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THE ROLE OF INTESTINAL MICROBIOTA IN THE DEVELOPMENT OF COMPLICATIONS IN PREGNANT WOMEN WITH GESTATIONAL DIABETES

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▪ Gestational diabetes mellitus (GDM) has been declared as one of the pandemics of our time and its prevalence is 5–20% in the European population. It causes the search for new pathogenetic risk factors in order to develop effective measures for the prevention and treatment of this disease. The intestinal microbiota plays an important role in maintaining the basic functions in the human body — metabolic, protective and trophic, and it undergoes significant changes during pregnancy. It has now been proven that dysbiosis alters intestinal metabolism and can lead to the development of diabetes. The direct relationships between intestinal microflora species and circulating levels of insulin, triglycerides and very-low-density lipoproteins were found. In a number of studies, associations of various concentrations of intestinal microbiota metabolites with the probability of developing GDM were analyzed. Studies conducted in a group of women with complicated pregnancy revealed changes in the diversity and structure of the intestinal microbiota in women with preeclampsia and arterial hypertension. Therefore, all authors emphasize the need for studies that expand our understanding of the relationship of various intestinal microbiota disorders with the risk of developing GDM and its specific progressing.

▪ **Keywords:** gestational diabetes mellitus; intestinal microbiota; insulin resistance; short chain fatty acids; preeclampsia; arterial hypertension.

РОЛЬ МИКРОБИОТЫ КИШЕЧНИКА В РАЗВИТИИ ОСЛОЖНЕНИЙ У БЕРЕМЕННЫХ С ГЕСТАЦИОННЫМ САХАРНЫМ ДИАБЕТОМ

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▪ Гестационный сахарный диабет объявлен одной из пандемий современности, и его распространенность составляет 5–20 % в европейской популяции. Это обусловливает необходимость поиска новых патогенетических факторов риска с целью разработки эффективных мер профилактики и лечения этого заболевания. Микробиота кишечника играет важную роль в поддержании основных функций в человеческом организме — метаболической, защитной и трофической и претерпевает значительные изменения во время беременности. В настоящее время доказано, что дисбиоз изменяет кишечный метаболизм и может приводить к развитию сахарного диабета. Обнаружены прямые взаимосвязи между представителями кишечной микрофлоры и уровнем инсулина,

триглицеридов и липопротеинов очень низкой плотности. В ряде работ были проанализированы ассоциации различных концентраций метаболитов микробиоты кишечника с вероятностью развития гестационного сахарного диабета. Исследования, проведенные в группе женщин с осложненным течением беременности, показали изменения в разнообразии и структуре кишечной микробиоты у пациенток с преэклампсией и артериальной гипертензией, поэтому все авторы подчеркивают необходимость проведения исследований, расширяющих представления о связи различных нарушений микробиоты кишечника с риском развития и особенностях течения гестационного сахарного диабета.

▪ **Ключевые слова:** гестационный сахарный диабет; микробиота кишечника; инсулинорезистентность; короткоцепочечные жирные кислоты; преэклампсия; артериальная гипертензия.

Gestational diabetes mellitus (GDM) complicates approximately 5%–20% of pregnancies [1].

To date, the frequency of obstetric and perinatal complications due to GDM exceeds the population level and is the cause of maternal and pediatric morbidity [2]. GDM can be considered as a multifactorial disease due to the great pathogenetic similarity with type 2 diabetes mellitus (DM). Therefore, this necessitates the search for new pathogenetic risk factors in order to develop effective prevention and treatment measures for this condition.

