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ABOUT COVER

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REVIEW

Gut microbiota in gastrointestinal diseases during pregnancy

Zhong-Zhen Liu, Jing-Hua Sun, Wen-Jing Wang

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Abstract

Gut microbiota (GM) is a micro-ecosystem composed of all microorganisms in the human intestine. The interaction between GM and the host plays an important role in maintaining normal physiological functions in the host. Dysbiosis of the GM may cause various diseases. GM has been demonstrated to be associated with human health and disease, and changes during individual development and disease. Pregnancy is a complicated physiological process. Hormones, the immune system, metabolism, and GM undergo drastic changes during pregnancy. Gastrointestinal diseases during pregnancy, such as hepatitis, intrahepatic cholestasis of pregnancy, and pre-eclampsia, can affect both maternal and fetal health. The dysregulation of GM during pregnancy may lead to a variety of diseases, including gastrointestinal diseases. Herein, we review recent research articles on GM in pregnancy-related gastrointestinal diseases, discuss the interaction of the GM with the host under normal physiological conditions, gastrointestinal diseases, and pregnancy-specific disorders. As more attention is paid to reproductive health, the pathogenic mechanism of GM in gastrointestinal diseases during pregnancy will be further studied to provide a theoretical basis for the use of probiotics to treat these diseases.

Key Words: Gut microbiota; Microbiome; Pregnancy; Gastrointestinal diseases; Hormones; Immunity; Metabolites

Core Tip: Pregnancy is a complicated physiological process, with interactions between pregnancy hormones, the immune system, metabolism and gut microbiota. The dysregulation between these systems can cause pregnancy-specific diseases, including pregnancy-specific gastrointestinal diseases. Here we summarize the current opinions on dysbiosis associated with pregnancy-related gastrointestinal diseases including pre-eclampsia, intrahepatic cholestasis of pregnancy, hyperemesis gravidarum and constipation. The composition of gut microbiota changes dramatically during these diseases.

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INTRODUCTION

Human gut microbiota (GM) is a micro-ecosystem usually regarded as a human "virtual organ"[1]. More than 10^{14} microorganisms, including > 1000 species live in this ecosystem. The genomes of microbiota, defined as the microbiome, are > 100 times larger than the human genome[2]. The microbiota colonizes the gut after birth[3] (or even as early as the first trimester[4], but this is controversial), and is present in the host for their entire life. The composition of GM is not invariable, on the contrary, it changes according to age, environment, physiological or pathological status. Pregnancy is a physiological status with dramatic changes in GM composition. The sex hormones, immune system, metabolism, and diet all change dramatically and play a role in the GM. The dysbiosis of GM can cause various diseases during pregnancy. In this review, we will summarize the current understanding of the role of GM in pregnancy and disease, especially in gastrointestinal (GI) diseases during pregnancy.

HUMAN GUT MICROBIOTA

Roles of the gut microbiota in human physiology

GM plays a role in human physiology. The GM benefits the host in several ways including (1) Fermentation of indigestible food components. Complex carbohydrates are hard to digest by human enzymes, but certain dominant species in the colon, including Bacteroidetes, contain a large number of active enzymes which degrade carbohydrates to obtain energy[5]; (2) Providing beneficial metabolites to the host. The by-product of complex carbohydrate fermentation, such as short-chain fatty acids (SCFAs), can be utilized by the host as an energy source. Moreover, some SCFAs have anti-inflammatory activity. Some vitamins, including the K and B vitamins, can be synthesized by the GM, and play important roles in some pathways in the host[6]; (3) Intestinal barrier protection. The intestinal barrier is composed of a monolayer of epithelial cells and a mucus layer, which can physically separate the immune system of the host and the commensal bacteria. The metabolites from gut bacteria can increase the function of the mucus layer. For example, butyrate produced by some bacteria can increase mucus secretion from goblet cells[7]; and (4) Regulation of immunity. The GM can increase the development of lymphoid structure, play a role in T cell composition and invariant T cells[8]. SCFAs are important in the interaction between the GM and immunity, which can activate the G-protein coupled receptors (GPCRs) and increase the levels of enzymes and transcription factors involved in the immunity provided by intestinal epithelial cells and the development of leukocytes[9]. Moreover, the GM can prevent toxic components from entering the GI tract[10] and inhibit certain harmful bacteria by out-competition[11].

