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INTESTINAL MICROBIOME ACTIVITY AND FORMATION IN CHILDREN IN INFANTS BORN FROM MOTHERS WITH GESTATIONAL DIABETES MELLITUS

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Abstract. The article presents the results of studies of gut microbiocenosis, as well as its metabolic features in young children born to mothers with gestational diabetes mellitus. The article examined the characteristics of gut microbiocenosis, as well as its metabolic features in early children born to mothers with gestational diabetes mellitus. The presence of intestinal microbiota balance disorders and its functional activity in the studied cohort of children is shown. Modern methods of gut microbiota investigation have been carried out and described. The gut microbiocenosis metabolite indices in the study groups of children were analyzed. It was concluded that the obtained results in the study groups of children have reliable deviations. Which makes experts pay attention to the possibility of the influence of the dysbiotic community of bacteria on the protective functions of biofilm and the impact on the health of the child as a whole.

Key words: *gut microbiocenosis; gestational diabetes mellitus; young children.*

ОСОБЕННОСТИ ФОРМИРОВАНИЯ МИКРОБИОТЫ КИШЕЧНИКА У ДЕТЕЙ РАННЕГО ВОЗРАСТА, РОЖДЕННЫХ ОТ МАТЕРЕЙ С ГЕСТАЦИОННЫМ САХАРНЫМ ДИАБЕТОМ

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Резюме. В статье приведены результаты исследований микробиоценоза кишечника у детей раннего возраста, рожденных от матерей с гестационным сахарным диабетом. Показано наличие нарушений баланса микробиома кишечника и его функциональной активности у исследуемой когорты детей. Проведены и описаны современные методы исследования микробиома кишечника. Статья заставляет обратить внимание специалистов на возможность влияния дисбиотического сообщества бактерий на защитные функции биопленки и воздействия на здоровье организма ребенка в целом.

Ключевые слова: *микробиом кишечника; гестационный сахарный диабет; дети раннего возраста.*

INTRODUCTION

In recent decades there is a large number of studies on the human gut microbiota in the medical community. Studies investigating the relationship between the structure of the gut microbiome and the presence of diabetes mellitus (DM) deserve special attention. In 2018, L. Zhou and X. Xiao conducted a study that found that altering a mother's microbiota prior to delivery has impact on her metabolism of carbohydrates and fats, which may negatively affect the structure of the child's gut microbiota. In this regard, the study of

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the state of intestinal microbiota in children born to mothers with diabetes mellitus is not only relevant, but also necessary.

AIM

The aim is to improve the diagnosis of gut microbial composition disorders in infants born to mothers with the gestational diabetes mellitus by determining the species composition and metabolic activity of the gut microbiome.

MATERIALS AND METHODS

The study of gut microbiome (GM) included 105 children aged 1–3 years among with 33 children from mothers with the gestational diabetes mellitus on insulin therapy (GDM IT), 42 children from mothers with the gestational diabetes mellitus on diet therapy (GDM DT), 30 children from mothers without the GDM (control group — CG) was carried out.

We studied: species composition of the intestinal microbiome; its functional state by concentrations of short-chain fatty acids (SCFA). The species composition was studied by ngs sequencing of faeces. The concentration of short-chain fatty acids was analyzed by gas-liquid chromatography of acidified supernatant of faeces. The biodiversity of the microbial community was taken as a measure of intestinal dysbiosis, which in biology is quantified by the Shannon index, corresponds to the number of microbial species in the intestinal microbial community and is calculated according to the formula:

$$H = -\sum_{i=1}^{n} p_i \log_2 p_i,$$

where

$$p_i = \frac{x_i}{\sum_{i=1}^{n} x_i}$$

The normalised Shannon index has a range of values from 0 to 1, which is suitable for interpreting the state of microbiocenosis. The data obtained during the study were statistically processed using Statistica 8.0 and MS Office Excel 2010 software packages.

RESEARCH FINDINGS

The study determined the distribution of microorganisms in the intestine of infants born to mothers with the GDM with a detailed breakdown by class and type using the 16s rRNA sequencing method (Table 1).

