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Intestinal microbiome in gestational diabetes — review

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Abstract: Gestational diabetes is one of the most common metabolic complications of pregnancy. Numerous studies have shown the gut microbiota changes significantly during pregnancy and intestinal microbiota also influences the development of diabetes during pregnancy. The aim of this study was to review the studies about gut microbiome in gestational diabetes.

Keywords: gestational diabetes, intestinal microbiome, gut microbiome.

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Gestational diabetes (GDM) is one of the most common metabolic complications of pregnancy. It is estimated to complicate between 7% and 14% of pregnancies worldwide, but the actual number is difficult to estimate [1]. The incidence of its occurrence is constantly increasing [2]. GDM diagnosis identifies a group of women and their offspring who are at higher risk of diabetes, obesity and premature cardiovascular disease in the future [3]. GDM is a condition where women without a previous diagnosis of diabetes exhibit abnormal blood glucose levels during pregnancy [4]. Pregnancy complicated by GDM is associated with an increased risk of maternal complications such as hypertension, polyhydramnios, operative delivery, preterm delivery, postpartum infection, recurrent urinary tract infections, development of type 2 diabetes (T2D)

after delivery [5] and a number of fetal complications: excessive fetal growth include birth trauma, maternal morbidity from cesarean deliveries, shoulder dystocia, and neonatal hypoglycemia. Other neonatal morbidities that potentially occur more frequently in infants of women with GDM include hyperbilirubinemia, hypocalcemia, erythema and respiratory distress syndrome [6]. Well-known risk factors for GDM include a family history of diabetes, a history of GDM, advanced maternal age, giving birth to a macrosomic baby, polycystic ovary syndrome, being overweight, and being obese [7].

Much is known about the pathogenesis of GDM, but many of the complex mechanisms underlying the development of GDM remain unclear. Metabolic abnormalities leading to GDM include increased insulin resistance and defects in the beta cells of the pancreas. GDM is characterized by the inability of beta cells to respond appropriately to the increased demand for insulin during pregnancy, resulting in varying degrees of hyperglycemia [8]. In recent years, there has been emerging evidence that the gut microbiota may play a significant role in the development of obesity, may have a significant impact on glucose metabolism [9], and may also affect insulin resistance, thus contributing to metabolic diseases and playing a role in the etiology of GDM [1, 10]. Increasing evidence suggests that the microbiota is involved in physiological and pathological processes [11], which is why it is the subject of many studies.

The term gut microbiota refers to all microorganisms that inhabit the human digestive tract [12]. The human microbiome is a complex ecosystem that inhabits the mucosa and skin in a symbiotic relationship [13]. These microorganisms (commensal symbionts) are in symbiosis with their host because they are able to obtain energy from foods that humans cannot digest, producing bioactive compounds, and so as a result of microbial fermentation of polysaccharides, compounds such as short-chain fatty acids (SCFA) are formed, which can only be metabolized by the human body [14]. Intestinal microbiota produce numerous compounds, including glycosyl hydrolases, which play key roles in the metabolism of starch, fructose, mannose, sucrose, galactose, and butanoate [15]. Intestinal microbiota supports food digestion, vitamin synthesis, and mucosal barrier function. Importantly, interactions between host cells and intestinal microbiota influence the host metabolism and immune response [16]. In a healthy organism, the dominant composition of the intestinal microflora is the species Bacteroidetes and Firmicutes [17]. An example of a command symbiont is butyrate-producing bacteria such as Faecalibacterium prausnitzii. They belong to the Firmicutes class and exhibit, among others, anti-inflammatory effects [18].

Pathobionts, in turn, are a group of bacteria that elicit a pathogenic inflammatory response, causing adverse effects on the human host when elevated [19], e.g. Proteobacteria is a pathobiotic that is responsible for inflammation in type 2 diabetics [20].

Dysbiosis, that is an altered composition of the microbiota, is thought to play a key role in the pathogenesis of many diseases, including metabolic diseases such as obesity, insulin resistance, and type 1 and 2 diabetes. Several mechanisms have been identified linking dysbiosis to conditions such as abnormal intestinal permeability, increased lipopolysaccharide (LPS) absorption, abnormal SCFA production, abnormal conversion of primary bile acids to secondary bile acids, and increased production of bacterial toxicants [21, 22]. These abnormalities lead to activation of inflammatory and autoimmune pathways, abnormal secretion of gut peptides, impaired insulin signaling, increased energy extraction, and storage of fat cells [23].