Changes in gut microbiota during gastrointestinal diseases

Disturbance of the structure or function of the GM, or intestinal dysbiosis can disrupt host-microbe homeostasis, correlating with GI diseases, including inflammatory bowel disease (IBD), colorectal cancer (CRC), celiac disease, and irritable bowel syndrome (IBS)[12]. IBD is a chronic, recurring inflammatory disease affecting the colon and small intestine. CRC is a common cancer which caused an estimated 0.9 million deaths in 2018. Developed countries are at the highest risk of CRC, mainly due to older age, male sex and lifestyles[13]. Celiac disease is an immune disease triggered by food containing gluten and the immune system can damage the small intestine. The worldwide prevalence of celiac disease is 1%-2%[14]. IBS is a GI disorder that includes abdominal pain and changes in the consistency of bowel movement[15]. Many factors are involved in GI diseases, including genetic susceptibility genes, environmental risk factors, pathogenic microbiota and metabolites[12].

GM plays an important role in inducing or exacerbating GI diseases. The alpha-diversity and richness of the GM are significantly different in various GI diseases. In IBD and CRC, these two indices are

reduced[16,17], while in celiac disease, the alpha-diversity is higher[18,19]. The overgrowth of specific pathobionts and the reduction of beneficial bacteria have been extensively reported. The colonization of *Prevotella* in wildtype specific pathogen-free mice results in serious intestinal inflammation[20] and is positively correlated with IBD in humans[21]. Colonization of *Akkermansia*, but not *Bacteroides vulgatus,* can cause colitis in GF interleukin (IL)-10$^{-/-}$ mice[22,23]. The severity of IBS in mice may be linked to a specific GM pattern, including enrichment of *Bacteroides*[24]. Newborn babies with HLA-DQ deficiency have a lower level of *Bifidobacteria*[25].

The shift in GM composition can induce various GI diseases based on several mechanisms. Alteration in GM metabolites is one of the most likely mechanisms. The colonization of *Prevotella* reduces the production of SCFAs (especially acetates), which can reduce the intestinal level of IL-18 and induce serious inflammation[20]. Butyric acid also plays an important role in maintaining the function of intestinal epithelial cell junctions and Treg cell differentiation. *Anaerostipes*, a genus of Lachnospiraceae, the main butyrate-producer, is lower in celiac disease patients[26]. The IgA coating of colitogenic bacteria is another potential mechanism in GI diseases. IgA is an antibody isotype mainly found on mucosal surfaces. It binds to colitogenic bacteria to protect the gut from infection[27]. If colitogenic bacteria accumulate, for example, induced by a high-fat diet, then serious inflammation will occur. Disorders of competitive inhibition between bacteria may also be responsible for GI diseases. The colonization of *Clostridium difficile* (*C. difficile*), which is promoted by primary bile acid (BA) and inhibited by secondary BA, is positively associated with IBD. *Clostridium scindens* (*C. scindens*) can process primary BA to secondary BA and inhibit *C. difficile.* The dysbiosis between *C. difficile* and *C. scindens* may cause IBD[28].

Both prebiotics and probiotics have been used to prevent or treat GI diseases. A series of clinical trials have proved that *Escherichia coli* Nissle 1917 is effective in the maintenance of IBD remission[29,30], and a compound probiotic named VSL#3, which contains 8 Lactic-acid producing bacteria, can reduce the rate of IBD relapses in 9 mo from 100% to 15%[31]. VSL#3 also has a potential role in treating celiac disease by effectively degrading gliadin peptides in wheat flour[32]. Certain strains of probiotics were also used to prevent or treat CRC by reducing the activities of the specific enzymes that can induce CRC [33,34].

GUT MICROBIOTA DURING PREGNANCY

Pregnancy is a complicated physiological process which includes changes in multiple systems. During pregnancy, the hormones, immune system, metabolites, weight and total blood volume change with the growth of the fetus. Moreover, the changes in maternal GM composition have become a focus of research.

