetic:propionic:butyric acid ratio** | | | | |
| Acetic acid, % | 86.5 [83.4 - 92.2] | 86.64 [83.5 - 89.6] | 79.4 [72.89 - 87.31] | 0.88 |
| Propionic acid, % | 7.17 [4.9 - 11.5] | 8.96 [4.9 - 10] | 11.52 [5.72 - 17.58] | 0.94 |
| Butyric acid, % | 3.75 [1.8 - 5.4] | 4.5 [1.7 - 7.5] | 6.05 [3.25 - 11.62] | 0.84 |
| **Relative concentrations** | | | | |
| Acetic, units | 0.85 [0.8 - 0.9] | 0.81 [0.8 - 0.9] | 0.772 [0.695 - 0.865] | 0.62 |
| Propionic, units | 0.07[0 - 0.1] | 0.09 [0 - 0.1] | 0.104 [0.054 - 0.174] | 0.98 |
| Isobutyric, U | 0.01 [0 - 0.01] | 0.02 [0 - 0.02] | 0.0096 [0.0043 - 0.017] | 0.11 |
| Butyric, U | 0.04 [0 - 0.1] | 0.04 [0 - 0.1] | 0.057 [0.031 - 0.11] | 0.88 |
| Isovalerian, U | 0.01 [0 - 0.01] | 0.01 [0 - 0.01] | 0.006 [0.0032 - 0.011] | 0.16 |
| Valerian, U | 0 [0 - 0.01] | 0 [0 - 0.01] | 0.0036 [0.0011 - 0.0061] | 0.77 |
| Isocapronic, U | 0 [0 - 0.01] | 0 [0 - 0.01] | 0.01 [0.01 - 0.02] | 0.35 |
| Capronic, U | 0 [0 - 0.01] | 0 [0 - 0.01] | 0.01 [0.01 - 0.02] | 0.77 |
| * Significant values are stated in bold ($p < 0.05$, $\chi^2$) | | | | |

***Table 1:*** *Functional activity of gut microflora in the studied groups of children, n = 60; mmoL/g.*

As emphasized earlier, the metabolic activity of microbiocenosis directly depends on its phylotype, qualitative composition, the interaction of bacteria, and on the macroorganism. Zatevalov A.M., *et al.* [8] revealed 2.2 mmol/g of butyric acid in feces to be a concentration critical for the metabolic links formation of indigenous microflora. Using this criterion to determine the normal symbiosis of gut microbiocenosis and the macroorganism, we determined its frequency as a function of the age of children in the first days of life in the 2 observation groups (Table 2).

| Age, days | GDM | Control | Significance, p* |
|---|---|---|---|
| 1 | 0.0 | 25.0 | 0.01 |
| 2 | 100.0 | 57.1 | 0.0006 |
| 3 | 33.3 | 40.0 | 0.44 |
| 5 | 45.5 | 47.4 | 0.84 |
| *Significant values are stated in bold ($p < 0.05$, $\chi^2$) | | | |

***Table 2:*** *Frequency of normal function of gut microbiocenosis in newborn from mothers with GDM versus control (n = 60), %.*

In newborns from mothers with GDM, microorganisms settle in the intestine on the 2nd day of life, while in the control group they do so from the 1st day of life. The probable cause is the normal staged intestinal colonization by indigenous microbiota from birth with formation of a strong symbiosis with the macroorganism to regulate healthy microbiocenosis formation. The microbiota differs in children born from mothers with GDM. Of note, the indices equalize in both groups by day 5. The studied groups showed different colonization of the intestine by indigenous microbiota.

The study compares the frequency of different types and classes of bacteria in the titer over 103 CFU/g and the intensity of bacterial colonization by the average lg CFU/g in the 2 groups (Table 3).

