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The Role of Intestinal Microbial Dysbiosis in the Pathogenesis of Pre-eclampsia

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Abstract

Pre-eclampsia (PE) is a multisystem disorder during pregnancy that profoundly impacts both the mother and the fetus. Pathophysiolology of PE involved in impaired angiogenesis, placental oxygenation, abnormal remodeling of placental spiral arteries, placental defects, oxidative stress at the maternal-fetal interface, activation of maternal circulating inflammation, and immune imbalance. With the emerging evidence of bioinformatics, the correlation between PE and intestinal microbial disorders has been increasingly recognized. In this review, we expatiate the characteristics of the human intestinal microbiota, the relationship of gut microbiota and PE. Furtherly, We deeply explore potential mechanisms underlying the association between gut microbiota and PE. At last, we provide strategies to prevent and treat PE by interfering with the gut microbiota.

Keywords: Pre-eclampsia; Gut Microbes; Pregnancy; Pathophysiolology; Angiogenesis; Oxygenation

Introduction

Hypertensive disorders of pregnancy (HDP) are one of the most commonly occurring complications of pregnancy, ranging in severity, including chronic hypertension, gestational hypertension, preeclampsia, severe preeclampsia and eclampsia. Preeclampsia as the severe forms of HDP affects 2-8% of pregnancies globally and is a major cause of maternal and perinatal morbidity and mortality. Hypertension and proteinuria are the cornerstone of the preeclampsia, severe forms of preeclampsia usually ensue multisystemic organ dysfunction mainly involving renal, cardiac, pulmonary, hepatic, and neurological dysfunction, ematologic disturbances, fetal growth restriction, stillbirth and maternal death, and induced corresponding clinical manifestation including massive proteinuria, hypertensive cardiopathy, blindness, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count syndrome), oligohydramnios and placental abruption.

From the aspect of long-term prognosis, women who survive preeclampsia often experience a reduced life expectancy and face an elevated risk of stroke, cardiovascular disease, and diabetes. Furthermore, infants born to mothers with preeclampsia are at increased risk for preterm birth, perinatal mortality, cardiovascular and metabolic diseases, as well as neurodevelopmental disorders later in life [1]. The etiology, pathological mechanisms, and predictive factors associated with preeclampsia remain poorly understood.

During recent years, the relationship of microorganisms and PE has been continuously explored, correlation between PE and intestinal microbiota attracted the attention of more and more scholars [2]. Human intestinal microbiota comprises of bacteria, archaea, viruses, fungi, and other microorganisms. These microorganisms collaborate to influence host health. Several studies showed gut microbiota imbalance correlated with obesity, metabolic syndrome and preeclampsia [3], The precise relationship between gut flora and preeclampsia, how gut flora disorders impact the initiation and development of preeclampsia, and underlying mechanisms are still not fully understood.

In this review, we present the characteristics of human gut microbes, difference of gut microbes in preeclampsia and normal pregnancy, discuss in-depth the relationship between preeclampsia and gut microbes, further explore mechanisms of gut microbes affecting preeclampsia. Provide the probiotics application meanings in preeclampsia.

Characteristics of the Human Intestinal Microbiota

Intestinal homeostasis is very important for normal growth and development of human beings, which appears to be mainly depends on the integrality of intestinal barrier function and the stability of intestinal flora.

Barrier Functions of Intestinal

The four barrier functions of intestinal include biological barrier, chemical barrier, mechanical barrier and immune barrier. biological barrier is mainly composed of the resident gut microbiota, can inhibits the binding of pathogenic bacteria to the intestinal epithelium through competitive inhibition of beneficial bacteria, secret short chain fatty acids(SCFAs: acetate, propionate, and butyrate), lactic acid that can inhibit the colonization and growth of pathogenic bacteria; chemical barrier is mainly composed of mucus and digestive fluid secreted by the intestinal epithelium, and normal bacterial communities can produce antibacterial substances that also play a role of chemical barrier function; mechanical barrier that is mainly composed of tight connections, adhesive connections, and desmosomes between intestinal epithelial cells, can effectively block the invasion of pathogenic substances; immune barrier is predominantly composed of intestinal lymphoid tissue and immune cells, under the stimulation of pathogenic substances, host immune response is intrigued, immune cells can recognizes antigens and produces antibodies to resist the invasion of pathogenic microorganisms.