Table 1. Species of intestinal microorganisms in young children in the study groups, n=105, (Me [min; max])

Таблица 1. Типы микроорганизмов кишечника у детей раннего возраста в исследуемых группах, n=105 (Me [min; max])

Типы микроорганизмов	ГСД ИТ, n=33	ГСД ДТ, n=42	КГ, n=30
Euryarchaeota	0 [0–0]	0 [0–0]	0 [0–0]
Actinobacteria	33,78** [17,29–42,05]	42,11 [38,24–56,08]	48,92 [32,8–69,15]
Bacteroidetes	0,37 [0,04–0,68]	0,11 [0,03–0,29]	0,17 [0,07–0,78]
Cyanobacteria	0 [0–0]	0 [0–0]	0 [0–0]
Firmicutes	63,25 [55,13–77,72]	57,62** [43,89–60,94]	48,99 [28,57–62,96]
Proteobacteria	0,33 [0,08–2,51]	0,17 [0,01–0,39]	0,51 [0,18–2,17]
Tenericutes	0 [0–0]	0 [0–0]	0 [0–0]
Verrucomicrobia	0 [0–0,02]	0 [0–0,02]	0 [0–0,19]

Notes.
GDM DT — the gestational diabetes mellitus, diet therapy; GDM IT — the gestational diabetes mellitus, insulin therapy; CG — control group; n – the number of children.
The Mann-Whitney U-criterion, $p<0.05$, was used to assess the statistical significance of the frequencies of occurrence: * in the GDM group; ** in the CG..

Примечания.
ГСД ДТ — гестационный сахарный диабет, диетотерапия; ГСД ИТ — гестационный сахарный диабет, инсулинотерапия; КГ — контрольная группа; *n* — количество детей.
Для оценки статистической значимости частот встречаемости использован U-критерий Манна–Уитни $p<0,05$: * в группе ГСД; ** в КГ

According to the data obtained (Table 1), children from mothers with GDM IT and GDM DT showed no statistically significant differences between each other. In general, *Actinobacteria* and *Firmicutes* are more frequently represented in the microbial landscape of young children. The *Firmicute*s is represented by obligate and facultative anaerobic bacteria and is the most common type of bacteria in the human intestine in the norm. Most representatives of the type are Gram-positive bacteria and are capable of forming endospores, which helps bacteria of this type to survive in unfavourable conditions and restore their population [1]. Actinobacteria type consists of both aerobic and anaerobic Gram-positive bacteria, but contains more guanine and cytosine in its DNA structure than *Firmicutes [2]*. *Bifidobacteria spp.* — are the most common bacteria within this type in young children in the colonic microbiota [3]. But *Actinobacteria* in children from mothers with GDM IT were isolated in lower numbers than in children from CG (p=0.03). More intensive growth of *Firmicutes* type bacteria was ob-

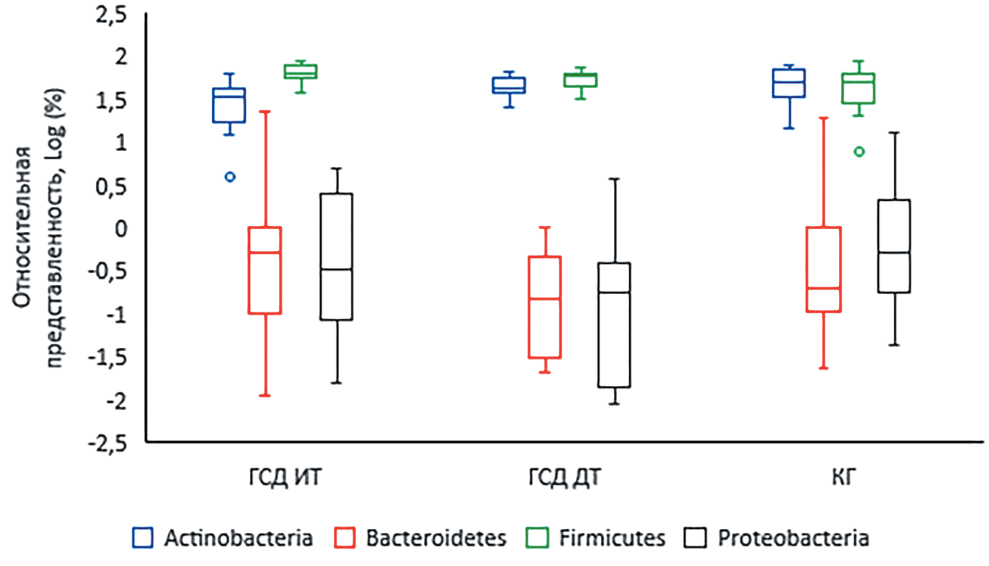

Fig. 1. Distribution of intestinal microorganism types in young children study groups
Рис. 1. Распределение типов микроорганизмов в кишечнике у детей раннего возраста исследуемых групп