The metabolic changes occurring in the body of a pregnant woman are associated with the development of a new organ, the placenta. The placenta is an endocrine organ that produces and releases several protein and steroid hormones into the bloodstream, such as chorionic gonadotropin, placental lactogenic hormone, progesterone, and estrogens. Metabolic changes during pregnancy are associated with an increase in the production of placental hormones in late pregnancy, and an increase in insulin resistance (IR), which reaches maximum values in the third trimester of pregnancy [3, 4]. It is believed that the decrease in insulin sensitivity in late pregnancy is a physiological mechanism that promotes the increased absorption of nutrients and fetal growth [5, 6]. In some pregnant women with a genetic predisposition, the insulin secretion level and its effect may be insufficient to maintain euglycemia, which leads to GDM. It has been proven that timely and effective treatment of maternal hyperglycemia can reduce morbidity in both the mother and the newborn [7, 8]. Undoubtedly, diet therapy represents a basic non-drug treatment for GDM that has proven to be effective; however, there is no consensus on the optimal dietary composition of macronutrients that best supports maternal euglycemia. Approximately 30%–50% of women cannot achieve physiological metabolic control and require insulin treatment [9]. It is believed that for each patient, an optimal set of products is required to maintain euglycemia, and it depends on the individual composition of the intestinal microbiota. Disorders in the composition and impairment in the function of the intestinal microbiome can be one of the provoking factors in the development of pathological IR, which leads to GDM.

The intestinal microbiota plays an essential role of maintaining the basic metabolic, protective, and trophic functions in the human body. It is one of the controlling factors involved in the digestion process. These processes include the fermentation of polysaccharides; production of short-chain fatty acids (SCFA); hydrogen utilization; lactate production; metabolism of amino acids, bile acids, and choline; and the production of vitamins and some biologically active compounds (anti-inflammatory, antimicrobial, immune-stimulating) [10, 11]. The term “dysbiosis” is currently used in reference to changes in the composition, structure, and function of the intestinal microbiota associated with health conditions and diseases. One of the most important metabolic functions of the microbiota is the production of SCFAs (acetate, propionate, and butyrate) through the fermentation of complex carbohydrates (oligosaccharides, resistant starch, and plant cells). SCFA transmit signals through G-protein-coupled receptors that affect critical processes (e.g., inflammation, tight junction protein expression, and enteroendocrine regulation) and play a major role in maintaining the pH by inhibiting the proliferation of certain pathogenic bacteria. The ability of the intestinal microbiota to alter the expression of genes in human monocytes and to reduce the production of pro-inflammatory cytokines and chemokines by monocytes, as well as to stimulate the production of regulatory T cells, thereby suppressing the function of inflammatory T cells, is of particular note. Butyrate (butyric acid) is able to block the release of the chemokine,

interferon-γ-inducible protein 10 (IP-10), in human colon subepithelial myofibroblasts. Thus, the immunoregulatory properties of SCFAs affect immune cells not only systemically, but also locally via the cells of the intestinal tissue. The functions of the microbiome (the totality of all microorganisms inhabiting the human body) are comparable, for example, with the activity of an organ such as the liver, and therefore, according to many researchers, it can be considered an independent organ [12–16].

It has now been proven that dysbiosis alters intestinal metabolism and can lead to a number of dysmetabolic conditions. In a review, A.S. Meijnikman et al. (2018) confirmed the effect of disorders in the composition of the intestinal microbiota on the development of abnormal intestinal permeability, increased absorption of lipopolysaccharides (LPS), and abnormal production of SCFA. Changes in the composition and function of the microbiota are believed to be of great importance in the development of conditions such as obesity, IR, and DM [17, 18]. Butyric acid deficiency can lead to the inhibition of the tricarboxylic acid cycle in colonocytes. A sufficient amount of butyric acid has been found to promote mitochondrial function and to prevent autophagy in colonocytes. Autophagy can lead to increased absorption of exogenous antigens such as LPS, which is accompanied by the development of chronic inflammation and IR. In addition, butyric acid acts as an inhibitor of histone deacetylase, which promotes the differentiation and proliferation of pancreatic β-cells and controls insulin secretion [19, 20]. Using sequencing technology, including studies of associations throughout the metagenome, J. Qin et al. found a correlation between specific types of intestinal bacteria, products of their metabolism, and the development of type 2 DM [21].

