MEDS Clinical Medicine (2025)
Clausius Scientific Press, Canada
DOI: 10.23977/medsc.2025.060418
ISSN 2616-1907 Vol. 6 Num. 4

Research Progress on the Correlation between Intrauterine Adhesion and Reproductive Tract Microecology

Fei Wang[1,a], Jin Lin[1], Yangjing Long[1], Yan Wang[2], Xu Ding[2], Yanhong Huang[2,*]
[1]Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China
[2]Xi'an International Medical Center Hospital, Xi'an, Shaanxi, 710100, China
[a]740735679@qq.com
[*]Corresponding author: 381874548@qq.com

Keywords: Intrauterine Adhesion, Reproductive Tract Microecology, Uterine Microecology, Vaginal Microecology

Abstract: Intrauterine adhesions (IUA) is a common complication after gynecological intrauterine surgery. Endometrial fibrosis and inflammatory response are considered the main causes of its occurrence and development. In recent years, an increasing number of research evidences have shown that IUA is closely related to the dysregulation of the reproductive tract microbiota, and the two may interact through pathways such as immune dysregulation, activation of the fibrosis pathway, and inflammatory response. This paper reviews the relevant research results of IUA and the reproductive tract microbiota, in order to provide new treatment ideas for exploring the pathogenesis of IUA and improving IUA from the perspective of adjusting the balance of the flora in the future.

1. Introduction

Intrauterine adhesion (IUA) is common after gynecological and obstetric intrauterine surgeries. It is mostly caused by iatrogenic injuries, infections, etc., which damage the basal layer of the endometrium, resulting in impaired endometrial repair, an abnormal increase in fibrous tissue, and subsequent scar formation. This in turn leads to symptoms such as scanty menstruation, abdominal pain, and in severe cases, amenorrhea, recurrent miscarriage, and infertility [1], seriously affecting the reproductive health of women of childbearing age. Currently, the transcervical resection of adhesions (TCRA) used clinically can improve menstruation, restore the shape of the uterine cavity, and optimize uterine cavity perfusion. However, the incidence of postoperative re-adhesion is relatively high, and the postoperative pregnancy rate is only between 22.5% and 33.3% [2-3]. The dynamic balance formed among the female genital microbiota, the endocrine system, the anatomical structure of the genital tract, and the local mucosal immunity constitutes the genital tract microecosystem, which affects female reproductive health [4]. In recent years, domestic and foreign studies have found that the occurrence and development of IUA are closely related to genital tract microecological disorders [5]. Exploring the role of the genital tract flora in the process of IUA may provide a new direction for clinical prevention and treatment strategies.

2. The characteristics of the reproductive tract microbiota in healthy women

2.1. Characteristics of the vaginal microbiota in healthy women

The vaginal microbiota shows structural characteristics of low diversity and high proportion of dominant bacteria. The vaginal microbiota mainly consists of Gram-positive aerobic and facultative anaerobic bacteria, Gram-negative aerobic and facultative anaerobic bacteria, obligate anaerobic bacteria, mycoplasma, Candida, etc. [6]. The vaginal flora is mainly composed of Firmicutes, among which Lactobacillus is considered the dominant genus in the vagina (accounting for up to 99.99%) [7]. The concept of CST (community state type) was proposed by Ravel et al. in 2011. The vaginal microbiota is classified into 5 types according to the composition and relative abundance of the flora. CST I, II, III, and V are mainly dominated by Lactobacillus crispatus, Lactobacillus gasseri, Lactobacillus iners, and Lactobacillus jensenii respectively, while CST IV is mainly dominated by anaerobic bacteria [8]. In addition, the vaginal flora of women of childbearing age shows temporal fluctuations due to changes in hormone levels. There are significant differences among different individuals due to various factors (such as race, sexual life, eating habits, etc.). Menstruation, pregnancy, vaginal douching behavior, and the irrational use of antibiotics can all change the composition of the vaginal flora in a short period [9]. The cervix, as an important passage connecting the vagina and the uterus, has its microbiota usually classified within the scope of the vaginal microecology and is studied in conjunction with the vaginal flora. The cervical microbiota is highly similar in composition to that of the middle part of the vagina. The dominant genus is Lactobacillus, but its relative abundance is slightly lower (accounting for 97.56%), and the species diversity shows an increasing trend [7]. To better evaluate the status of the vaginal microecology, domestic experts issued a clinical expert consensus in 2016, proposing a relatively complete evaluation system for the vaginal microecology. This consensus clearly defines the main contents of vaginal microecology detection and the characteristics of a normal microecology. According to the consensus, if there are changes in the density, diversity, and dominant bacteria of the vaginal flora, or any abnormality in the inflammatory response indicators (such as the white blood cell count in vaginal secretions), pH value, and the function of Lactobacillus, it can be determined that the vaginal microecology is imbalanced [6].