The main types of intestinal epithelial cells include absorptive cells, goblet cells, Paneth cells, endocrine cells, and tuft cells. Among four barrier functions, the mucosal layer serves as the chemical barrier consisting of mucus and mucin and provide protection microorganisms from contacting epithelial cells. These epithelial cells can also help to restrict intercellular

permeability by secreting antibacterial substances and establishing tight junctions. Intestinal immune cells, such as dendritic cells, T cells, B cells, and macrophages, collaborate closely with epithelial cells to maintain intestinal homeostasis. Immune cells and microorganisms together regulate intestinal immune response for supporting healthy intestinal function [4].

Sability Categories and Function of Intestinal Flora

Due to the large number of gut microbiota, its genome is known as the "second human genome". Intestinal microbiota refers to the gut microbiota and its corresponding ecological environment where it resides. According to the classification of gut microbiota, human gut microbiota can be divided into two categories. The first category is normal microbiota community, which is comprised of microorganisms that regularly settles in specific parts of the body, plays a beneficial role in the host, and can maintain the balance between the host and other microflora. Normally, there is no harm to the host's health. By contrast, the second category is passing microbial community, which originates from the surrounding environment or other external sources, is harmful to the body, and often includes pathogens or conditional pathogens. When the dynamic balance between microbiota is destroyed, the passing microbiota multiplies in large numbers in a short period of time, result in a pathological state of the organism.

Further, human gut microbiota has its own unique and stable characteristics, first appearing in fetuses in the second trimester [5-7]. In the neonatal period, the abundance and diversity of bacteria increase [8,9], and the of gut microbiota gradually stabilizes in early childhood [10,11]. Whereas in adults, Bacteroidetes and Firmicutes usually dominate, whereas Actinobacteria, Proteobacteria, and Verrucomicrobia are frequent but generally minor constituents [12]. In the human beings, various bacterial communities maintain a relatively stable state at the corresponding phylum level, but there are significant differences in genus and species.

Disease and Intestinal Flora

Imbalances in the gut microbiota have been shown to play a significant role in the pathogenesis of many chronic diseases. For example, there is a remarkable correlation between diabetes, obesity and cardiovascular disease and changes in the gut microbiota [13]. In addition, the gut microbiota not only influences the physiological state of the body, but also the nervous system. Experimental studies in animals have demonstrated a correlation between alterations in the composition of the gut microbiota and the onset of neuropsychiatric disorders, including depression and anxiety [14]. Goltsman's reported that dietary modifications during pregnancy resulted in alterations of maternal gut microbiome, which implying potential impacts on maternal health [15]. Further research also indicates that diet can influence changes in the maternal gut microbiome [16], which may contribute to pregnancy complications such as preeclampsia [17].

Many factors such as region, diet, ethnicity, exchange of maternal microbiota at birth, use of antibiotics or hormones, and exercise habits can affect the diversity, composition, and metabolites of human gut microbiota [13,14,18,19]. It is particularly noteworthy that diet has an important influence on the composition of intestinal flora composition, which is considered to be the determinant of balance of intestinal flora. Notably, differences in intestinal flora are also closely linked to their residence and cultural dietary practices [20,21]. For instance, traditional Chinese diets are characterized by a high intake of vegetables and grains, whereas Western diets tend to be more abundant in red meat, fats, and processed foods [20]. These divergences in dietary habits result in significant alterations in the composition and functionality of the gut microbiome [22,23].

Further, intestinal microbiota and their metabolites participate in various metabolic mechanisms of the body, such as nutrient absorption, material metabolism and immunity. For example, the gut microbiota in the distal gut promotes the fermentation process of dietary fiber, typically producing SCFAs, which are the main nutritional sources for the cecal colon epithelium [24]. This has profound implications for intestinal barrier function.