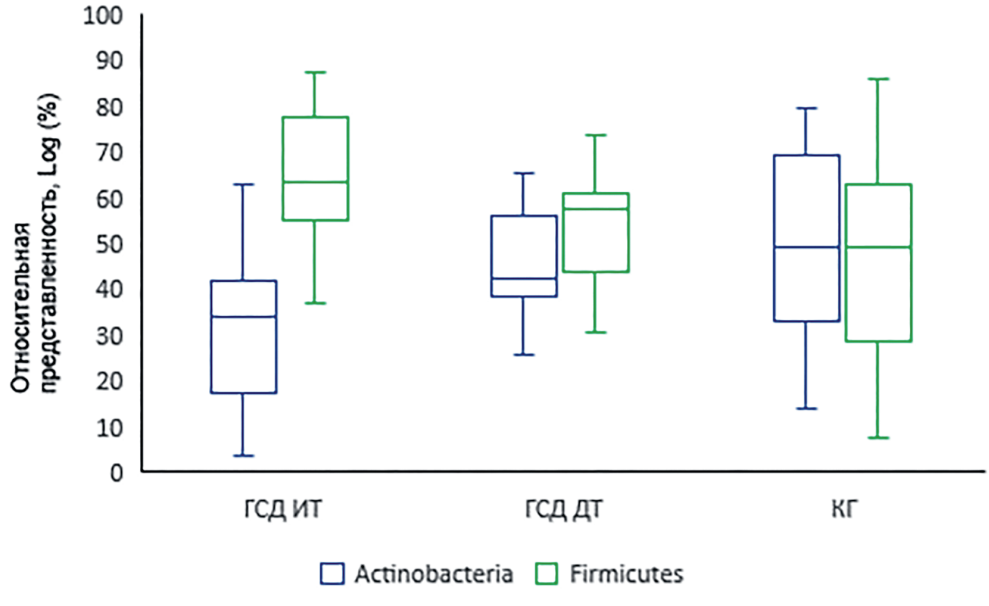

Fig. 2. Ratio of Actinobacteria and Firmicutes in the intestines of young children study groups
Рис. 2. Отношение *Actinobacteria* и *Firmicutes* в кишечнике детей раннего возраста исследуемых групп

served in children from mothers with GDM DT in early childhood than in CG (p=0.04), which may indicate the presence of favourable conditions for uncontrolled growth of opportunistic and pathogenic bacteria, disturbance of balance within the microbial community and formation of dysbiosis. *Proteobacteria* and *Bacteroidetes* are inferior in number to *Actinobacteria* and *Firmicutes*, which corresponds to the structure of differentiated gut microbiome of young children [4]. *Verrucomicrobia, Euryarchaeota, Tenericutes* and *Cyanobacteria* are isolated in smaller numbers.

Let us consider the Figure 1 in order to illustrate the quantitative distribution of intestinal microorganism types in children of the studied groups.

Thus, Figure 1 clearly depicts the obtained data: *Actinobacteria* and *Firmicutes* have the highest representation among other types of microorganisms. It can be noted that for all the studied groups of children at early age, the ratio of *Proteobacteria* and *Bacteroidetes* has no statistical significance or a pronounced tendency to favour one or the other type of bacteria.

We were interested to study the ratio between *Actinobacteria* and *Firmicutes* bacterial types, which is presented in Figure 2.

Based on the data obtained (Figure 2), it can be assumed that in children from mothers with GDM in general there is a tendency to decrease the relative representation of *Actinobacteria* to *Firmicutes*. The median values and variation of the relative representation of *Actinobacteria* and *Firmicutes* in children from mothers with GDM are significantly different from those in the CG. This indicates that the balance in the microbial community is disturbed, which may lead to increased risks of pathological processes associated with dysbiosis starting in the early age in children of the experimental groups.