2.2. Characteristics of the uterine microecology in healthy women

The uterine microbiota shows characteristics of lower species abundance and higher species diversity compared to the vaginal microbiota. At the phylum level of species, in addition to Firmicutes, Proteobacteria, Actinobacteria, and Bacteroidetes account for a relatively large proportion. It is generally recognized that Lactobacillus remains the dominant genus. Chen et al. [7] conducted 16S rRNA sequencing on endometrial samples from 110 reproductive-aged women and found that Lactobacillus was still the dominant genus, but its proportion was only 30.6%. Bacteria such as Pseudomonas, Acinetobacter, Vagococcus, and Sphingobium constituted an important part of the uterine microbiota. They also found that the uterine microbiota had approximately 70% similarity with the microbiota in the fallopian tubes and peritoneal fluid in the Douglas pouch. Therefore, it is speculated that the uterine microbiota may originate from the upward migration of the lower genital tract microbiota or the migration of the microbiota in the fallopian tubes and peritoneal fluid. The relatively closed uterine environment makes its microecology more stable than that of the vagina. However, its dynamic balance can still be disrupted by factors such as the menstrual cycle, age, hormone levels, intrauterine operations, childbirth, and genital tract infections

[10].

3. The characteristics of the reproductive tract microecology in patients with intrauterine adhesion (IUA)

3.1. The vaginal microecological characteristics of patients with intrauterine adhesion (IUA)

Patients with intrauterine adhesion (IUA) generally have the phenomenon of vaginal microecological imbalance. Dun et al. [11] found that the vaginal microecological indicators of IUA patients usually show a decrease in lactobacilli, an increase in pH value, and a significantly increased infection rate of trichomoniasis vaginitis and bacterial vaginitis. The change in the structure of the vaginal microflora is mainly manifested by a decrease in species diversity. At the genus level, the relative abundances of beneficial bacteria such as Lactobacillus and Bifidobacterium are significantly reduced, while the relative abundances of conditional pathogenic bacteria such as Gardnerella, Prevotella, and Dialister increase. At the phylum level, the proportion of Firmicutes increases, and phyla such as Euryarchaeota and Acidobacteria are hardly detectable [12-13]. Xiaoqing Li et al. [14] pointed out that the Shannon index, the abundance of Bacteroides, and the species richness index are significantly positively correlated with the hematocrit, and the Simpson index is significantly positively correlated with the creatinine level. Therefore, it is speculated that the hematocrit and creatinine level may, to a certain extent, reflect the distribution characteristics of vaginal microorganisms. Hua X et al. [15] believe that the severity of IUA is related to the change in the abundance ratio of Firmicutes to Acinetobacter in the cervical canal. This finding indicates that the microbial community composition can be used as a potential biomarker to evaluate the severity of IUA. In addition to bacterial microorganisms, there is also an enrichment of fungal genera in the vagina and cervix of IUA patients, manifested by an increase in the relative abundances of Filobasidium and Exophiala [16]. These changes in the composition of the microbiota may not only be involved in the occurrence and development of IUA but also have potential impacts on its treatment effect and recurrence risk.

