

# THE EFFECT OF INTESTINAL MICROBIOTA DISORDERS ON THE DEVELOPMENT OF PREMATURE BIRTH

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**Abstract.** *Pregnancy is a complex and delicate process, the maternal body undergoes changes in hormones, immunity and metabolism during pregnancy to support fetal development. Microbes in the human body mainly live in the gut, and human gut microbiomes are complex and consist of more than 500-1500 different bacteria, archaea, fungi and viruses. Studies have shown that these microbes are not only involved in the digestion and absorption of food, but are also indispensable in regulating the health of the host. In recent years, there has been increasing evidence that microbiomes are important for pregnant women and the fetus. During pregnancy, there will be big changes in the gut microbiomes.*

**Keywords:** *intestinal flora, premature birth, Clostridium taxonomic, microbiota.*

Pregnancy is a unique event accompanied by many hormonal, immune and metabolic changes in the body. Some changes in the body during pregnancy may be closely related to changes in the composition and diversity of intestinal microbiomes. Changes in the composition and diversity of GMs can ultimately affect the host's immunity, metabolism, digestion, and nervous development. Therefore, focusing on GMs can give a positive view of pregnancy. The composition and diversity of maternal GMs gradually change every 3 months of the gestational period. However, GMs are mostly unchanged during the first 3 months of pregnancy, for example, gram-positive and gram-negative bacteria. The human gastrointestinal tract contains approximately 500~1000 microbes and more than 3 million genotypes. The ratio of microbial cells to human cells is 10:1, and the ratio of genotypes is 100:1. Studies have shown that GMs play a vital role in human immunity and digestion and are involved in the development of chronic diseases such as diabetes, hypertension and inflammatory bowel diseases. More and more evidence indicates that the structure and composition of GMs are usually determined by host genetic factors, environmental factors, and dietary habits. During pregnancy, changes in the diversity and composition of GMs can naturally occur in many parts of the mother's body, including the oral cavity, vagina, intestines and breast. However, the relationship between maternal GMs and complex physiological conditions during pregnancy has not yet been sufficiently discussed. Many scientists have begun to study the relationship between GMs imbalance and complications during pregnancy. The regulation of intestinal microbiomes has a beneficial effect on the health of the mother and fetus. In addition, many complications during pregnancy such as gestational diabetes, obesity, preeclampsia, digestive disorders and autoimmune diseases are associated with gut microbiomes. In addition, microbiomes in breast milk and the vagina are closely related to microbial colonization at an early age of infants. In this review, we systematically examine the role of maternal intestinal microbiomes in various gestational complications, as well as elucidate the function and mechanism of maternal intestinal microbiomes (hereinafter GMs) in the nervous development and immune system of offspring. They will provide a clear knowledge structure or potential research direction for researchers in related fields.

Gestational GMs is not only closely related to the health of pregnant women, but also affects the health of offspring. The most important link between mother and fetus is the placenta, and placental microbiomes include Tenericutes, Fusobacteria, Bacteroidetes, and Firmicutes, all of which are non-pathogenic bacteria. However, factors such as maternal gestational diabetes, obesity, vaginal infections, and antibiotic use have led to changes in the composition of placental microbiomes. For example, recent studies have shown that excessive weight gain during pregnancy is associated with risk factors such as disorders of the placental microbiome and premature birth. In addition, in the postpartum environment, the relationship between the GMs of infants and the microbiome of breast milk is attracting increasing attention. A prospective study has shown that bacterial species in maternal breast milk are most prevalent in the offspring's GMs in the first month after birth, suggesting that breastfeeding is closely related to the child's GMs at an early age.