During pregnancy, the pregnancy hormones, especially progesterone and estrogen, rise dramatically and peak in the 3rd trimester. After delivery, most of the pregnancy hormones markedly decrease, while prolactin, which promotes milk secretion, increases markedly[35]. The changes in pregnancy hormones have an important role in the regulation of GM in pregnant women. The immune system in pregnant women also undergoes considerable changes. There is a balance between maternal immunity that allows maternal-fetal tolerance and necessary immunity to protect against infection[36]. Several unique immune cells with cytotoxicity and tolerance to trophoblast cells, including uterine natural killer cells, decidual macrophages, T helper 2 and CD4+CD25+ Tregs are markedly increased during pregnancy[37-41]. The serum concentration of pro-inflammatory cytokines also increases, and the mucosal layer of the GI tract is in a moderate inflammatory state. The immune changes cause an increase in the GM correlation with inflammation[42]. Maternal metabolism during pregnancy changes similar to that in metabolic syndrome. For example, insulin resistance induced by placental growth hormone can help the absorption of nutrients to promote the growth of the fetus[43]. The insulin resistance status is similar to diabetes mellitus and disappears shortly after delivery. The GM in late pregnancy is similar to that in obesity or the diabetic state[44].

The GM changes during pregnancy have been extensively studied. Beta diversity during a healthy pregnancy dramatically increases from the first trimester (T1) to the third trimester (T3). On the other hand, the alpha-phylogenetic diversity is significantly reduced from T1 to T3. Most of the increased abundance of operational taxonomic units (OTUs) in T1 belongs to Clostridiales, such as *Faecalibacterium* and *Eubacterium*. OTUs enriched in T3 samples include members of the *Enterobacteriaceae* family and *Streptococcus* genus[45]. *Faecalibacterium*, a butyrate producer, is also decreased in the metabolic syndrome similar to diabetes mellitus and obesity[46,47]. The low α-diversity seen in T3 is also found in obesity[48]. These results indicate the similarity between T3 and metabolic syndromes. After transferring T1 and T3 microbiota to germ-free mice, T3 microbiota induced serious adiposity and inflammation compared to T1 microbiota, indicating that the GM from T3 is similar to that in obesity [45].

Studies on both pregnant women and mice showed that the probiotic *Bifidobacterium* increased during T3. *In vitro* culture experiments further confirmed that progesterone can directly increase the number of *Bifidobacterium*. This study proved that pregnancy hormones have a causative role in enhancing the numbers of *Bifidobacterium*[49]. The mechanism underlying the promotion of *Bifidobacterium* by proges-

terone may be due to the presence of the enzyme hydroxysteroid dehydrogenase on the cell membrane of *Bifidobacterium*, which is involved in the metabolism of progesterone. This enzyme acts as a sensor of progesterone to regulate the number of this bacteria. Another study in Phayre's leaf monkeys found that the diversity of GM decreased in pregnant female monkeys. Progesterone in feces was negatively correlated with this diversity. This conclusion is consistent with the aforementioned result[50]. Progesterone can also affect the translocation of GM metabolites. One study showed that progesterone can enhance the tight junctions between intestinal epithelial cells by increasing the transcription level of occludin. With the strengthening of tight junctions, the amount of GM metabolites in the intestine of pregnant women, such as lipopolysaccharide (LPS), that enter the plasma through translocation is reduced. Therefore, plasma LPS in pregnant women is negatively correlated with the level of progesterone. *In vitro* experiments further confirmed that progesterone can inhibit the activation of nuclear factor-kappa beta (NF-κB) caused by LPS, thereby reducing the inflammatory response[51]. LPS is one of the major components on the cell membranes of Gram-negative bacteria, and can efficiently activate the NK-κB-mediated immune response in the host. Excessive NK-κB activation is related to preterm labor and pre-eclampsia (PE) during pregnancy[52,53].

The GM of pregnant women transfers to newborns before or during labor. When the initiation of microbiota colonization in the fetal gut occurs is still controversial[54]. The uterus was initially considered as a sterile environment, which excluded the probability of GM colonization prior to delivery[55]. Subsequently, the microbiome was detected in various placental tissues[56-58], especially when the bacteria were detected in the intestines of early aborted fetuses on scans[59]. There is a counterview that the microbiome is due to contamination[60]. It was deduced that the microbiome signal detected in the placental tissues was microbiome-derived particles which were transported to the fetal gut through the placenta. These particles could prime the fetal immune system[61].

Nevertheless, it is undisputed that the microbiome colonizes during delivery, and the mode of delivery significantly affects the GM composition of newborn babies. Compared to caesarean section, *Bifidobacterium spp.* are enriched, and both *Enterococcus* and *Klebsiella spp.* are reduced in vaginally delivered infants. The GM composition at delivery is correlated with respiratory infection over the next year[62]. *Bifidobacterium* is a probiotic which can maintain gut health and defense against pathogens. *Enterococcus* and *Klebsiella,* on the other hand, are potential pathogens included in the ESKAPE family [63].