Gut Microbiota and PE

Adaptive changes in the gut microbiota during pregnancy

Women multiorganicsystems undergo changes during pregnancy to support foetal growth and development. For instance, in a healthy pregnancy, the maternal cardiovascular system experiences notable alterations, such as an increase in plasma volume and cardiac output as early as 3-4 weeks of gestation. These changes occurrence can prevent a rise in blood pressure through mechanisms like decreasing systemic peripheral vascular resistance, increasing arterial compliance, promoting peripheral vasodilation, and moderating contractility. Additionally, there is an enhancement in endothelial release of vasodilator factors and activation of the renin-angiotensin-aldosterone system [1]. Simultaneously, the gut microbiota also undergoes significant shifts during pregnancy [15]. A study [25] revealed that maternal gut microbiota resembled that of non-pregnant women during the first trimester, but atthe third trimester, there were substantial changes characterized by reduced flora diversity, decreased beneficial flora abundance, and increased pathogenic bacteria presence [26]. Another study noted that disruptions in the gut flora of preeclampsia persisted up to 6 weeks postpartum [27,28].

Chen's study analyzed the intestinal bacterial community reveal a total of 379 genera from 18 phyla [27] in preeclampsia (PE) and normotensive individuals. The microbial composition at both phylum and genus levels differed significantly between two groups. Specifically, the predominant genera Clostridium, Dialister, Veillonella, and Fusobacterium were of significantly enriched in PE patients, while Lachnospira, Akkermansia, and Faecalibacterium were depleted. These findings highlight substantial alterations in the intestinal microbiome of individuals with PE, underscoring the potential role of gut microbes in the development of PE.

Fecal microbiota transplantation (FMT) plays a key role in variety of disease area, including cardiovascular, metabolic disease, neurological, and inflammatory diseases and other diseases, which have also been apllicated in investigating various treatment approaches, such as ulcerative colitis [29,30], neurological disorders [31], and cancer [32]. The practice of FMT, dating back to the 4th century, has gained significant recognition since its approval for treating recurrent and refractory Clostridium difficile infections in 2013 [33].

More recently, FMT has also been utilized in studying the pathophysiological mechanisms and treatment of PE. To further investigate the alterations changes in gut microbiota of PE, researchers transplant faecal extracts from healthy donors into the intestines of PE patients, the results showed PE women restored normal intestinal components and ameliarated manifestations of PE.

Researchers transplanted the intestinal microbiota from PE patients into a model mice treated with antibiotics to induce the pre-eclamptic phenotype [27] After confirming the successful colonization of the microbiota, the FMT mice exhibited significant increase in systolic blood pressure before pregnancy and further increase during pregnancy period, presented following manifestations: significant increase in urine protein concentration, and significant reductions in the number of live fetuses, fetal mouse weight, and placental weight compared with control mice. Meanwhile the absorption rate of the placenta increased, and there were significant changes in the placental structure of FMT mice. However, there were no significant differences in alpha or beta diversity among the fecal transplants derived from subgroups of PE patients with and without severe features or between the early and late onset of PE. This experiment also demonstrated that transplantation of the gut microbiota of PE led to immune impairment characterized by proportional changes in regulatory T cells (Tregs) and T help type 17 (Th17) cells, which is relateed to intestinal barrier dysfunction, identified higher levels of total bacteria and Fusobacterium in the placenta of PE. Taken together, the above results indicate that pregnancy is disturbed by changes in the gut microbiome occurring in preeclampsia

Gut-placenta Axis and PE

Intestinal barrier dysfunction is related to metabolic diseases, including imbalance of intestinal flora, destruction of intesti-

nal mucosal integrity, increased intestinal mucosal permeability, excessive proliferation of small intestinal bacteria, and decreased intestinal tight junction proteins [34]. Maintaining the integrity of the intestinal mucosa is critical for barrier function of intestinal mucosa, preventing intestinal microorganisms and their toxins from migrating into extraintestinal tissues and organs [35]. Placenta as a source and target of multiple pathological factors, play a central role during the pathogenesis of preeclampsia [1]. The debate over whether the human placenta is sterile or not, whichremains ongoing and inspired extensive research in the scientific community [36-40]. Current research has found that disorders of intestinal microorganisms can lead to damage to the intestinal barrier function and further affect placental function, which has a certain impact on the occurrence and development of preeclampsia.