The revealed peculiarities of the ratio of dominant types of bacteria are associated with changes in gut microbiome biodiversity. It is known that changes in biodiversity are characterised by the Shannon alpha biodiversity index, which increases with the number of species representation [5]. Changes in the Shannon index in the studied groups of children are presented in Figure 3.

According to the results (Fig. 3), there is a tendency to increase the degree of biodiversity from KG to GDM DT and further to GDM IT, which once again indicates a violation of get microbiome formation and the presence of dysbiotic changes in children of this cohort.

Table 2. Species composition of the gut microbiome of young children study groups, n=105 (Me [min; max])

Таблица 2. Видовой состав микробиома кишечника детей раннего возраста исследуемых групп, n=105 (Me [min; max])

Species of microorganisms / Виды микроорганизмов	GDM IT, n=33 / ГСД ИТ, n=33	GDM DT, n=42 / ГСД ДТ, n=42	CG, n=30 / КГ, n=30
Actinobacteria			
Actinomyces spp.	4,57** [0–14,8]	0 [0–17,7]	0 [0–0,1]
Bifidobacterium bifidum	0 [0–0]	0 [0–0]	0 [0–0]
Bifidobacterium spp.	2,4 [0–7,8]	0,07 [0–0,73]	0,17 [0–3,13]
Varibaculum spp.	0 [0–0]	0 [0–0,03]	0 [0–0]
Adlercreutzia spp.	0 [0–0,13]	0 [0–0,37]	0 [0–0]
Rothiamucilaginosa	1,9 [0,43–6]	0,77 [0,33–1,63]	0,5 [0–2,47]
Eggerthella spp.	0,03 [0–0,2]	0,2** [0,03–0,67]	0 [0–0,07]
Collinsella stercoris	0 [0–0,07]	0 [0–0]	0 [0–0,03]
Eggerthella lenta	0 [0–0,07]	0 [0–0]	0 [0–0]
Bifidobacterium adolescentis	0,13 [0,03–2,2]	0,07 [0–0,5]	0,37 [0,1–2,53]
Bacteroidetes			
Sediminibacterium spp.	0 [0–0]	0 [0–0,03]	0 [0–0,17]
Bacteroideso vatus	0 [0–0,53]	0 [0–0]	0 [0–0,4]
Bacteroides caccae	0 [0–0,07]	0,03 [0–0,13]	0 [0–0]