The alpha diversity of the GM increases and the beta diversity decreases gradually over time during the first several years[64]. Breastfeeding is one of the most significant factors correlated with the microbiome composition. Breastfeeding is positively correlated with *Bifidobacterium.* Cessation of milk feeding promotes the maturation of the GM, marked by an increase in the phylum Firmicutes. The location and presence of siblings or furry pets also affect the GM composition[65].

GUT MICROBIOTA CHANGES IN DISEASES DURING PREGNANCY

Gut microbiota changes in obesity during pregnancy and gestational diabetes mellitus

Pregnant women who are obese have a higher risk of developing pregnancy disorders, including gestational diabetes mellitus (GDM), PE, or preterm delivery[66]. GDM is one of the most common pregnancy complications which affects 3%-9% of pregnancies worldwide[67]. GDM is characterized by increased insulin resistance and blood glucose during pregnancy. Obesity during pregnancy is an important risk factor for GDM. It is reported that the risk of GDM in obese pregnant women is 4 to 8 times greater than that in normal pregnant women[67]. This is because obesity and pregnancy are both risk factors for GDM; thus, the risk is much higher. Both obesity and pregnancy can cause inflammatory changes, an increase in insulin resistance, and a decrease in lipid circulation[68].

Changes in GM in obesity during pregnancy and GDM were investigated. It was shown that compared with non-GDM pregnant women, the abundance and alpha diversity were reduced in GDM pregnant women. There were differences in the overall microbial composition between the two groups. The Firmicutes/Bacteroidetes (F/B) ratio was increased in GDM women[69-71]. Differences in specific bacteria were found between non-GDM and GDM women and in mice models[72-74]. The abundance of Firmicutes and the F/B ratio were also found to be higher in overweight and obese pregnant women [75].

A nested case-control study profiled the GM during early pregnancy, before the onset of GDM. The 16S sequencing data set was then used to establish an early identification model of GDM, which can predict the occurrence of GDM. The results indicated that the change in GM may be the cause of GDM [69]. Moreover, germ-free mice receiving fecal microbiota from a GDM donor, developed hyperglycemia compared with mice receiving fecal microbiota from a non-GDM donor, indicating that the change in GM is sufficient to cause GDM[76].

The underlying mechanisms of the changes in GM causing GDM or obesity in pregnancy can be summarized in two aspects. Firstly, SCFAs in GDM women are reduced compared to those in non-GDM women. This is caused by a reduction in SCFA-producing bacteria. In the GDM group, the butyrate-producing bacteria *Coprococcus* and the lactate-producing bacteria *Streptococcus* were both lower in

abundance in both the first and second trimesters[77]. In diet-induced obese pregnant mice, *Lachnospira* and *Ruminococcus*, both of which are butyric acid-producing bacteria, were also decreased[78]. SCFAs have been proven to play an important role in host glucose metabolism through G protein-coupled receptors (GPR) 41 and GPR43[79]. The intestinal expression of the SCFA receptor, GPR41, also decreased, while GPR43 did not change in obese mice[78]. Secondly, secretion of LPS is greater in obese and GDM pregnant women. The elevation in plasma LPS is either due to the increase in Gram-negative bacteria, or the increased translocation of pathobionts through the "leaky gut". For example, *Prevotella* can degrade mucin, and was increased in GDM women[80,81] and obese pregnant mice[78].

Premature delivery

Premature delivery is a global health problem that affects up to 20% of pregnancies. Preterm birth results in a variety of neurodevelopmental sequelae in newborns and contributes to 85% of perinatal morbidity and mortality[82]. Many factors are involved in premature delivery. Recently, the role of GM was also revealed.

One study found that the alpha diversity of the GM in the second trimester in a spontaneous preterm delivery group was significantly reduced[83]. Compared with the full-term group, the abundance of *Bifidobacterium*, *Streptococcus*, *Clostridium* and *Bacteroides* in preterm pregnant women was lower, while the level of *Lactobacillales* was higher[84,85]. *Streptococcus* and *Bifidobacterium* can produce lactic acid as well as SCFAs[86]. *In vitro* experiments indicated that SCFAs may reduce preterm labor by preventing muscle layer contraction and membrane rupture. SCFAs can inhibit pro-inflammatory cytokines as well as the expression of enzymes involved in myometrial remodeling and fetal membrane degradation[87]. *Clostridium* and *Bacteroides* have been shown to induce Treg cells in mice. Intestinal Treg cells can prevent preterm birth by inhibiting inflammation through the production of interleukin-10. In IL-10 knockout mice, a very small amount of LPS can induce preterm labor[88].