Pengsheng Li and his colleagues carried out a two-sample Mendelian randomization (MR) study [41], they discovered a correlation between eight bacterial genera and PE. These bacterial genera include Adlercreutzia, Bifidobacterium, Collinsella, Enterorhabdus, Eubacterium (ventriosum group), Lachnospiraceae (NK4A136 group), Methanobrevibacter, and Tyzzerella 3. Moreover, several genera of gut microbiota exhibit protective effects against PE, including Collinsella, Enterorhabdus, Eubacterium (ventriosum group), Lachnospiraceae (NK4A136 group), and Tyzzerella 3.

Intestinal barrier dysfunction and immunologic imbalance of PE

The gut-placental axis refers to the interaction between gut microbiota and placenta through immune and metabolic pathways.

The human placenta is the anatomo-physiological barrier between mother and fetus. Disturbances of the gut-placenta axis can lead to a variety of pregnancy complications, including fetal growth restriction [42] and pre-eclampsia [27], the main theoretical mechanism is the disruption of the intestinal barrier function due to various causes, which allows the maternal intestinal microbiota and its metabolites or pathogenic bacteria to be transferred from the gut to the placenta, leading to an abnormal immune response in the placenta which in turn affects the development of the foetus.

It is possible that intestinal microbial dysbiosis may result in increased intestinal permeability, thereby allowing bacterial comstituents, such as endogenous lipopolysaccharide (LPS) to enter bloodstream. The entry of these substances can trigger a systemic inflammatory response and negatively affect placenta tissue [27-41]. Meanwhile, this inflammation can interfere with normal functions of placenta, including the transport of nutrients and secretion of hormones [43]. In this study [27], when the normal pregnant mice feed with intestinal microbiome from pre-eclampsia for several weeks, these mice revealed hypertension and proteinuria, Treg and Th17 cells imbalance, increased Fusobacterium residue in the placenta and exacerbating inflammation reponse. Intestinal microbiome of PE could attack intestinal mucosal epithelium, induced intestinal leakage, intestines pathogenic bacteria breakthrough impaired intestinal barrier entering microcirculation, then transmit and residue in placenta, ultimately triggering an abnormal immune response [40].These studies indicates that the 'gut-placenta' axis could be crucial in comprehending the development of PE [27].

More specifically, lipopolysaccharide (LPS) can cause placental inflammation, leading to inadequate trophoblast invasion and spiral arterial remodelling. Under impaired intestinal barrier function, LPS produced by intestinal flora enters the bloodstream, leading to immune imbalance and impaired placental function. Additionally, LPS has also been reported to cause vascular dysfunction [44]. An impaired intestinal barrier, that allows LPS to enter the bloodstream [45], results in the activation of the Toll-like receptor 4 (TLR4) signalling pathway in vascular endothelial cells, which then releasing cytokines that induce the expression of various inflammatory products. These influcence leads to placental inflammation, insufficient trophoblast invasion, and disruption of spiral arterial remodelling, which may result in "superficial or shallow placental implantation" and also associated with the development of PE.