| Organism class/species | Frequency of occurrence above 103 CFU/g | | | Intensity of bacterial colonization, mean lg CFU/g | | |
|---|---|---|---|---|---|---|
| | GDM | CG | Significance, p* | GDM | CG | Significance, p* |
| *Firmicutes* | 73.68 | 90.91 | 0.179 | 4.2 [2.2 - 4.9] | 5.9 [4 - 6.3] | 0.02 |
| *Clostridium difficile* | 9.09 | - | 0.003 | 2.75 [1.5 - 4] | 1.65 [1 - 2.45] | 0.53 |
| *Clostridium leptum* | 15.79 | 45.45 | <0.01 | 2.15 [1.5 - 3.7] | 2.5 [2.4 - 3.3] | 0.60 |
| *Enterococcus* spp. | 36.84 | 72.73 | 0.001 | 4.45 [2.9 - 4.9] | 5.5 [4.1 - 6] | 0.13 |
| *Staphylococcus* spp. | 47.37 | 72.73 | 0.021 | 3.3 [3.05 - 3.9] | 4 [2.4 - 4.6] | 0.52 |
| *Anaerococcus* spp. | - | - | - | 1.9 [1.9 - 1.9] | 1.1 [0.4 - 2] | <0.01 |
| *Erysipelotrichaceae* | 9.09 | - | 0.003 | 6 [6 - 6] | - | <0.01 |
| *Lactobacillaceae* | - | 18.18 | <0.01 | 1.4 [1.1 - 2.4] | 2.55 [2.2 - 3] | 0.01 |
| *Lactococcus lactis* | - | - | - | 1.6 [1.6 - 1.6] | 2.6 [2.6 - 2.6] | <0.01 |
| *Streptococcus* spp. | 42.11 | 72.73 | 0.004 | 3.7 [1.95 - 4.8] | 4.45 [3.2 - 5.5] | 0.34 |
| *Actinobacteria* | 21.05 | 27.27 | 0.37 | 0.5 [0 - 2.7] | 1 [0 - 4.9] | 0.37 |
| *Bifidobacterium* spp. | 21.05 | 27.27 | 0.37 | 2.6 [0.5 - 5.1] | 2.5 [0.95 - 6] | 0.71 |
| *B. dentium* | - | 9.09 | 0.003 | - | 4.9 [4.9 - 4.9] | <0.01 |
| *B. adolescentis* | - | 18.18 | <0.01 | - | 6.2 [2.1 - 6.8] | <0.01 |
| *B. bifidum* | 5.26 | - | 0.022 | - | 7 [7 - 7] | <0.01 |
| *B. longum* | - | 18.18 | <0.01 | - | 4.9 [3.4 - 6.4] | <0.01 |
| *B. animalis lactis* | - | - | - | 2.2 [2.2 - 2.2] | - | <0.01 |
| *Coriobacteriia* | - | 18.18 | <0.01 | 2.6 [2.6 - 2.6] | 5.6 [4.6 - 6.6] | <0.01 |
| *Bacteroidetes* | 21.05 | 45.45 | 0.003 | 4.95 [4.3 - 5.45] | 5.2 [3.1 - 6.1] | 0.76 |
| *Bacteroides* spp. | 21.05 | 45.45 | 0.003 | 0 [0 - 0] | 2.3 [0 - 5.8] | 0.02 |
| *Parabacteroides* spp | - | 18.18 | <0.01 | 1.5 [1.4 - 2.1] | 2.9 [2.5 - 4.1] | 0.25 |
| *Butyricimonas* | - | - | - | - | 2.9 [2.9 - 2.9] | <0.01 |
| *Prevotella* spp. | - | - | - | - | 2.5 [2.5 - 2.5] | <0.01 |
| *Alistipes* spp. | - | 9.09 | 0.003 | - | 3.3 [3.3 - 3.3] | <0.01 |
| *Proteobacteria* | 54.55 | 47.37 | 0.477 | 5.7 [2.1 - 6.7] | 2.5 [1.9 - 5.5] | 0.37 |
| *Enterobacteriaceae* | 54.55 | 47.37 | 0.477 | 6.4 [2.3 - 6.7] | 2.95 [1.9 - 5.5] | 0.13 |
| *E. coli* | 45.45 | 42.11 | 0.720 | 5.1 [1.3 - 5.7] | 4 [1.7 - 4.9] | 0.48 |
| *Pseudomonas* spp. | - | - | - | 1.95 [1.9 - 2.2] | 1.9 [1.9 - 2.1] | 0.74 |
| *Bdellovibrio* | - | - | - | - | 0.7 [0.7 - 0.7] | <0.01 |
| *Sutterella wadsworthensis* | - | - | - | 2.8 [2.8 - 2.8] | - | <0.01 |
| Dialister Alisonella Megaspherae Vellonella | 5.26 | 18.18 | 0.008 | 0 [0 - 0] | 0 [0 - 1.8] | 0.22 |
| *Significant values are stated in bold ($p<0.05$, Mann-Whitney U test and $\chi^2$) | | | | | | |

***Table 3:*** *Species composition of the microbiocenosis and intensity of bacterial colonization of the intestine in newborns of the study groups; n = 60 (CFU/g).*

