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Research progress on the correlation between intrauterine adhesions and vaginal microecology

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Abstract: Intrauterine adhesions is a gynecological disease associated with an abnormal endometrial repair process, which seriously affects women's fertility. Many studies have found that vaginal microecology is related to the occurrence of uterine adhesions. Through the collation and analysis of relevant literature, the relationship between vaginal microecology and intrauterine adhesions was understood and explored, the pathogenesis of intrauterine adhesions was further studied, and the evaluation methods of vaginal microecology, the composition and classification of normal vaginal microecology were summarized. Based on the recent research progress and achievements of domestic and foreign scientists, scholars and related clinical workers on intrauterine adhesions and vaginal microecology, this paper briefly describes the cytological mechanism of intrauterine adhesions, describes the mechanism of vaginal microecology disorder in intrauterine adhesions, and the significance of studying the correlation between intrauterine adhesions and vaginal microecology. The aim is to provide a new idea and direction for the prevention and treatment of intrauterine adhesions.

Intrauterine adhesions (IUA) is a gynecological disorder characterized by partial or total adhesions of the anterior and posterior walls of the uterine cavity following endometrial injury. Clinical manifestations include irregular menstruation, amenorrhea, infertility, placenta previa, repeated abortion, premature birth, placental adhesion, fetal implantation difficulties, placental dysplasia, etc., but there are also no symptoms of uterine adhesion [1]. German doctor Fritsch reported the first case of IUA in 1894, and Israeli obstetrician and gynecologist Asherman first gave a complete description of the disease in 1948, such as common abortion curettage, postpartum curettage, myomectomy and endometrial ablation, etc., but the cause of IUA is not single. Not all uterine operations can cause IUA, and some women with no history of uterine operations may also develop IUA clinically, and the main cause may also be related to intrauterine infection, endometrial hypoperfusion or other factors [2]. It can be seen that there may be other synergistic factors in the occurrence of IUA in addition to uterine manipulation. The current treatment of IUA is mainly hysteroscopic surgery followed by prevention of readhesion. However, one study found that the readhesion rate after mild

and moderate IUA treatment was 30%, and the readhesion rate was as high as 62.5% in severe cases. Moreover, the pregnancy rate is only 22.5~33.3%, which is far from satisfactory [3]. Therefore, the prevention and treatment of IUA, especially severe IUA, is a common challenge faced by all obstetrics and gynecology clinicians. In the past studies on the pathogenesis of IUA, the signaling pathways and parameters involved in the formation of tissue fibrosis were discussed.

With regard to immune factors, few studies have proposed external coordinating factors that may be involved in the occurrence of IUA. The microbiota localized along the female reproductive tract has been reported to potentially contribute to female reproductive health and the development of diseases such as endometrial cancer, endometrial polyps, infertility, and preterm birth [4]. Current studies have found that the etiology and progression mechanism of microbe-induced IUA is similar to that of other fibrotic tissues and organs [5]. The vagina is part of the reproductive tract and is the channel for uterine operation. As the gateway of the whole reproductive tract, the vagina is the front line to resist invading microorganisms, so it is inferred that the vaginal microbiota is related to the occurrence of IUA, and the vaginal microbiota is the most important part of the vaginal microecology. Therefore, whether there is a correlation between vaginal microecology and IUA, and how the correlation occurs, this question deserves more in-depth discussion. Based on the review and analysis of relevant literatures, this paper deeply understands and explores the relationship between vaginal microecology and intrauterine adhesions, and provides theoretical basis and practical guidance for the prevention, diagnosis and treatment of intrauterine adhesions.

1. The pathogenesis of intrauterine adhesions

More than 40 years ago, a study found that the histopathology of IUA compared to normal uterine cavity showed an abnormal increase in uterine fibroid tissue. In the injured endometrium, insufficient renewal ability of functional cells can lead to wound exposure to pathogens and dead cells, infiltrating immune cells, and other effector cells, ultimately guiding the emergency response of secreted large amounts of extracellular matrix to seal the wound and form IUA. Similar phenomena have also been observed in fibrosis of the heart, liver, kidneys, and lungs. Currently, the inflammatory factor signaling pathway (TLR4/NF-κB). And fibrotic signaling pathway (TGF-β1/SMAD) synergistic mediation is the most widely recognized mechanism for the formation of endometrial fibrosis.