Also, Further, gut microbial metabolites, short-chain fatty acids, associated with PE occurrence and development. These

fatty acids serve as an energy source for the colon and can also be absorbed into the bloodstream. These SCFAs exert their biological effects through various mechanisms involving G-protein coupled receptors (GPR41, GPR43), olfactory receptor 78 (Olfr78), and Gpr109a [46]. Specific gut microbiota components linked to preeclampsia, such as Bifidobacterium, Collinsella, Eubacterium (ventriosum group), Lachnospiraceae (NK4A136 group), and Tyzzerella 3, are notable, because these specific gut microbiota are source of SCFA [41]. Short chain fatty acids, predominantly acetic acid and butyric acid can improve endothelial function by restoring Th17/Treg imbalance and alleviating arterial inflammation [47], decrease of butyric acid produced by the gut microbiota is associated with preeclampsia [48], sodium butyrate improves hypertension and proteinuria in PE rats by regulating gut microbiota and its metabolite SCFA, alleviate PE symptoms by reducing placental anti angiogenic factors (sFlt1 and soluble endogenin [sEng]) and increasing angiogenic (placental growth factor [PLGF]), meanwhile reducing placental and intestinal inflammation [49]. Butyrate in short chain fatty acids has also been shown to enhance intestinal epithelial barrier function by upregulating transcription of tight junction protein Claudin-1 [50].