Another study using a mouse model also proved the importance of butyric acid-producing bacteria. A high-fat diet affects the maternal GM and transcriptome in the uterus, thus, enhancing the premature birth rate. The high-fat diet can reduce colonization of the *Lachnospiraceae_NK4A136_group*, which can produce butyric acid. Spontaneous preterm delivery enhanced by a high-fat diet is mediated by increased inflammation, oxidative stress, and enteric malnutrition. Immune tolerance induced by endotoxin can reverse these effects and decrease spontaneous preterm birth[89].

Acute fatty liver of pregnancy

Acute fatty liver of pregnancy (AFLP) is a pregnancy complication that can be fatal to both the mother and the fetus. Symptoms of AFLP in the mother include anorexia, nausea and vomiting. Most AFLP patients develop jaundice and fever[90]. In majority of patients, a series of biochemical indexes such as aspartate aminotransferase, alanine aminotransferase, bilirubin, and alkaline phosphatase are elevated. The incidence of AFLP is relatively low, ranging from 1/15000 to 1/10000, but the modality of mothers and fetuses is as high as 18% and 23%, respectively[91]. A recent study found that AFLP patients have a higher alpha diversity than normal pregnant women. The abundance of 13 genera in the AFLP patients increased, and five genera decreased. Among the increased genera in AFLP, *Acinetobacter*, *Enterococcus*, *Weissella* and *Lysinibacillus* are potential pathogenic bacteria, which may be related to digestive system diseases during pregnancy[92].

Anemia in pregnancy

Anemia is a very common condition during pregnancy. According to statistics from the World Health Organization, in 2011, more than 40% of pregnant women worldwide were estimated to have anemia [93]. In developing countries, the prevalence is even more[94]. Anemia in pregnancy may bring a series of adverse consequences to both mothers and fetuses, including preterm birth, low birth weights, and even maternal and fetal death[95]. Many factors can cause anemia in pregnancy. One of the most important reasons is iron deficiency. In addition, lack of vitamin B12, vitamin D and folate can also cause anemia in pregnancy[96].

A matched case-control study found that compared to healthy controls, the α-diversity of the gut microbiome was significantly reduced in gestational anemia (GA) during the third trimester[92]. The abundance of *F. prausnitzii* in GA women significantly decreased. *F. prausnitzii* has been reported to decrease in several gastrointestinal diseases including Crohn's disease and celiac disease[97,98]. Another genus, *Ruminococcus*, was also reduced in GA patients compared with healthy control. Both *Faecalibacterium* and *Ruminococcus* were reported to produce butyrate and prevent inflammation and metabolic diseases[99].

In summary, these studies indicate that diseases during pregnancy have common characteristics, including decreased alpha diversity, increased opportunistic pathogenic bacteria and fewer beneficial bacteria. LPS and SCFAs are the main mediators in inducing pregnancy-specific diseases.

PREGNANCY-SPECIFIC GASTROINTESTINAL DISEASES

Most pregnant women may experience a variety of GI disorders, including gastroesophageal reflux, constipation, hyperemesis gravidarum (HG) and Pre-eclampsia (PE), *etc*.[100]. The relationships between GM dysbiosis and GI disorders during pregnancy are reviewed.

Pre-eclampsia

PE is a specific complication that usually occurs after 20 wk of pregnancy. It is mainly characterized by hypertension, proteinuria and multiple organ damage. In severe cases, it may cause eclampsia and HELLP (Hemolysis, Elevated Liver enzymes and Low Platelets) syndrome including red blood cell failure, low platelet count and liver function damage. PE affects 2%-8% of pregnant women[101,102].

Previous studies have indicated that the main cause of PE is the reduced ability of trophoblast cells to invade maternal spiral arteries, and vascular endothelial cell dysfunction caused by oxidative stress induced by placental ischemia and hypoxia. In addition, increased secretion of anti-angiogenic factors elevates blood pressure. The immune imbalance at the maternal-fetal interface also plays an important role in PE[103].