1.1. TGF-β1/SMAD

IUA is a phenomenon in which fibrosis occurs in the damaged lining of the uterus without sufficient self-repair. Several studies have reported highly expressed fibrotic markers in endometrial tissues of IUA patients or animal models Volunteers, such as TGF-beta. The TGF-β1/SMAD pathway plays a dominant role in the molecular network that induces fibrosis in various organs. One of the mechanisms of IUA is the imbalance between synthesis and degradation of the extracellular matrix (ECM). Numerous studies have confirmed that transforming growth factor-1 (TGF-β1) related to ECM is closely related to the severity of adhesion and can activate multiple signal transduction pathways, among which TGF-β1/Smad signaling pathway plays the strongest role. It can stimulate the growth of stromal cells and promote the proliferation and differentiation of fibrocytes, thus inhibiting the degradation of ECM and promoting fibrosis repair. It has been reported that the expression of TGF-β1 and SMAD3 protein in IUA patients and animal models was significantly higher than that in the normal control group [6]. Therefore, the main regulator of IUA pathogenesis is the TGF-β1/SMAD signaling pathway, which further confirms that the occurrence of IUA is the result of excessive fibrosis of endometrial tissue.

1.2. TLR4/NF-κB

TLR-4 is one of the pathogen pattern recognition receptors, which can activate nuclear factor-related cytokines (NF-κB) after recognizing the pathogen molecular pattern, forming the TLR-4/ NF-κB pathway, thereby enhancing the expression level of inflammatory factors and inducing the production of a large number of fibrotic cytokines. It causes tissue fibrosis in the body [7]. Relevant studies have found that the expression level of TLR-4 in various tissues is positively correlated with the degree of fibrosis. Thus, activation of the TLR4/NF-κB pathway in the tissue of the endometrium promotes fibrotic progression in IUA. In addition, the JAK-STAT3 signaling pathway is also involved in the process of tissue fibrosis. NK cells are activated by IL-21, and fibroblasts are over-prolifized through the JAK-STAT3 signaling pathway, thus participating in the process of tissue fibrosis. Animal experimental studies [8] have found that the degree of pulmonary fibrosis in mice is positively correlated with the expression level of IL-21. It can be proved that IL-21 acts on the body to promote the occurrence of tissue fibrosis, which also proves that inflammation is one of the risk factors for the formation of IUA.

2. Overview of vaginal microecology

2.1. Composition and Functions of vaginal microecology

The composition of vaginal microecology includes vaginal microflora, vaginal pH value, H2O2 enzyme, sialidase and leukocyte lipase [9]. The Lactobacillus in the vaginal microbiota produces an appropriate amount of lactic acid to maintain the slightly acidic (pH (3.5-4.5)) environment of the vagina. Bacteriocin and hydrogen peroxide can inhibit the invasion of pathogenic bacteria and improve the resistance of the vagina to disease [10]. Mania-Pramanik et al. [11] proposed that abnormal vaginal pH value may be one of the risk factors for infertility and adverse pregnancy outcomes. Studies have also shown that Lactobacillus can produce a large amount of hydrogen peroxide (H2O2), which together with biosurfactants promote the self-cleaning of the vaginal environment, can promote the synthesis of peripheral interleukin 23(IL-23), and then activate the helper T cell 17(Th17) lymphocyte pathway, and inhibit the invasion of gram-negative bacteria. At present, there has been a large amount of evidence that the reproductive tract flora dominated by Lactobacilli plays a defense role against the invasion of bacteria, viruses and other microorganisms [12]. It can also be seen from the above statements that the vaginal microflora plays a major role in the vaginal microecology and is the main force affecting the vaginal microecology and surrounding tissues.