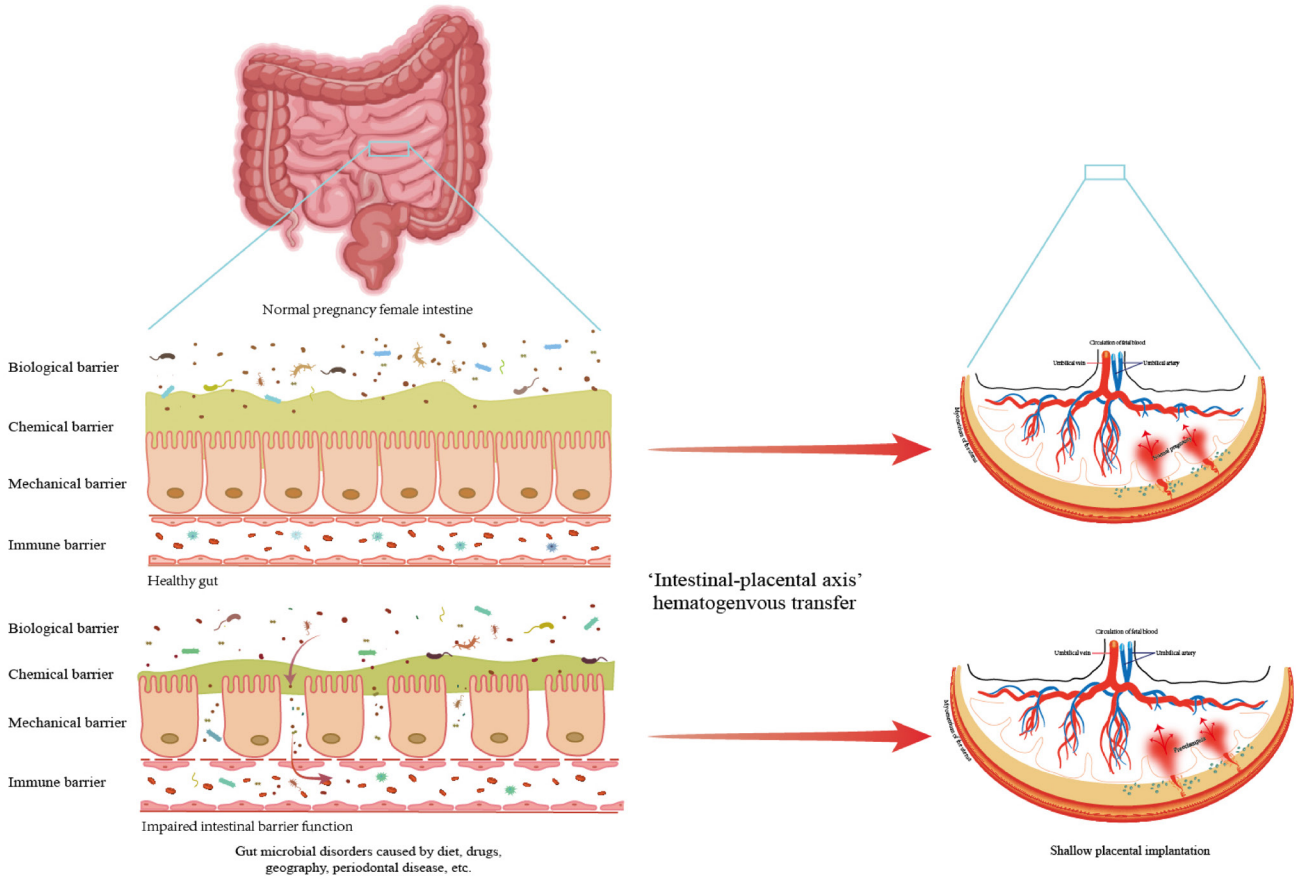

Figure 1: 'Gut Placenta' Axis

Moreover, dysbiosis of microbiota may lead to changes in the number and morphology of villi, which may affect nutrient and oxygen supply to the fetus. Short-chain fatty acids are products of intestinal bacterial metabolism that have anti-inflammatory effects and promote placental health. The gut microbiota of preeclampsia presented significantly reduced numbers of SCFAs-producing bacteria, which may contribute to the reduced anti-inflammatory ability of the placenta [2,51]. Dysbiosis of microbiota may affect placental health by altering inflammatory responses and metabolic status [52,53].These researches show gut health is critical to the immune regulatory and placental metabolic functions.What needs to be emphasized is that multiple studies have found that Bifidobacterium has a protective effect on preeclampsia [2,41,54]. Although changes in intestinal flora can impair intestinal barrier function, certain beneficial bacteria can also maintain in-

testinal barrier function by producing SCFAs or by stimulating the expression of mucins 3(MUC3) in intestinal epithelial cells [41]. Elevated levels of trimethylamine n-oxide (TMAO) and its precursor trimethylamine (TMA) were found in PE patients, which could induce spiral arterial remodeling defects by increasing sFlt-1 and reactive oxygen species (ROS) levels in the placenta. As methanogenic archaea, Methanobrevibacter can convert TMA to methane and thereby reduce the risk of PE [41,55].

Finally, a specific diet may promote the growth of specific bacterial strains, prompting the host to change the fermentation metabolic pathway, thereby affecting the intestinal pH value, which may be the reason for the development of pathogenic microbiota. In addition, a high-fat diet can promote the development of pro-inflammatory intestinal microbiota, thereby increasing intestinal permeability and circulating lipopolysaccharide (LPS) levels [56].

Based on the above research, disturbance of intestinal microorganisms is closely related to the occurrence of preeclampsia and may become an important means to intervene in preeclampsia pathophysiology process.

Strategies to Prevent and Treat PE by Interfering with the Gut Microbiota

Obesity women complicated intestinal microbiota disorders usually presented a higher risk of PE [51,56]. but its intrinsic mechanism has not been fully elucidated. Studies found disorders of gut microbiome could induce lipid metabolism imbalance. Therefore, researcher want to change dietary fiber for improving intestinal microecology and lipid metabolism imbalance, ultimately reduce the incidence of PE. Calorie restriction and exercise can change gut microbiome of the obese women compared with the non-obese women [57]. Combining fecal microbiota transplantation (FMT) from various donors with dietary fiber intervention, research has revealed that this approach can improve distinct gut microbiota composition patterns. Moreover, the impact of dietary fiber in shaping gut microbiota may be even more significant than that of FMT [58]. In summary, diet can reduce the incidence of PE by regulating lipid metabolism in the gut microbiome.

Recent studies also indicate that stress can lead to compromised gut barrier by impacting on the gut microbiota. These stressors may stem from socio-economic disparities, high levels of social pressure, and mental stress. Maternal stress links to an increase in placental inflammatory factors and adverse intrauterine environment. Therefore, addressing prenatal stress effectively in pregnant women has the potential to mitigate disturbances in gut microbiota, which could potentially reduce the incidence of preeclampsia [40].