3.2. The endometrial microecological characteristics of patients with intrauterine adhesion (IUA)

Qiu Tianmei et al. [17] analyzed the intrauterine cavity microbiota of patients with intrauterine adhesion (IUA) and women with normal endometrium through Illumina sequencing in 2020. They found that the endometrial microbiota of IUA patients was mainly composed of Proteobacteria, Firmicutes, Bacteroidetes, and Actinobacteria at the phylum level, and the community evenness and species composition might change in the early stage of the disease. In 2021, Qiu et al. [18] used 16S rRNA sequencing technology to analyze endometrial samples from IUA patients and infertile patients without intrauterine cavity lesions. The results showed that the relative abundances of Klebsiella, Shewanella, and Lactobacillus in the IUA group increased, while the relative abundance of Acinetobacter decreased. Moreover, the abundance of Lactobacillus was correlated with the severity of adhesions. However, the study by Chen Mingqian et al. [19] suggested that there was no statistically significant difference in species diversity between IUA patients and infertile patients without IUA ($P>0.05$), and it was found that the abundance of Lactobacillus inertis in the intrauterine cavity of the IUA group decreased. Due to the technical complexity of sampling in the upper reproductive tract and the limitations of existing research methods, the current understanding of the interaction relationships between the endometrial microbiota and the intrauterine environment, as well as between IUA and the intrauterine microecology, is still in the preliminary exploration stage and remains controversial.

4. The relevant mechanisms between the occurrence and development of IUA and the imbalance of the reproductive tract microecosystem

4.1. The increased risk of pathogenic bacteria colonization

The reproductive tract microbiota is a dynamically balanced system. Microorganisms maintain the stability and diversity of the microbiota through competition, symbiosis, and antagonism. Under normal circumstances, Lactobacillus, as the dominant genus in the lower reproductive tract, decomposes glycogen to produce lactic acid, which can maintain the acid-base balance of the vaginal environment and inhibit the overgrowth of harmful bacteria. The vaginal microbiota dysbiosis in patients with intrauterine adhesions (IUA) is mainly manifested by a decrease in the relative abundance of Lactobacillus and an increase in the pH value, which can increase the colonization risk of opportunistic pathogens [20]. Ningning LIU et al. [16] found a specific site cross-kingdom correlation between fungi and bacteria at the cervical os, suggesting that a decrease in the relative abundance of beneficial bacteria can also increase the risk of fungal infection. The cervical mucus plug has a certain barrier function. When the relative abundance of Lactobacillus decreases and the vaginal pH value increases, the thinning of the mucus may allow pathogenic bacteria (such as Gardnerella vaginalis) to break through the mucus barrier and enter the uterus, triggering endometrial inflammation [10, 18]. Intrauterine operations may also allow pathogenic bacteria to enter the uterine cavity along the operating instruments. In addition, the animal experiment by Wen et al. [21] also found that Mycoplasma pneumoniae can be transmitted through the bloodstream and colonize in the uterus of rats, causing IUA.

4.2. The genital tract microbiota induces immune dysregulation

Microorganisms can communicate through small molecules and proteins, influencing the immune responses and tissue functions of host cells. Under normal circumstances, Lactobacillus can participate in non-specific immune regulation by enhancing the mucosal barrier function, increasing the activity of phagocytes, and stimulating the production of immune factors. At the same time, it can also affect T cell differentiation and B cell proliferation, thus achieving specific immune regulation effects [22]. Damage to the endometrial tissue and a decrease in the relative abundance of Lactobacillus can lead to the recruitment and activation of innate and adaptive immunity, and then the release of a large number of pro-inflammatory and profibrotic cytokines, which promotes the occurrence and development of intrauterine adhesion (IUA) [23]. On the other hand, harmful bacteria stimulate the body to release a large number of pro-inflammatory factors (such as TNF-α, IL-6, etc.), which inhibit the normal functions of immune cells in the body, preventing the effective initiation of specific immune responses [24]. This may exacerbate the inflammatory damage of local tissues and also activate fibrosis-related pathways [25].