In general, *Firmicutes* class microorganisms dominate in infants born from GDM and CG mothers (73.7% and 90.9%, respectively). *Clostridium difficile* and *Erysipelotrichaceae* types of bacteria were found more frequently in the GDM group. *Clostridium difficile* can cause intestinal mucosal inflammation when local immunity is weakened, and *Erysipelotrichaceae* take part in lipid metabolism but is not studied well. Also, children born from mothers with GDM have only one species of *bifidobacterium, Bifidobacterium bifidum*, less amount of *Enterococcus* spp., *Staphylococcus* spp., *Streptococcus indigenous* at the stage of intra-intestinal conditions preparation to anaerobic conditions. Small amounts of normal microflora are isolated: *Actinomyces, Parabacteroides, Veillonella, Bacteroides*, which play an important role in protein metabolism. CG neonates showed *Cl. leptum* more frequently than the GDM group ($p < 0.01$). The role of this bacterium is not well known at present, but one foreign study found its ability to modulate adaptive immunity and the decrease in inflammatory bowel diseases [9]. *Proteobacteria* and *Tenericutes* types include many pathogenic bacteria, and were found in the GDM group more frequently. *Proteobacteria* have a high potential for overgrowth and intestinal dominance, which can lead to inflammatory intestinal diseases and impair digestion and metabolism. The intensity of individual bacterial species colonization in the GDM group reaches 103 - 104 lg CFU/g compared to 105 - 106 lg CFU/g in control. Microbiome having a symbiotic relationship with the macroorganism adjusts its work more quickly and better from the initial stages of settlement in the intestine. But children from mothers with GDM have a pronounced microbial biodiversity of opportunistic bacteria and an impoverished community of indigenous microbiota with changes in the dominant microbial species without the macroorganism involvement.

In the next step, we assessed the correlation between the key indices of the gut microbiome metabolic activity and the bacteria identified (Figure 1 and 2).

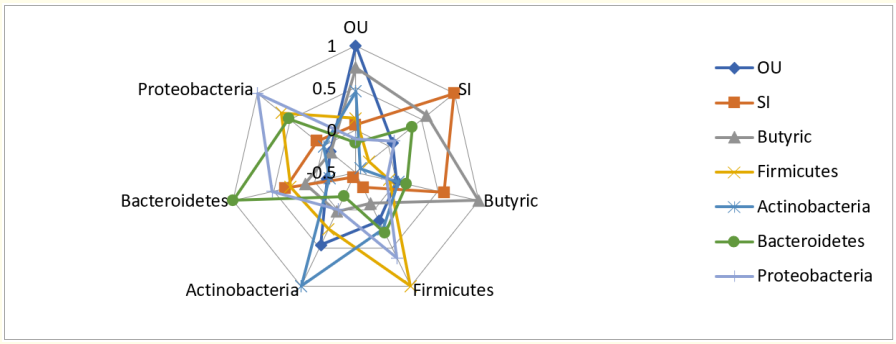



***Figure 1:*** *The role of metabolic activity of the gut microbiome and the intensity of bacterial colonization of feces in infants born from mothers with GDM.*

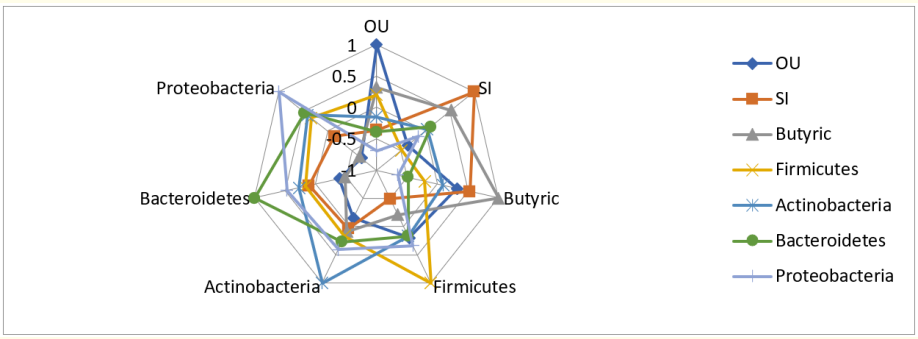
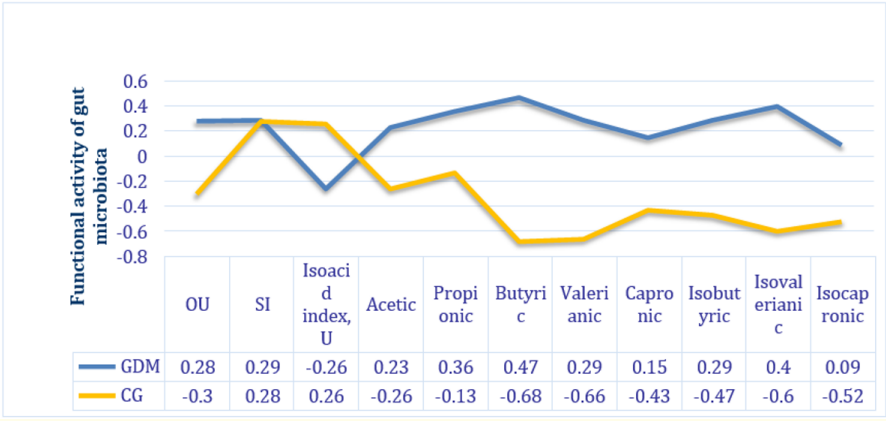