Continuation of the Table 2 / Продолжение табл. 2

Species of microorganisms / Виды микроорганизмов	GDM IT, n=33 / ГСД ИТ, n=33	GDM DT, n=42 / ГСД ДТ, n=42	CG, n=30 / КГ, n=30
Prevotella copri	0 [0–0,03]	0 [0–0,03]	0 [0–0]
Parabacteroides spp.	0 [0–0,03]	0 [0–0,07]	0 [0–0]
Bacteroides uniformis	0 [0–0,03]	0 [0–0,07]	0,03 [0–0,9]
Bacteroides spp.	0 [0–0,17]	0,03 [0–0,1]	0 [0–0,07]
Firmicutes			
Coprococcus catus	0,07** [0,03–0,07]	0,03 [0–0,1]	0 [0–0,03]
Clostridiales	0,03 [0–3,8]	1,6 [0–3,4]	0 [0–8,7]
Dialister spp.	0,47 [0–5,7]	0 [0–8,73]	0 [0–4,3]
Bulleidiamoorei	9,77 [2,8–33,8]	21,4 [13,2–37,7]	45,8 [24,5–56,8]**
Lactococcus spp.	0 [0–0]	0 [0–0]	0 [0–0]
Lachnospira spp.	0 [0–0,07]	0 [0–0]	0 [0–0]
Veillonella spp.	0 [0–0]	0 [0–0]	0 [0–0]
Ruminococcus spp.	0 [0–0]	0 [0–0]	0 [0–0]
Turicibacter spp.	0,27 [0–0,5]	0,13 [0–0,53]	0,13 [0–0,73]
Coprococcus spp.	0 [0–0]	0 [0–0]	0 [0–0]
Anaerostipes spp.	0 [0–0,47]	0,03 [0–1,4]	0 [0–0,07]
Clostridium neonatale	0 [0–0,03]	0,03 [0–0,13]	0,07 [0–0,47]
Peptoniphilus spp.	1,83 [0,23–7,27]	1,43 [0,17–6,1]	0,67 [0,2–1,17]
Clostridium butyricum	0 [0–0,2]	0 [0–0,03]	0 [0–0]
Ruminococcus bromii	0 [0–0]	0 [0–0,03]	0 [0–0]
Peptostreptococcus anaerobius	0,07 [0–1,67]	0 [0–1,37]	0,03 [0–0,3]
Clostridium hiranonis	8,4 [1,97–12,3]	4,2 [0,57–8,5]	0,43 [0–2,33]**
Lactobacillales	0 [0–0]	0 [0–0]	0 [0–0]
Dorea formicigenerans	0 [0–0,03]	0 [0–0]	0 [0–0]
*Peptostreptococcus*spp.	0,1 [0–0,2]	0 [0–0,1]	0 [0–0,03]
Lachnospiraceae	0,07 [0–1,83]	0 [0–0,03]	0 [0–0]
Anaerococcus spp.	0 [0–0]	0 [0–0]	0 [0–0]
Ruminococcus spp.	0 [0–0]	0 [0–0,03]	0 [0–0]
Roseburia spp.	0 [0–0,2]	0 [0–1,03]	0 [0–0]
Veillonellaceae	0 [0–1,77] **	0 [0–0]	0 [0–0]
Blautia producta	0,5 [0–0,8] *	0 [0–0,13]	0 [0–0,37]
Ruminococcus torques	0 [0–0,03]	0 [0–0,03]	0 [0–0,03]
Lactobacilluszeae	0 [0–0]	0 [0–0,03]	0 [0–0]
Lachnobacterium spp.	0 [0–0,03]	0 [0–0,03]	0 [0–0,03]
Enterococcaceae	0 [0–0]	0 [0–0]	0 [0–0]
Dorea spp.	0,03** [0–0,3]	0,17 [0,03–0,5]	0,5 [0,07–1,83]
Clostridium perfringens	0 [0–0,03]	0 [0–0]	0 [0–0]
Streptococcus spp.	16,4 [2,57–25,5]	16,8 [8,03–24,7]	10,2 [0,13–22,4]
Staphylococcus spp.	0 [0–0]	0 [0–0]	0 [0–0]

Ending of the table 2 / Окончание табл. 2

Species of microorganisms / Виды микроорганизмов	GDM IT, n=33 / ГСД ИТ, n=33	GDM DT, n=42 / ГСД ДТ, n=42	CG, n=30 / КГ, n=30
Streptococcus agalactiae	0,33 [0,03–1,1]	0,23 [0,1–3,17]	0,07 [0–0,37]
Lactobacillus spp.	0 [0–0]	0 [0–0]	0 [0–0]
Lactobacillaceae	0,03 [0–0,07]	0 [0–0,03]	0 [0–0,03]
Eubacterium spp.	0 [0–0]	0 [0–0]	0 [0–0]
Coprobacillus spp.	0 [0–0]	0 [0–0]	0 [0–0]
Blautia spp.	0 [0–0]	0 [0–0]	0 [0–0]
SMB53 spp.	0 [0–0]	0 [0–0]	0 [0–0,03]
Bacillus spp.	0 [0–0]	0 [0–0]	0 [0–0]
Erysipelotrichaceae	0 [0–0]	0 [0–0]	0 [0–0,3]
Proteobacteria			
Alphaproteobacteria	0 [0–0]	0 [0–0]	0 [0–0]
Acetobacteraceae	0 [0–0]	0 [0–0]	0 [0–0]
Vibrionaceae	0 [0–0,07]	0 [0–0]	0 [0–0,17]
Burkholderiabryophila	0 [0–0,03]	0 [0–0]	0 [0–0]
Proteobacteria	0 [0–0]	0 [0–0]	0 [0–0]
Sutterella spp.	0 [0–0]	0 [0–0]	0 [0–0]
Bilophila spp.	0,13 [0,03–0,5]	0,03 [0–0,47]	0,07 [0–0,5]
Nitrosomonadaceae	0,83 [0,17–6,6]	2,3 [0,2–3,83]	0,43 [0–2,9]
Thiotrichaceae	0 [0–0]	0 [0–0,07]	0 [0–0]
Acinetobacter spp.	2,37 [0,87–6,63]	2,13 [1,07–6,9]	3,5 [0,67–12,3]
Hydrocarboniphaga spp.	0,03 [0–0,43]	0,2 [0–0,33]	0 [0–0,2]
Enterobacteriaceae	0 [0–0]	0 [0–0]	0 [0–0]
Xanthobacteraceae	1,77** [0,87–3,93]	0,33 [0,07–4,7]	0,53 [0–1,1]
Tenericutes			
RF39	0 [0–0]	0 [0–0]	0 [0–0]
Verrucomicrobia			
Akkermansia muciniphila	0 [0–0]	0 [0–0]	0 [0–0]
Cyanobacteria			
Streptophyta	0 [0–0]	0 [0–0]	0 [0–0]
Euryarchaeota			
ANME-1	0 [0–0]	0 [0–0]	0 [0–0]
Bacteria			
Bacteria	0,27 [0–2,77]	0,63 [0,03–3,93]	0,17 [0–1,07]