Probiotics can exert their beneficial functions at different levels, including antagonizing pathogens, metabolizing nutrients, improving intestinal barrier function, protecting against physiological stress, participating in signal transduction, and inducing immune regulation. Research suggests that probiotics may have a beneficial effect in gestational complications such as preeclampsia, gestational diabetes, vaginal infections, maternal and infant weight gain, and allergic diseases [59].

Bing and his colleagues [60] used L-NAME (N-nitro-L-arginine methyl ester) to inhibit NO induced PE mouse model and intestinal microbiota disturbance. Detection revealed that the gut microbiota diversity and Lactobacillus and Lactobacillus reuteri are significantly reduced. However, after in vivo and in vitro experimental treatment with Lactobacillus reuteri, gut microbiota disorder is significantly improved, the diversity of beneficial bacterial content massively increased, meanwhile NO synthesis, angiogenesis, inflammation, and oxidative stress also ameliorated in PE mice. Lactobacillus reuteri can also improve L-NAME mediated NO synthesis, endothelial dysfunction, and inflammation in vitro. This experiment demonstrates that Lactobacillus reuteri can be used for symptoms improvement in PE by regulating intestinal microbiota.

Furthermore, probiotic supplementation during pregnancy can reduce the risk of pregnancy-related complications ranged from mild to severe [61]. Research reported that probiotics, prebiotics, synbiotics, and postbiotics (PPSP) mixtures can alleviate metabolic diseases in most cases, the combined intervention of multiple live strains is a promising probiotic

application method [62]. The main mechanism of PPSP in regulating metabolic diseases is related to the modulation of gut microbiota and their metabolites composition, aiming to improve intestinal barrier function. PPSP can regulate gut microbial metabolites involving acetic acid, propionic acid, butyric acid, isovaleric acid, lactic acid, and inhibit the production of LPS and TMAO. Probiotics and short chain fatty acids may help women maintain intestinal barrier function prevent placental inflammation caused by pathogen migration; ultimately lower the risk of PE [41].

Conclusions

The intestinal flora, called 'humanity's second gene pool', is an important part of the human body. Multiple studies showed that the intestinal flora of PE patients underwent significant changes, mainly manifested by a decrease in beneficial bacteria, an increase in harmful bacteria, or an imbalance in the ratio of beneficial bacteria to harmful bacteria. These changes can trigger the activation of placental inflammation and immune deficiency, lead to the occurrence of PE. Possible involved mechanisms include intestinal leakage inducing bacterial translocation to the placenta, imbalance of production of intestinal microbial metabolites, inflammatory activation, and immune imbalance. The composition, diversity, and function of gut microbiota, as well as the uniqueness of individual gut microbiota, may provide key information for personalized nutritional treatment and drug use strategies for many diseases.

Further experimental research is warranted to explore the causal relationship between disturbances in intestinal microbiota and PE. It is essential to develop new experimental methods that can effectively mitigate the impact of pollution on experimental results. Additionally, we need to identify specific components of intestinal microbiota that could potentially influence the development of PE. To validate the effectiveness and rationality of preventive measures, both experimental and clinical studies are necessary. These measures include dietary changes, consumption of probiotics and their combinations. It is also vital to acknowledge the role of social, economic, and mental pressure in influencing intestinal microbial disorders, as they may also play a significant role.

In this review, we summarize the characteristics and structure of normal human gut microbiota, changes in gut microbiota in PE, and possible related theoretical mechanisms. We also described the application of diet, probiotics, and other factors that may provide corresponding guidance strategies for the prevention and treatment of preeclampsia. Indeed, the association between changes in intestinal microbiota and preeclampsia requires continuous investigation in future. As our understanding of this relationship advances, it has the potential to offer deeper insights into its etiological mechanisms and pave the way for innovative treatment strategies for PE.

Declarations

Ethics Approval and Consent to Participate

Not applicable

Consent for Publication

Not applicable

Availability of Data and Material

Not applicable

Disclosure of Interest

The authors report there are no competing interests to declare.

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Authors' Contributions

CXY was a major contributor to writing the manuscript. WX was responsible for checking and reviewing the manuscript. Both authors read and approved the final manuscript.

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