Type 2 DM is associated with the increased expression of genes involved in oxidative stress and a pro-inflammatory bacterial community in the microbiome. It has been suggested that intestinal microbial markers may be markers of type 2 DM. Several studies have shown that the presence of *Akkermansia muciniphila* in the intestine, which accounts for 3%–5% of the intestinal microbiota, correlates negatively with body weight in rodents and humans, although the physiological mechanisms of this phenomenon are not well understood. It is not entirely clear where inflammatory processes are initiated, but altered microbiota of the gastrointestinal tract may be one of the reasons for the development of inflammation and IR [22, 23].

Dysbiosis leads to the activation of inflammatory and autoimmune pathways, stimulation of the endocannabinoid system, aberrant secretion of intestinal peptide, impaired insulin signaling, and accumulation of body fat. Endogenous cannabinoids are now known to regulate the energy balance in the body at various levels, which involve 1) the limbic system (the hedonistic effect of food); 2) hypothalamus (integrative functions); 3) the gastrointestinal tract; and 4) adipose tissue. The main reasons for the increased tone of the endocannabinoid system are presumably an increase in the arachidonic acid level (a precursor of endocannabinoids) with excess fat level in the diet, leptin and IR, and genetic disorders of the endocannabinoid inactivation mechanisms [24, 25].

Insulin plays a major role in the utilization of adipose tissue, liver, and skeletal muscles as biological buffers against excess nutrient intake. This is important because excess consumption and conversion of a number of macronutrients can activate inflammation [26].

The amount and different types of fatty acids are known to play an important role in the formation of IR. Several systems in the human body provide a stable level of glucose in the blood and prevent the rapid change of its level. Insulin is the central hormone involved in this metabolic communication system. Increased inflammation, as manifestation of dysbiosis, can disrupt these complex regulatory systems. The primary mediators of inflammation are tumor necrosis factor α (TNFα) and inflammatory protein kinases such as c-JUN N-terminal kinase and IκB kinase [27]. The fact that inflammation may be associated with IR was assumed more than a hundred years ago, when it was found that some anti-inflammatory drugs (salicylates and aspirin) reduced the glycemia level in DM patients. These drugs are now known to be inhibitors of the phosphorylating action of the complex of kinase IκB enzymes [28].

The excessive intake of a number of macronutrients can indirectly induce inflammation in the hypothalamus by activating toll-like receptors (TLR-4) in the brain microglia, which ultimately causes inflammatory damage to neurons in the

hypothalamus and can lead to the development of diseases associated with inadequate feeding. It has been demonstrated that the long-term intake of diets rich in fats decreases the number of neurons responsible for generating signals of satiety in the hypothalamus. Based on experimental animal models, the relationship between the intestinal microbiota state and the gut-brain axis was revealed. It has been found that intestinal bacteria produce and/or consume a wide range of neurotransmitters. One of the intestinal microbial metabolites is γ-aminobutyric acid, which is produced by several strains of *Lactobacillus* and *Bifidobacterium*. It is known that *L. reuteri* is capable of producing histamine, while acetylcholine is produced by both bacteria and fungi. In addition, the enzyme, tryptophan decarboxylase, has been found in the human intestine; therefore, it can be assumed that the intestinal microbiota produces the neurotransmitter tryptamine. The activity of intestinal microbial β-glucuronidase can also increase the concentration of catecholamines in the form of norepinephrine and dopamine [29].

The microbiota may be a source of chronic intestinal inflammation through endotoxemia mediated by the lipopolysaccharide component of gram-negative bacteria, which interacts with TLR-4. The level of TNFα is increased in the ileum with a diet rich in fats, even before the experimental animals gain weight. With excessive fat consumption, LPS fragments that enter the bloodstream are transported by chylomicrons to the lymphatic system, where they can interact with TLR-4 receptors, increasing TNFα levels, which can contribute to the development of IR in various organs, starting with the hypothalamus [30, 31].

In addition to genetic factors, the composition of the intestinal microbiota is influenced by comorbidities, antibiotic use, dietary habits, and pregnancy.