Notes.
GDM DT — the gestational diabetes mellitus, diet therapy; GDM IT — the gestational diabetes mellitus, insulin therapy; CG — control group; n – the number of children.
The Mann-Whitney U-criterion, $p<0.05$, was used to assess the statistical significance of the frequencies of occurrence: * in the GDM group; ** in the CG..

Примечания.
ГСД ДТ — гестационный сахарный диабет, диетотерапия; ГСД ИТ — гестационный сахарный диабет, инсулинотерапия; КГ — контрольная группа; n — количество детей.
Для оценки статистической значимости частот встречаемости использован U-критерий Манна–Уитни $p<0,05$.
Достоверные различия обозначены в таблице: * — между ГСД ИТ и ГСД ДТ; ** — между ГСД и КГ.

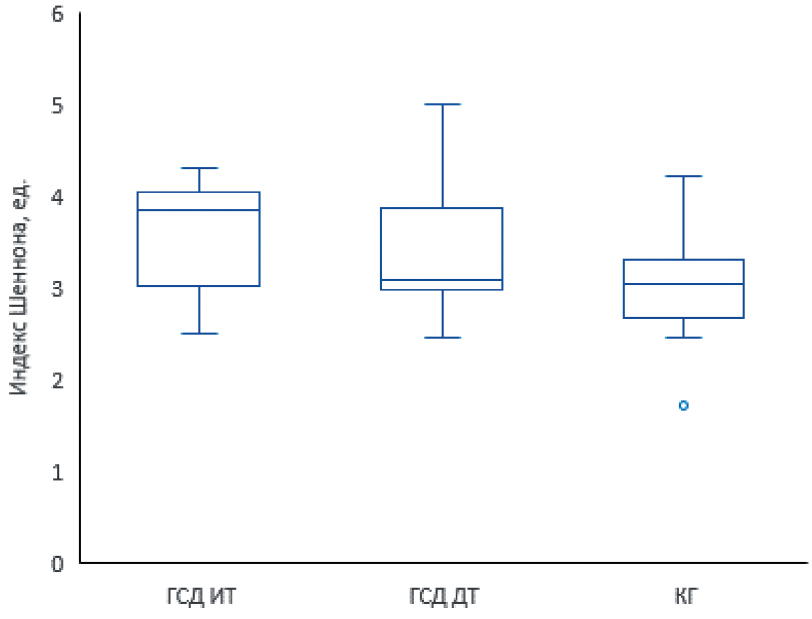

Fig. 3. Gut microbial community biodiversity index in young children study groups
Рис. 3. Индекс биоразнообразия микробного сообщества кишечника у детей раннего возраста исследуемых групп

To assess in detail the changes in gut microbiome composition in the studied groups of children, the species composition of microorganisms was studied (Table 2).