In recent years, a large number of studies have demonstrated that GM dysbiosis affects the function of endothelial cells and maternal-fetal immune balance and plays a role in PE pathogeny. Compared with normal pregnant women, the alpha diversity of the intestinal microbes in PE patients is reduced, and the abundance of multiple bacteria is significantly different from that in the control group. The changes of GM composition at different taxonomic ranks (S: species, G: genus, F: family, O: order, C: class, P: phylum) in PE patients are shown in Table 1. In pregnant women with PE, the intestinal microbiota is enriched with opportunistic pathogens, including *Fusobacterium*, *Veillonella*, *Clostridium perfringens* and *Bulleidia moorei*. The beneficial bacteria, including *Faecalibacterium*, *Akkermansia* and *Coprococcus catus*, were significantly reduced in PE[104,105]. Following transplantation of feces from PE patients, mice showed PE-like symptoms during pregnancy, including increased blood pressure, proteinuria and embryo absorption, decreased fetal and placental weight, indicating that the intestinal microbiota has an effect on PE. It is worth noting that the hypertensive effects of intestinal microbiota disorders may not be related to pregnancy, as mice that receive feces from PE patients may develop hypertension before pregnancy[104]. In addition, the microbiota dysbiosis pattern in women with non-pregnancy hypertension is similar to that in PE women, such as reduced microbial diversity. Moreover, many of the different bacteria between PE and normal pregnant women are related to blood pressure [106].

The levels of butyric acid and valeric acid in the feces of PE patients are significantly reduced, as well as the abundance of butyric acid-producing genera. The fecal levels of SCFAs are positively correlated with *Coprococcus* (belonging to Firmicutes), and negatively correlated with Proteobacteria[105]. At 16 wk of pregnancy, the number of butyrate-producing bacteria in the GM are negatively correlated with blood pressure and the level of plasminogen activator inhibitor 1 Level in overweight and obese pregnant women, further proving the relationship between microbial dysbiosis and elevated blood pressure[107]. SCFAs can bind to different GPCRs in various organs and regulate the abundance of Treg cells through DNA methylation[108].

Abnormal microbial metabolites in PE patients, for example, LPS, can cause inflammation and increased intestinal permeability. Studies on animal models and PE women showed that the function of microbial genes related to LPS biosynthesis in the fecal microbiome in the PE group was higher than that in the control group, while the abundance of the GPCR pathway was significantly reduced. In addition, the fecal and plasma LPS concentration and plasma trimethylamine N-oxide concentration in PE patients were higher than those in healthy controls[109]. Oral butyrate can significantly reduce blood pressure in rats with pregnancy-induced hypertension mediated by LPS[105]. Previous studies have shown that the induction of PE-like conditions induced by LPS in mice leads to insufficient remodeling of the placental spiral artery, and local and systemic inflammation[110]. At the same time, in the intestines and spleens of mice with PE fecal transplantation, and in the intestines of PE patients, it was observed that pro-inflammatory T helper 17 (Th17) cells increased significantly, and the ratio of Treg/Th17 decreased significantly, indicating that intestinal microbes in PE patients may be caused by the inflammatory pathway induced by LPS[104,111]. The combination of LPS and Toll-like receptor 4 signals can induce endothelial cell damage by oxidative stress and vascular inflammation by MAPK and NF-κB[112].

A large number of bacteria were observed in the placenta of PE mice. This is speculated to be caused by the translocation of bacteria from the intestine to the placenta. At the same time, a significant increase in the level of placental inflammatory cytokines was observed[104].

It was proved in mice that dietary fiber digested by intestinal microbes can regulate blood pressure and heart function through SCFAs, and prevent the occurrence of PE hypertension[108]. According to one report, there is a positive correlation between organic vegetable consumption and a lower risk of PE [113]. Studies have shown that compared to women with the lowest dietary fiber intake, the risk of PE was reduced by 67% in women with the highest dietary fiber intake before conception and early pregnancy[114]. Experiments in mice have shown that the intake of probiotics can maintain the stability of the intestinal microbiota, enhance vascular endothelial function, and keep lower blood pressure[115].