***Figure 2:*** *The role of the metabolic activity of the gut microbiome and the intensity of fecal bacterial colonization in infants born from mothers without GDM.*

According to figure 1 and 2, butyric acid concentration correlates directly with the total SCFA and the structural index in children from mothers with GDM. The Proteobacteria colonization correlates with those by Firmicutes and Bacteroidetes. We can assume, therefore, an increase in the functional activity of opportunistic and pathogenic microorganisms. The concentration of butyric acid corresponds to the energy requirements of the dysbiotic microbiome, creating favorable conditions for its further growth and an increase in proteolytic activity. The control newborns showed an inverse correlation between Proteobacteria and the butyric acid concentration. Thus, the normal indigenous gut microbiota regulates its qualitative composition to support further growth and development of a harmonious microbial community supporting symbiotic relationships with the macroorganism.

We also correlated the Shannon index and the microbiocenosis functional activity to identify the presence and direction of the correlation relationship (Figure 3).




| | OU | SI | Isoacid index, U | Acetic | Propionic | Butyric | Valerianic | Capronic | Isobutyric | Isovaleriianic | Isocaproic |
|---|---|---|---|---|---|---|---|---|---|---|---|
| GDM | 0.28 | 0.29 | -0.26 | 0.23 | 0.36 | 0.47 | 0.29 | 0.15 | 0.29 | 0.4 | 0.09 |
| CG | -0.3 | 0.28 | 0.26 | -0.26 | -0.13 | -0.68 | -0.66 | -0.43 | -0.47 | -0.6 | -0.52 |

***Figure 3:*** *Functional activity of gut microbiocenosis indices in newborn infants born from mothers with GDM, according to Shannon diversity index and correlation analysis of dependence, mmol/g.*

Figure 3 shows a direct correlation of Shannon diversity index and the concentration of butyric acid in feces in children born from mothers with GDM ($p < 0.05$). In the CG, Shannon's index correlates inversely with the butyric acid concentration. GDM group has greater concentration of butyric acid, thus confirming the abovementioned higher biodiversity of the gut microflora.

## Conclusion

In newborns from mothers with GDM, the gut microbiome develops later and less intense bacterial colonization compared to CG, but faster because of an increase in species biodiversity, which can transform the dominant bacterial types [10]. In newborns from the GDM group, a landscape of indigenous microbiota is scanty: *Lactobacillus, Bifidobacteria*, and *Bacteroidetes*. These types of bacteria are mandatory to form a normal gut microbiome from birth [11]. The GDM group only has *Erysipelotrichaceae* taking part in lipid metabolism [12]. The functional activity of the microbiome depends on the qualitative composition and the interactions of the bacterial community [13]. In newborns from mothers with GDM, feces showed more SCFA, showing proteolytic activity of the intestinal microbiota. This confirms the failure of the intestinal microbiota in these children to metabolize heavy SCFAs in the lungs, which play a major role in the body's regulation of metabolic processes. The intensity of bacterial colonization correlates directly with total SCFA concentration and structural index

with the butyric acid concentration, and of Proteobacteria with Firmicutes and Bacteroidetes, which may show the intestinal dysbiosis and decreased controllability of microbial community by the macroorganism. This predisposes to pathology reactions, failure of compensatory mechanisms, and triggering the metabolic disorders [14]. In addition, GDM differs gut microbiota in late pregnancy compared with women without GDM [15].

Thus, in the early stages of life, the microbiota normally balances the microorganism species, preventing from excessive growth of pathogens. With age, this tactic leads to the formation of normal gut microbiocenosis. It is the violation of the formation of microbiocenosis we observe in newborns from mothers with GDM. It can subsequently lead to uncontrolled growth of pathogenic bacteria, further inhibiting the indigenous microbiota. The development of primary care measures based on the Face-it program may be of practical importance [16].

## Conflict of Interest

The authors declare no conflict of interest. The article is not sponsored.

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