The composition of the bacterial gut microbiota depends on its location and is influenced by many factors. Prevotella copri and Bacteroides vulgatus have been identified as the main species responsible for the association between insulin resistance and glucose intolerance [24]. Bacteroides

spp. and Staphylococcus aureus are significantly more common in overweight women compared to women with a normal BMI [25]. A prospective study found that high levels of Bacteroides spp. were associated with excessive weight gain during pregnancy, suggesting that the gut microbiota may influence women's weight during pregnancy [25]. One of the proposed mechanisms of the influence of gut microbiota on weight gain during pregnancy is increased absorption of glucose and fatty acids, induction of catabolic pathways and stimulation of the immune system [26].

Therefore, research has begun to investigate whether intestinal microbiota also influences the development of diabetes during pregnancy.

In a study by Ya-Shu Kuang *et al.*, the gut microbiome composition of 43 pregnant women with GDM was compared with 81 healthy pregnant women by sequencing the entire metagenomes of fecal samples collected between 21 and 29 weeks of gestation. Parabacteroides distasonis, Klebsiella variicola were found to be increased in pregnant women with GDM, whereas Methanobrevibacter smithii, Alistipes spp., Bifidobacterium spp., and Eubacterium spp. were more abundant in women with normal pregnancies. The study found an association between the gut microbiome and the occurrence of GDM and suggested that changes in microbial composition could potentially be used to identify individuals at risk of GDM [10]. In an Italian study, the authors also found changes in the microbiome of pregnant women with GDM. They assessed the microbiome between 24 and 28 weeks of gestation and after 38 weeks of gestation. During this period, an increase in Firmicutes bacteria and a reduction in Bacteroidetes and Actinobacteria were observed. In addition, patients received nutritional recommendations. Patients who followed the nutritional recommendations showed a better metabolic and inflammatory pattern at the end of the study and a significant decrease in Bacteroides [27]. Gomez-Arango *et al.* investigated the relationship between gut microbiota and metabolic hormones in early pregnancy in overweight or obese patients. They found that obese pregnant women had a less diverse gut microbiome and a predominance of Firmicutes over Bacteroidetes compared to overweight women [28]. Cortez *et al.* assessed the composition of the microbiome of pregnant women and assessed its relationship with the occurrence of GDM. The study included patients in the third trimester of pregnancy — 26 patients with GDM and 42 without this diagnosis. They assessed the microbiome from oral, vaginal and fecal samples. Analysis of the oral microbiome did not show significant differences in both groups. However, patients with GDM presented a specific composition of the vaginal and intestinal microbiome indicating dysbiosis in relation to the control group. The authors concluded from the study that the composition of the vaginal and intestinal microbiome may be involved in the development of GDM [29]. Another study also suggests that the composition of the intestinal microflora may contribute to the development of this condition. Mokkala *et al.* included 75 patients in early pregnancy with overweight and obesity in their study. The composition of the intestinal microflora in the feces of the patients was examined in the first trimester. Among the patients studied — 15 of them were diagnosed with GDM (on average at 25 weeks). The composition of the gut microbiota, especially the Ruminococcaceae family, has been shown to differ in women who develop GDM compared to women who do not develop GDM. The authors conclude that the relative abundance of Ruminococcaceae in early pregnancy is associated with the risk of developing GDM later in pregnancy and that the gut microbiota may be considered as a potential target for modification by specific dietary approaches to reduce the risk of GDM [30]. In another study, oral and intestinal microbiota were compared in the third trimester of pregnancy in 30 patients with GDM and 31 pregnant women with physiological pregnancy. Differences in the microbiota were demonstrated in both groups. Patients with GDM showed significant differences

in β diversity and increased Gammaproteobacteria and Hemophilus in the gut microbiota. In addition, GDM cases showed lower α diversity, increased Selenomonas and Bifidobacterium, and decreased Fusobacteria and Leptotrichia in the oral microbiota [31]. Crusell *et al.* compared the composition of the oral microbiota in pregnant women with GDM (n = 50) to pregnant women without this diagnosis (n = 160) in the third trimester of pregnancy and 9 months after delivery. GDM was found to be associated with minor changes in the salivary microbiota in late pregnancy and after delivery [32].