Table 1 Changed bacteria in gastrointestinal diseases during pregnancy

Disease	Bacteria	Ref.
PE	*Clostridium perfringens* (S) ↑, *Bulleidia moorei* (S) ↑, *Coprococcus catus* (S) ↓,	[140]
	Coprococcus (G) ↓	[141]
	Clostridium (G) ↑, *Dialister* (G) ↑, *Veillonella* (G) ↑, *Fusobacterium* (G) ↑, *Lachnospira* (G) ↓, *Akkermansia* (G) ↓, *Faecalibacterium* (G) ↓,	[104]
	Firmicutes (P) ↓, Clostridium (C) ↓, Clostridiales (O) ↓, Ruminococcaceae (F) ↓, Rikenellaceae (F) ↓, *Faecalibacterium* (G) ↓, Alistipes (C) ↓, *Bacteroides stercoris* (S) ↓, Bacteroidetes (P) ↑, Proteobacteria (P) ↑, Actinobacteria (P) ↑, Bacteroidia (C) ↑, Gammaproteobacteria (C) ↑, Enterobacteriales (O) ↑, *Enterobacteriaceae* (G) ↑, *Bacteroides_coprocola* (S) ↑, *Bacteroides_fragilis* (S) ↑,	[109]
	Fusobacteria (P) ↓, Tenericutes (P) ↓, Verrucomicrobia (P) ↓, *Faecalibacterium* (G) ↓, *Gemmiger* (G) ↓, *Akkermansia* (G) ↓, *Dialister* (G) ↓, *Methanobrevibacter* (G) ↓, *Blautia* (G) ↑, *Ruminococcus* (G) ↑, *Bilophila* (G) ↑, *Fusobacterium* (G) ↑, *Oribacterium* (G) ↑, *Parvimonas* (G) ↑, *Anaerococcus* (G) ↑, *Abiotrophia* (G) ↑,	[142]
	Firmicutes (P) ↓, Clostridia (C) ↓, Clostridiales (O) ↓, Bifidobacteriales (O) ↓, Lachnospiraceae (F) ↓, Ruminococcaceae (F) ↓, Streptococcaceae (F) ↓, Bifidobacteriaceae (F) ↓, *Blautia* (G) ↓, *Streptococcus* (G) ↓, *Eubacterium_rectale* (G) ↓, *Eubacterium_hallii* (G) ↓, *Bifidobacterium* (G) ↓, Proteobacteria (P) ↑, Gammaproteobacteria (C) ↑, Enterobacteriales (O) ↑, Enterobacteriaceae (F), ↑ Veillonellaceae (F) ↑, *Escherichia_Shigella* (G) ↑	[105]
HG	*Clostridium spp.* (S) ↑, *Candida spp.* (S) ↑, *Bifidobacterium spp.* (S) ↓	[126]
ICP	*Blautia* (G) ↑, *Citrobacter* (G) ↑, *Streptococcus* (G) ↑, Enterobacteriaceae (F) ↑, Leuconostocaceae (F) ↑, Streptococcaceae (F) ↑, Bacilli (C) ↑, Gammaproteobacteria (C) ↑, Enterobacteriales (O) ↑, Lactobacillales (O) ↑, *Streptococcus luteciae* (S) ↑,	[121]
	Firmicutes (P) ↓, Bacteroidetes (P) ↑, *Faecalibacterium* (G) ↓, *Bifidobacterium* (G) ↓, *Blautia* (G) ↓, *Parabacteroides* (G) ↑, *Bilophila* (G) ↑, *Bacteroides* (G) ↑, *Escherichia* (G) ↑	[123]

PE: Pre-eclampsia; HG: Hyperemesis gravidarum; ICP: Intrahepatic cholestasis of pregnancy.

In addition, the intake of probiotics (*Lactobacillus acidophilus*, *Bifidobacterium lactis* and *Lactobacillus rhamnosus*) food can reduce the risk of PE in primiparous women[116].

Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disease with an incidence between 0.2% and 2%. Symptoms of ICP include itching without a rash, elevated levels of liver enzymes and serum bilirubin in pregnant women, and preterm delivery, meconium-stained amniotic fluid, neonatal depression, and respiratory distress syndrome in the affected fetus[117]. Reproductive hormones, genetic and environmental factors are all involved in ICP[118-120]. Recently, the functions of GM in ICP were investigated. One study on ICP microbiota indicated that compared to normal controls, the alpha and beta diversity showed no differences. At the family level, *Enterobacteriaceae, Leuconostocaceae* and *Streptococcaceae* were higher in ICP patients[121]. *Enterobacteriaceae* is a pro-inflammatory and potentially pathogenic taxa involved in cirrhosis[122].