Currently, there is evidence that the intestinal microbiota composition is changed in pregnancy from the first to the third trimester. It was confirmed that in GDM women, there was already a decrease in the richness (alpha diversity) and an increase in the individual diversity (beta diversity) of the microbiota in early pregnancy. Their microbiota is enriched in taxa *Eisenbergiella*, *Tyzzerella* 4, and *Lachnospiraceae* NK4A136. Moreover, these intestinal bacteria have been associated with dysbiosis in previous studies [5, 32]. M. Crusell et al. (2018) showed a correlation between pathological weight gain during pregnancy (as a risk factor for GDM) and the genus *Eisenbergiella*, and other authors found an association with the levels of *Bacteroides*, *Staphylococcus*, *Enterobacteriaceae,* and *Escherichia coli*, a decrease in the number of *Bifidobacterium* and *Akkermansia muciniphila,* and a lower α-diversity [33, 34]. Both *Eisenbergiella* and *Tyzzerella* 4 correlated positively with fasting blood glucose levels, which may be the basis for considering them as predictors of GDM in late pregnancy.

A number of researchers have confirmed that the development of IR is associated not only with a change in the *Firmicutes*/*Bacteroidetes* ratio, but also with the development of metabolic dysbiosis caused by a decrease in the number of butyrate-producing bacteria such as *Roseburia* and *Faecalibacterium prausnitzii* [35–38].

Several studies have identified several correlations between the level of microbial endotoxins and biochemical and hormonal parameters characteristic of the metabolic syndrome. A direct relationship between *Collinsella* and levels of insulin, triglycerides, and very low-density lipoproteins has been revealed, as well as between *Sutterella* and C-reactive protein levels; between the *Ruminococcaceae*/*Lachnospiraceae* ratio and leptin levels; between the concentration of grehlin and *Bacteroidaceae*; and between the amount of *Coprococci* and the gastrointestinal polypeptide. An inverse relationship was found between the count of *Blautia* and insulin level; the *Faecalibacterium*/*Fusobacterium* ratio and blood glucose level; between *Odoribacter* and blood pressure level; between *Ruminococcaceae* and gastrointestinal polypeptide; as well as between *Prevotellaceae* content and ghrelin level.

Activation of specific G-protein-coupled receptors expressed on L-cells during dysbiosis triggers the secretion of glucagon-like peptide (GLP-1). Propionate, butyrate, and acetate induce the local release of peptide YY (PYY) and GLP-1 from enteroendocrine L-cells, which regulate digestion and alter liver function by modulating lipid metabolism with an indirect effect on the storage of fatty acids in the liver. Intestinal peptides are known to control energy homeostasis, glucose metabolism, intestinal barrier function, and metabolic inflammation [6, 39–41].

Y. Guangyong (2019) analyzed functional changes in the intestinal microbiota based on 16S rRNA sequencing data in GDM women in the state of carbohydrate metabolism compensation (GDM1), in GDM women who did not achieve compensation (GDM2), and in the control group. Disorders were revealed in the insulin signaling pathway, peroxisome proliferator-activated receptor (PPAR), and the adipocytokine signaling pathway, which were deficient in the patients of the GDM2 group compared to the control group and the GDM1 group patients. The correlation analysis of the above indicators with the *Faecalibacterium*, *Blautia,* and *Eubacterium hallii* group revealed that PPAR correlated positively with the relative prevalence of *Faecalibacterium* ($r = 0.52$, $p = 8.2$) and correlated negatively with the relative count of *Blautia* ($r = 0.43$, $p = 0.0015$). The counts of the *Blautia* and *Eubacterium hallii* groups increased gradually in order from the control group to GDM1 and GDM2, while the analysis of *Faecalibacterium* showed opposite results. These data indicate that enrichment in *Blautia* is combined with an unfavorable metabolic profile in pregnant women with GDM [42, 43].

Intestinal bacteria can use dietary methylamines (choline, L-carnitine, and phosphatidylcholine) and produce trimethylamine (TMA), which is then oxidized to trimethylamine oxide (TMAO) by the liver enzyme flavin-containing monooxygenase. Red meat, eggs, dairy products, and sea fish are the main dietary sources of methylamines. It has been suggested that elevated blood levels of TMAO are associated with the excessive consumption of red meat and the risk of T2DM and cardiovascular diseases.