In their study, Koren *et al.*, showed that the gut microbiome changed radically during pregnancy from the first to the third trimester, with an overall increase in Proteobacteria and Actinobacteria while the overall diversity of the microbiome decreased [26]. Chen *et al.* conducted a case-control study of 110 patients with GDM and 220 healthy pregnant women who provided stool samples for 16S ribonucleic acid sequencing in the second trimester of pregnancy. They found that patients with GDM had lower α-diversity, which was significantly associated with glycemia. Among patients with GDM, seven genera in the phylum Firmicutes and two in the phylum Actinobacteria were significantly decreased, and four genera in the phylum Bacteroidetes were increased. An association was found between the altered composition of the gut microbiota in the second trimester of pregnancy before the diagnosis of GDM and fasting serum metabolite levels, which may have implications for the diagnosis, prevention, and treatment of GDM [33]. In a Danish study on the gut microbiota, 50 patients with GDM and 157 patients with physiological pregnancy were examined. It was found that GDM diagnosed in the third trimester of pregnancy is associated with a disturbed composition of the gut microbiota compared to pregnant women with normoglycemia, and 8 months after pregnancy, differences in the composition of the gut microbiota are still detectable. The composition of the gut microbiota of women with GDM resembles the abnormal gut microbiome found in patients T2D [34]. Sililas *et al.* aimed to determine the relationship between the types and amounts of intestinal microflora and the development of GDM. The study included 88 pregnant women (39 without GDM and 49 with GDM). The stools from the patients were collected at the time of GDM diagnosis (24–28 weeks of gestation) and after 37 weeks of gestation. It was found that the number of Lactobacillales bacteria in the mother was reduced compared to the baseline value until the time before delivery in both women without GDM and GDM. The ratio of Firmicutes/Bacteroidetes (F/B) bacteria before delivery (after 37 weeks of gestation) was higher in the group of patients with GDM. It was found that although the researchers found a small difference in the intestinal microflora between the microbiome of patients with and without GDM, the intestinal microflora may play an important role in the development of GDM [35]. Some studies suggest that the composition of the gut microbiome may serve as an early biomarker of GDM. One study comparing the composition of the gut microbiome of pregnant women between the first and second trimesters of pregnancy showed that women (n = 31) who developed GDM had less dynamic microbiome changes than those who had normoglycemia during pregnancy (n = 103) [36]. Another study also compared the composition of the gut microbiome based on 16S rRNA microarrays conducted on stool samples from 30 women with GDM and 28 healthy pregnant women. Among patients with GDM, the amount of Peptostreptococcus anaerobius was inversely correlated with fasting glucose levels, whereas some species (e.g. Aureimonas altamirensis, Kosakonia cowanii) were positively correlated with fasting glucose. This study suggests that there is large taxon differentiation between GDM and the control group at the genus and species level [37].

Many studies have investigated the effect of prophylactic administration of probiotics, and thus altering the microbiome, on the development of gestational diabetes. The evidence on the effect of probiotics on blood glucose levels in women with GDM is inconsistent. Homayouni *et al.* in their work analyzed articles based on clinical trials from 2000 to 2017 that investigated the prevention of GDM. The authors concluded from their review that experimental and clinical evidence supports the assumption that modulation of the gut microbiota by probiotic microorganisms may be effective in preventing the development of GDM [38]. One study involved 439 obese or overweight pregnant women. They were divided into 4 cohorts. In one group, the patients used fish oil + placebo, in the second — probiotics (Lactobacillus rhamnosus and Bifidobacterium animalis ssp lactis) + placebo, in the third group — fish oil + probiotics, and in the fourth — placebo + placebo. The primary endpoints were the occurrence of GDM and the change in fasting glucose during the intervention period, but neither group showed any benefit in terms of reducing the risk of GDM or improving glucose metabolism [39]. Another randomized, double-blind study (probiotics vs. placebo) examined whether the administration of probiotics to overweight or obese pregnant women from the second trimester would prevent the development of GDM. The study was completed by 411 women. It was found that the probiotics used in this study did not prevent GDM in overweight and obese pregnant women [40]. In their meta-analysis, Tzu-Rong *et al.* included 12 randomized controlled trials. The studies found that probiotics significantly lowered fasting blood glucose levels in pregnant women who had not been diagnosed with GDM [41]. Another meta-analysis also found that probiotic supplementation is associated with improved glucose and lipid metabolism in pregnant women and may help reduce the risk of GDM. Supplementation with specific probiotics may be a promising preventive and therapeutic strategy for GDM. Additionally, it was shown that after probiotic supplementation in pregnant women, the HOMA-IR index decreased — probiotic supplementation for 6-8 weeks resulted in a significant reduction in insulin resistance in pregnant women diagnosed with GDM. The use of probiotic supplementation is promising as a potential supportive therapy for GDM treatment [42].

The gut microbiota changes significantly during pregnancy [26] and may therefore contribute to the development of pathologies such as GDM [43]. These studies suggest that pregnancy is associated with major changes in the gut microbiome that may play an important role in the observed increase in inflammation during pregnancy, potentially contributing to the development of GDM. Compared with healthy pregnant women, pregnant women with GDM have fewer distinct gut microbial species (lower microbial diversity or richness) [44]. The association between GDM and the gut microbiota appears to be similar to that observed in T2D and metabolic syndrome [13].

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Conflict of interest

None declared.

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