Another study found that the beta diversity between ICP patients and healthy controls was different. The relative abundance of Firmicutes was lower and Bacteroidetes was higher in ICP patients. The genera that can produce SCFAs, including *Faecalibacterium*, *Blautia* and *Eubacterium hallii* were depleted, while the BA metabolism-associated bacteria including *Parabacteroides* and *Bilophila* were higher in ICP patients[123] (Table 1).

HG

HG is a pregnancy disorder with symptoms including nausea, vomiting, and weight loss. In severe cases, it can cause dehydration and electrolyte imbalance. HG affects approximately 0.3%-2% of pregnant women. It usually occurs in the first trimester and improves after 20 wk, but it may continue throughout the pregnancy[124].

A recent study indicated that in pregnant women with HG, the alpha diversity of GM is higher, with a higher average number of different OTUs. In addition, more groups were observed in the HG group, including *Bacteriodaceae*, *Bacteroides*, *Firmicutes*, *Clostridia* and *Betaproteobacteria*. The greater clustered alpha diversity in HG may be induced by new metabolic products from the microbiota. The functions of the altered bacterial groups in HG are unclear. Whether this is a direct consequence of the change in the GI in pregnant women with HG or a complementary mechanism to provide more metabolites is still to be elucidated[125].

Another study that identified the HG-specific microbiome based on culture was conducted recently and found an increase in *Clostridium spp.* and *Candida spp.*, and a decrease in *Bifidobacterium* in patients with HG. The microbiota dysbiosis determined by a stool microbiota scan, showed a significant difference between HG patients and the control group[126]. The genus *Clostridium* includes several pathogens which can cause GI disorders ranging from mild diarrhea to severe colitis[127]. *Candida* is a

type of yeast, and the overgrowth of this genus is associated with ulcerative colitis and Crohn's disease [128]. There are also interactions between these two opportunistic pathogens. *Clostridium* can survive under ambient aerobic conditions with the help of *Candida*, and *Clostridium* affects the hypha formation of *Candida* through the excretion of p-Cresol[129] (Table 1).

The stomach-specific resident, *Helicobacter pylori*, seems to be associated with HG[130-132]. *H. pylori* should be considered as one of the risk factors for HG, especially in developing countries. However, this opinion is challenged by other studies, which show no significant correlation between *H. pylori* and HG [133]. The relationship between GM and HG requires extensive investigation in the future.

Constipation

Constipation is a common complaint during pregnancy, which affects 11%-38% of pregnant women [134]. The changes in pregnancy hormones, especially progesterone, are responsible for constipation in several ways. The high level of progesterone can reduce the motility of intestinal smooth muscle, and increase water reabsorption by elevating the secretion of renin aldosterone[135]. The GM functions in constipation during pregnancy require further study. Several studies have focused on the probiotic treatment of constipation during pregnancy. One study on pregnant women with constipation provided a daily dose of a combination of 6 probiotics (3 from the genus *Bifidobacterium* and 3 from *Lactobacillus*). After 4 wk, several indices including the sensation of anorectal obstruction and incomplete evacuation, straining during defecation, episodes of abdominal pain and the presence of reflux episodes all significantly decreased without side effects[136]. The underlying mechanisms of probiotics to prevent such diseases are also needed to be further evaluated. As in the studies of vaginal microbiota transplantation or probiotic combination, which could rescue the dysbiosis of the vagina in both human or animal models[137-139]. The probiotics will provide a promising treatment for gastrointestinal diseases in pregnancy.

CONCLUSION

The gut microbiota plays an important role in maintaining the normal physiological conditions of the intestines. The dysbiosis of the microbiota is related to the development of a variety of intestinal diseases. The gut microbiota during pregnancy changes profoundly. During this period, the dysbiosis of microbiota in pregnant women is related to a variety of diseases in pregnancy, including pregnancy-specific gastrointestinal diseases, such as PE, ICP, HG, and constipation during pregnancy. Current studies have shown that the gut microbiota of patients with pregnancy-specific gastrointestinal diseases is significantly different from that of healthy pregnant controls, including the expansion of pathogenic bacteria and the suppression of beneficial bacteria. Although this field has made great progress in the past few years, there is still a lot of work to be done, including the functional characterization of the gut microbiota and the mechanism underlying the correlation between GM and pregnancy-specific gastrointestinal diseases. Effective probiotics with low side effects provide promising therapeutic interventions.

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FOOTNOTES

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