Currently, few studies have been conducted to understand the pathogenetic role of TMAO in glucose metabolism. In addition, information on the taxonomic composition of bacteria producing TMAO under conditions when *Firmicutes*, *Actinobacteria,* and *Proteobacteria phyla* are widespread in the body is limited. An increasing number of studies associate an increased level of TMAO with the development of DM [44, 45].

In 2018, in a large crossover study, the relationship between plasma TMAO concentration in early and late pregnancy and the probability of GDM was analyzed [46]. In 276 GDM female patients and 552 pregnant women in the control group, plasma concentrations of TMAO were determined by liquid chromatography with stable isotope dilution by tandem mass spectrometry. In the first part of the case-control study, with an adjusted odds ratio (OR) of developing GDM, the highest TMAO quartile was compared with the lowest quartile, and it amounted to 1.94 (95% CI 1.28–2.93). Each increase in the plasma standard deviation (SD) of TMAO was associated with a 22% increase in the probability of developing GDM (95% CI 5–41) [46, 47]. In the second part of the study, women in the highest quartile also had an increased probability of GDM (adjusted OR 2.06; 95% CI 1.28–3.31) compared with women in the lowest quartile. The adjusted OR for GDM with the increase in SD of TMAO in plasma was 1.26 (95% CI 1.08–1.47). The authors concluded that the data obtained confirm a positive relationship between plasma TMAO concentrations and the risk of GDM [46, 47].

The incidence of GDM increases in parallel with an increase in overweight and the severity of obesity in women of reproductive age. In the short term, the risk of preeclampsia increases in GDM women, as well as the frequency of preterm birth and operative delivery by cesarean section; and in the long-term, there remains a risk of obesity, type 2 DM, and hypertensive disorders in both the mother and the newborn [48, 49].

Dysbiosis is known to induce an inflammatory response in the body by altering the function of the endothelium, which determines the condition of the cardiovascular system. The review by L.F. Gomez-Arango et al. presents data on the mechanisms by which the intestinal microbiota influences the blood pressure. Bacteria belonging to the genera *Streptococcus, Escherichia, Lactobacillus,* and *Bifidobacterium* can synthesize neurotransmitters. Changes in the composition and functional activity of the intestinal microbiota can act as pathological factors in the development of arterial hypertension. This is confirmed by the data on the relationship between the SCFA production and the blood pressure level [6, 50–52].

The main producers of butyrate in the human intestine belong to the phylum *Firmicutes* (*Coprococci*, *Eubacterium*, *Roseburia*, and *Faecalibacterium*). SCFA-producing bacteria can influence blood pressure indirectly through a plasminogen activator inhibitor-1 (PAI-1). It was established that butyrate

increases the content of PAI-1 mRNA in cultured hepatocytes [53].

The experiment showed that the intestinal microbiota of rats with hypertensive disease contains fewer bifidus bacteria and fewer types of bacteria producing SCFA. Treatment with minocycline (a group of tetracyclines) increased the number of SCFA-producing bacteria and, at the same time, decreased the blood pressure. The results of the study confirm the need to further study the allelic variants of SCFA receptors as candidate genes for interactions between the host and the microbiota, promoting increased sensitivity to salt and the development of hypertension.

L.F. Gomez-Arango et al. [6] confirmed that systolic blood pressure correlates negatively with the counts of *Odoribacter* and *Clostridiaceae* butyrate producers in overweight and obese pregnant women at 16 weeks of gestation. The results of this study suggest that expression of the butyrate kinase gene of *Odoribacteraceae* and *Clostridiaceae* in pregnant women at a gestational age of 16 weeks is associated with a decrease in blood pressure. The pathway for butyrate production that is primarily utilized by the intestinal microbiota is still unclear, but studies have shown that butyrate kinase is present in most intestinal ecosystems. Oral administration of butyrate decreased IL-1 and TNFα concentrations in response to a high-fat diet in mice. Consequently, lowering butyrate levels may increase blood pressure in pregnant women.