Premature birth is the main cause of perinatal morbidity and mortality in developing and developed countries. The rate of preterm birth ranges from 5% to 9% in many countries of the world, and there is a continuing trend towards an increase in their frequency. Spontaneous premature birth is considered as a syndrome that occurs for several reasons, including intrauterine infection, systemic inflammatory reaction, stress, adverse socio-economic conditions and excessive stretching of the uterus. Risk factors in Western countries include a previous history of premature birth, belonging to the black race, periodontal disease, low maternal BMI, short cervix, use of steroid medications (for bronchial asthma or collagenosis), low level of education and a male fetus. Although antibiotic treatment can help with the development of BV during pregnancy, it has been found that the overall risk of BV in pregnant women is not significantly reduced when antibiotic therapy is prescribed. Until recently, when using molecular methods, an association between preterm birth and the intestinal microbiota was not found, although a link with changes in the vaginal microbiota in the gestational period has been proven. A dramatic remodeling of the intestinal microflora during pregnancy was described, which was studied using genomic analysis based on 16S DNA. These changes in the intestinal microbiota caused insulin resistance during pregnancy. In another study, using T-RFLP analysis, the microbiome in feces and vaginal secretions was studied to determine microbiota differences between three groups of women: pregnant women who gave birth to full-term babies without premature birth; pregnant women who had premature birth, but almost full-term babies were born; and women who had premature births premature babies. It has been proven that the gut microbiota in women with and without premature birth has significant differences. The levels of Clostridium clusters XVIII and IV, subcluster XIVa and Bacteroides in the fecal microbiota in women with premature birth are significantly reduced. This study included women with urgent and premature births. In the first group, the indicators of Clostridium taxonomic units of cluster XVIII were  $2.12 \pm 0.34$ , cluster IV —  $0.52 \pm 0.15$ , subcluster XIVa —  $1.85 \pm 0.75$ , Bacteroides —  $0.84 \pm 0.13$ ; The indicators in the group of women with premature birth of Clostridium cluster XVIII were  $0.70 \pm 0.35$ , cluster IV —  $0.18 \pm 0.18$ , subcluster XIVa —  $0.33 \pm 0.27$ , Bacteroides —  $0.60 \pm 0.27$  ( $p = 0.015$ ). In addition, more recent studies have shown that bacteria from the oral cavity are most often found in the amniotic fluid of patients with premature birth. Thus, periodontal pathogens and by-products of their vital activity are able to reach the placenta and spread through the fetal circulatory system, as well as enter the amniotic fluid. The results of these studies may indicate that the oral and/or intestinal, rather than vaginal, microbiota is able to induce the synthesis and secretion of inflammatory mediators, which,

in turn, causes premature birth or dysbiosis, and as a result makes the uterus and placental tissue susceptible to infection. It has been established that microorganisms of the genus *Clostridium* are inducers of CD4+, CD25+, Foxp3+ and regulatory T cells (Tp); it has also been shown that *Bacteroides fragilis* activate Tp cells in mice. It has been suggested that polysaccharide A produced by *B. fragilis* enhances the suppressive activity of regulatory lymphocytes. The balance between beneficial and potentially dangerous species in the commensal microbial community is often associated with the development of inflammatory bowel diseases. At the same time, intestinal Tr cells play a key role in the regulation of inflammation due to the production of IL-10 and other inflammatory mediators. Premature birth can be considered as an inflammation caused by an incorrect ratio of components of the normal bacterial community. The reduced content of *Clostridium* in the intestine cannot ensure the activation of an adequate volume of Tr cells, which leads to increased susceptibility to inflammation. A decrease in the volume and function of Tr cells in peripheral blood was also recorded in preterm labor, but the levels of intestinal Tr cells were not studied in these studies.

Further observations are needed to establish the relationship between the intestinal microbiota and the content of peripheral and intestinal Tr cells. The study of intestinal microflora during pregnancy can provide important information about the relationship between fluctuations in the quantitative and qualitative composition of microbial communities and the risk of adverse gestation outcomes, such as premature birth. Of interest is a study showing a reduction in the risk of spontaneous premature birth and preeclampsia when eating a sufficient amount of probiotic food. Thus, it can be seen from the above data that maternal microbiomes play a vital role in the offspring's immune system. The regulation of the microbiomes of pregnant women is of great importance for the health of offspring, which may provide a new understanding of the management of pregnant women in clinical practice.

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