2.2. Classification of vaginal microbiota

With the advent of 16sRNA gene sequencing technology, scientists have established unique community state types (CSTs). According to the abundance difference of Lactobacillus genus, it is divided into five types: CST-I, CST-II, CST-III and CST-V. Currently, it has been reported that CST-I, CST-II, CST-III, and CST-V are probiotics, respectively, with Lactobacillus capillaris, Lactobacillus gardneri, Lactobacillus inerta, and Lactobacillus Jansseni, while CST-IV, the type of anaerobic bacteria as the dominant bacterial group, is a pathogenic bacterium that is mixed with a variety of compositional anaerobic bacteria and low levels of lactobacillus [9].

2.3. Effects of vaginal microbiota on the uterine cavity

The reproductive tract microbiota includes both uterine and vaginal microbiota, which share the responsibility for protecting reproductive health. In general, the normal vaginal flora of healthy

women consists mainly of lactic acid bacteria, but also includes a small number of fungi and parasitic bacteria. An imbalance in the distribution of vaginal microbes increases the risk of a variety of infectious and non-infectious diseases, such as endometritis, premature birth, infertility, spontaneous abortion, and delivery of low birth weight babies. Previously, it was thought that the uterine cavity was sterile, but a growing number of studies have found that this is not the case. The changes of uterine microbiome are closely related to various intrauterine diseases such as endometritis, endometriosis and endometrial polyps [13]. Studies [14] have found that the uterine microbiota is similar to the vaginal microbiota, but the content of the microbiota is less than that of the vaginal microbiota, which indicates that the uterine microbiota may come from the vaginal microbiota. If the uterine microbiota is affected by the vaginal microbiota, the incidence of chronic endometrial inflammation will be greatly increased, and IUA will be more likely to occur. It has been speculated that the microorganisms inhabiting the female upper reproductive tract may migrate from the lower reproductive tract or transfer from the peritoneal fluid [13].

3. Correlation between uterine adhesions and vaginal microecology

In recent years, some scholars still use different evaluation methods to carry out experiments on this research, and have obtained constructive results. Ueda [15] et al. compared the vaginal microecological indicators of 100 clinical IUA patients with normal women, and found that the rate of vaginal microbiota imbalance in IUA patients was significantly increased in normal women ($p<0.05$), and lactobacillus was no longer dominant. This study suggested that the occurrence of uterine adhesion was correlated with the imbalance of vaginal microbiota. Zhao Tian et al. [16] retrospectively selected gynecological patients who underwent hysteroscopy in their hospital as research objects, and divided them into mild IUA group, moderate IUA group, severe IUA group and normal uterine chamber group. The results showed that there were differences in bacterial diversity, dominant bacteria, pH value, bacterial vaginosis, positive rate of H2O2 and positive rate of SNA in severe IUA group compared with mild IUA group, moderate IUA group and normal uterine chamber group ($p<0.05$). Further analysis showed that bacterial diversity and bacterial vaginosis were independent influencing factors of severe IUA. These findings suggest that vaginal microbial imbalance is closely related to the occurrence of IUA, especially in patients with severe IUA, the vaginal microecology is more prone to imbalance, which should be paid more attention to. Yang Li et al. [17] found that the incidence of aerobic vaginitis (AV) in IUA patients was higher than that in healthy women. The study of Yang Hairong et al. [18] showed that the AV infection rate in IUA patients was higher than that in healthy group (23.33%vs14.17%, $p<0.05$). Dun et al. [19] collected vaginal samples from 119 IUA patients and 150 healthy controls and found that the number of IUA patients with vaginal pH less than 4.5 (89, 59.3%) was significantly lower than that of the control group (123, 82%), suggesting that the vaginal pH of IUA patients was elevated. Lactobacillus is a common vaginal dominant bacteria in the general population. Of the 150 healthy volunteers, the dominant vaginal species was Lactobacillus in 119 patients and lactobacillus was the dominant vaginal species in only 96 patients, significantly lower than in the control group. In addition, the bacterial species diversity and distribution density in the vagina of IUA patients were significantly lower than that of healthy individuals. The incidence of TV and BV in IUA patients was significantly higher than in the control group. This further suggests that the occurrence of IUA is related to the vaginal microbiome.