A study conducted in a group of women with complicated pregnancies revealed changes in the richness, diversity, and structure of the intestinal microbiota in women with preeclampsia. A decrease in the number of *Ruminococcus and Clostridiales,* and an increase in the level of gamma-proteobacteria and enterobacteria were registered in women with preeclampsia compared with healthy pregnant women [54–57].

J. Liu et al. investigated the intestinal microbiota in women with preeclampsia and found a decrease in the content of the probiotic bacteria *Coprococcus catus* and an increase in *Clostridium perfringens* and *Bulleidia moorei* (pathogenic bacteria) [54].

Another study noted an increase in the number of Blautia, *Ruminococcus, Bilophila,* and *Fusobacterium*, as well as decrease in *Faecalibacterium, Gemmiger*, and the populations of *Akkermansia, Dialister,* and *Methanobrevibacter* in samples collected before delivery from women with preeclampsia compared to a control group. In addition, the researchers reported that liver enzyme levels and blood pressure in pregnant women correlated positively with *Anaerococcus*, *Ruminococcus*, and *Oribacterium* levels. There was a negative correlation between the level of LPS in maternal blood and the content of *Akkermansia*, while the level of IL-6 correlated positively with the concentration of *Oribacterium* and *Bilophila* [58].

The possibility of altering the intestinal microbiota through dietary interventions during pregnancy is of growing interest, given the potential impact on the health of mothers and newborns. To date, there is insufficient data on the relationship between the composition of the diet and the state of the intestinal microbiota during GDM-complicated pregnancy. Diet can change the composition of the microbiota over a short period of time [59, 60]. Historically, the main principle of the diet in GDM is the restriction of easily digestible carbohydrates, because this leads to a decrease in blood glucose levels after meals, which neutralizes the effect of hyperglycemia on the fetus and reduces the risk of macrosomia [61]. However, T. Korem et al. (2017) demonstrated a high interpersonal variability of postprandial glycemia, which was previously confirmed in the works of D. Zeevi et al. (2015) [62, 63]. Recent studies suggest the presence of significant differences between individual responses to certain macronutrients and that these differences may be due to genetic, epigenetic, and microbial influences. The need for a personalized approach to diet in patients with impaired carbohydrate metabolism is widely discussed in the literature. The metabolic response to various foods based on the individual composition of the intestinal microbiota is one of the new and important topics of interest in the field of personalized nutrition [64, 65].

The intake of probiotics is one of the possible ways to alter the composition and function of the intestinal microbiome. In a recent randomized controlled study of probiotic intervention in women of normal weight during pregnancy, a combined approach to diet and the intake of probiotics decreased the incidence of GDM from 34% to 13% [66].

A decrease in the incidence of preeclampsia in pregnant women taking probiotics has been confirmed. The authors suggested that blood pressure was normalized due to the release of peptides that

inhibit angiotensin converting enzyme and decrease the production of pro-inflammatory cytokines [67–69].

Many researchers emphasize the need to conduct randomized controlled trials to confirm or refute the effectiveness of using probiotics for the prevention of obstetric and perinatal complications in GDM female patients.

Several studies have now proven the beneficial metabolic effects of a diet based on the characteristics of the intestinal microbiota of patients. These data are important and indicate that it is necessary to adhere to an individual approach to the diet of pregnant women with metabolic disorders. The potential impact of lifestyle modification and certain dietary interventions on the composition and function of the intestinal microbiota is of considerable interest in terms of the search for an optimal strategy for the prevention and treatment of GDM.

Conclusion

The data presented in this review helps to state that the intestinal microbiota significantly affects the metabolic processes in the body of a pregnant woman, and determines its course and outcomes. Any changes in the structure and composition of the maternal intestinal microbiota can be risk factors for GDM and pregnancy complications such as preeclampsia and hypertensive disorders. Improvement of diagnostic methods for the species composition and functional state of the microbiota, as well as development of personal dietary recommendations can be an effective reserve for the treatment of pregnancy complications in women with GDM. Based on this, all authors agree on the need to conduct studies that increase our understanding of the relationship between various disorders of the intestinal microbiota and the development of diseases that are included in the list of modern pandemics, namely GDM, obesity, and hypertensive disorders.

Additional information

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