The data presented in Table 2 confirmed that the largest number of microbial species determined by NGS sequencing were Firmicutes. The number of represented bacterial species of this type decreases in a row:

- in the GDM IT group: *Streptococcus* spp. — 16%, *Bulleidiamoorei* — 10%, *Clostridium hiranonis* — 8%, *Actinomyces* spp. — 5%, *Bifidobacterium* spp. — 2%, *Acinetobacter* spp. — 2%, *Rothiamuci laginosa* — 2%, *Peptoniphilus* spp. — 2%, *Xanthobacteraceae* — 2%;
- in the GDM DT group:: *Bulleidiamoorei* — 21%, *Streptococcus* spp. — 17%, *Clostridium hiranonis* — 4%, *Nitrosomonadaceae* — 2%, *Acinetobacter* spp. — 2%, *Clostridiales* — 2%, *Peptoniphilus* spp. — 1%;
- in the control group: *Bulleidiamoorei* — 46%, *Streptococcus* spp. — 10%, *Acinetobacter* spp. — 3%.

Thus, 9 dominant microorganism species were detected in children born to mothers with the GDM IT, 7 microorganism species in the GDM DT group, and 5 microorganism species in the CG group. In the GDM IT group *Streptococcus* spp. was the dominant microorganism, but among other dominant opportunist species *Bifidobacterium* spp. were identified. *Bulleidiamoorei* dominates in the GDM DT and in the CG. But *Bulleidiamoorei* was significantly less frequent in children from mothers with the GDM IT (9.77 Lg/KOU ($p<0.01$)) and the GDM DT (21.4 Lg/KOU ($p=0.033$)) than in CG (45.8 Lg/KOU). *Clostridium hiranonis* was isolated in higher numbers in children from mothers with the GDM IT (8.4 Lg/COE ($p=0.023$)) and the GDM DT (4.2 Lg/COE ($p=0.041$)), relative to the CG (0.43 Lg/COE). *Clostridium hiranonis* belong to cluster XI of the genus *Clostridium* (a cluster including pathogens such as *C. difficile*) and can cause infectious diseases under favourable conditions [6]. Increased representation of *Actinomyces* spp. was observed in the GDM IT group, which was not observed in the CG ($p=0.023$). Representatives of the Actinomyces are saprophytes of humans, can cause actinomycosis, but their ability to secrete biologically active substances capable of selectively inhibiting the viability of other bacteria has also been established [7]. Eggerthella spp. (which associated with lipid metabolism, is a representative of the wall-adhered microbiota, a representative of normal flora, but in immunocompromised people causes bacteraemia [8, 9]), in greater numbers isolated in children from mothers with the GDM DT than in the CG ($p=0.029$). *Coprococcus catus* (which can switch from butyrate to propionate production, is a representative of resident microflora, but under certain conditions can cause inflammation in the intestine [10]), more isolated

in children from mothers with the GDM IT than in the CG (p=0.045). *Veillonellaceae* (is a representative of resident microflora, but under certain conditions can cause inflammation in the intestine [11]), more isolated in children from mothers with the GDM IT than in the CG (p=0.04). Blautia producta (the representative of resident microflora, elevated levels observed in irritable bowel syndrome, now identified as potentially probiotic for humans [12]), more isolated in children from mothers with the GDM IT than in the GDM DT (p=0.049). *Dorea* spp. (which associated with flatulence syndrome [13]), isolated in lower numbers in children from mothers with the GDM IT than in the CG (p=0.037). *Xanthobacteraceae* (which incompletely studied) was isolated in higher numbers in children from mothers with the GDM IT than in the CG (p=0.025).

Thus, in children born to mothers with the GDM, an increase in dysbiotic changes and biodiversity of potentially pathogenic bacteria in the intestine is noted. But in children from mothers with GDM IT also revealed an increase in beneficial bacteria and microorganisms capable of competing with pathogens for nutrient substrate and restrain their growth in the gut microbiota.

Despite the fact that compensatory mechanisms of gut microbiota regulation are presented both in children from mothers with GDM IT and in children from mothers with GDM DT, changes in the microbiocenosis may lead to disorders of digestion (malassimilation) and absorption (malabsorption). Nutrient deficiencies, the predominance of catabolism over anabolism, metabolic disorders in the future will have a negative impact on the growth and development of children from mothers with GDM.

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