4. The mechanism of vaginal microbiota in the development of uterine adhesions

An animal experiment [20] showed that the endometrial injury combined with infection was more stable than the IUA animal model with simple endometrial injury. Therefore, iatrogenic trauma,

mainly caused by uterine operation, is a direct factor in the occurrence of IUA. These injuries, combined with infection of pathogenic bacteria, mediate the inflammatory response of the genital tract mucosa, affect the abundance of vaginal flora, change the original flora composition, and promote the colonization of pathogenic bacteria. Studies [21] have shown that vaginal flora can promote the production of macrophages and neutrophils, and at the same time activate the immune system to produce a large number of pro-inflammatory and pro-fibrotic cytokines mediated by TLR4/NF-κB signaling pathway and TGF-β1/SMAD signaling pathway, thus leading to the development of IUA.

Th response is an important link in humoral immunity. When pathogenic bacteria invade, the immune system is activated, auxiliary Th1 in Th cells will release a wide range of pro-inflammatory cytokines, and Th2 immune response will also be activated to accelerate the formation of fibrosis. If the number of pathogenic bacteria is large, the balance of microflora will be destroyed, resulting in the abundance of Lactobacillus and the concentration of metabolites will be reduced, the growth of other pathogenic bacteria will not be inhibited, the number of pro-inflammatory factors will increase, and the fibrosis process will be accelerated [20]. Kong Y et al. [22] reported that the engineered strain *L.Rispatus-PMG36emCXCL12* was constructed by transforming Pmg36e plasmid of exogenous *CXCL12*, which can promote tissue regeneration and repair by recruiting immune cells, into bacteria. The strain was administered to evaluate the positive effect of IUA prevention after intrauterine surgery in normal and diabetic mice. The results showed that transvaginal administration of *L.Rispatus-PMG36EMCXCL12* significantly decreased the levels of pro-inflammatory factor interleukin-1b (lL-1b) and tumor necrosis factor, and increased the abundance of *Lactobacillus*, thereby reducing the number of *Klebsiella* pathogens. Inhibiting inflammatory factor signaling pathway (TLR4/NF-κB) and fibrosis signaling pathway (TGF-β1/SMAD) in uterine tissue effectively alleviates inflammation and fibrosis in uterine cavity of diabetic mice, and promotes the balance of vaginal microflora in diabetic mice. In addition, another study [23] through high-throughput sequencing technology and ITS2rDNA sequencing analysis found that compared with healthy subjects, IUA patients had specific changes in vaginal bacteria, such as the increase of *Dialister* and the decrease of Bifidobacterium. And an increase in fungal genera such as *Filobasidium* and *Exophiala*. Site-specific fungus-bacterial associations have been found in samples from IUA patients' cervical canal (CC) and middle vagina (MV). Studies have shown that, with the exception of *Candida albicans* and *Candida maltosa*, *Candida parapsilosis* prevents the worsening of inflammatory activity, thereby preventing fibrosis and alleviating the occurrence of IUA. It can also be inferred that the imbalance of vaginal microbiota is an important risk factor for the formation of IUA.

5. Conclusions

Taken together, it can be concluded that there is a correlation between the vaginal microbiome and IUA. The imbalance of vaginal microbiota was mainly manifested in increased bacterial density, decreased bacterial diversity, abnormal dominant bacterial types, trichomoniasis infection and bacterial vaginosis infection, etc. These indicators were particularly obvious in patients with severe uterine adhesion. These results provide a new idea and basis for the prevention and treatment of intrauterine adhesions. However, there are still some problems in the current research, and the understanding of uterine adhesions and vaginal microbiota is not perfect, which needs further experimental and clinical studies to verify and explore. Future studies can explore interventions related to vaginal microbiome regulation, further clarify the pathogenesis of IUA and vaginal microbiome, and provide more effective means and strategies for the prevention and treatment of IUA.

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