4.3. Immune dysregulation triggers an inflammatory response, which activates the fibrotic pathway

TGF-β1 is a key cytokine that regulates the tissue repair process and is mainly released by platelet degranulation. The NF-κB nuclear transcription regulatory factor plays an important role in processes such as the body's inflammatory response, cell apoptosis, and immune response. Both are closely related to the occurrence and development of intrauterine adhesions (IUA) [1]. Lipopolysaccharide in the cell wall of Gram-negative bacteria can bind to Toll-like receptor 4 to induce immune cells to release immune factors, thereby activating the NF-κB signaling pathway, triggering a series of inflammatory reactions, upregulating the expression of TGF-β, interfering with the normal metabolic and repair processes of endometrial cells, and making it difficult for the damaged endometrium to return to a normal state [26]. Candida parapsilosis can reduce the activity of the inflammatory response by inhibiting the expression levels of NF-κB and IL-6. At the same time, it can inhibit the fibrosis process by suppressing the expression of TGF-β1, collagen-1, and the biomarker Smad2 [16]. The study by Qingjie Fan et al. [27] found that the metabolites of Lactobacillus iners can activate the Wnt/β-catenin pathway. There is a close association between IUA and the overactivation of the Wnt/β-catenin signaling pathway. This overactivation can promote endometrial fibrosis by regulating the process of epithelial-mesenchymal transition (EMT) [28]. It is thus speculated that Lactobacillus iners may be involved in the fibrosis process of IUA by activating the classical Wnt pathway.

4.4. Genital tract microecological imbalance may be the key link connecting intrauterine adhesions (IUA) with various gynecological diseases

Current research shows that intrauterine adhesions (IUA) are closely related to chronic endometritis (CE) and infertility. Iatrogenic injuries during intrauterine operations can lead to a decrease in the number of endometrial cells, impaired function, local ischemia and hypoxia, etc., which may change the colonization environment of intrauterine microorganisms and result in microecological imbalance. When the structure of the uterine flora changes, it will affect the decline of endometrial receptivity, which is not conducive to embryo implantation and pregnancy maintenance. Research has shown that a uterine microecology with Lactobacillus as the dominant flora can improve the success rate of in vitro fertilization and pregnancy outcomes, while an increase in the relative abundance of Gardnerella, Klebsiella, Staphylococcus, Streptococcus, Chryseobacterium, etc. will reduce the live birth rate of fetuses [29]. Clinical studies have shown that the incidence of CE in patients with IUA is twice that of non-IUA patients, and the postoperative re-adhesion rate is higher [30]. Chronic endometritis patients are commonly infected with Gram-negative strains, such as Escherichia coli and Gardnerella vaginalis. The occurrence of IUA may change the uterine environment and function, affect the richness and evenness of the flora, cause uterine microecological disorders, and further lead to CE. Persistent dysbiosis will affect the severity of adhesions and increase the risk of postoperative re-adhesion.

Zhao Tian et al. [31] conducted a clinical retrospective analysis which indicated that bacterial vaginitis and positive SNA are independent risk factors for severe intrauterine adhesions (IUA) ($P<0.05$). In addition, other studies have shown that the incidence of high-risk HPV infection combined with vaginal microecological imbalance in the IUA group is significantly higher than that in the control group [32]. Thus, it can be seen that IUA can lead to vaginal microecological imbalance and increase the risk of lower genital tract bacterial infections. Vaginal flora imbalance can also lead to the occurrence of cervical cancer, premature birth, infertility, and other common sexually transmitted diseases [33]. Patients with vaginal microecological disorders are more likely to develop IUA after intrauterine procedures, and it is related to the degree of adhesions. Zhong Sujing et al. [25] confirmed that reproductive-aged women with a history of bacterial vaginitis or aerobic vaginitis are more prone to IUA. It is thus speculated that specific changes in the genital tract microbiota may determine the development direction of the disease.

5. The development prospects of different intervention strategies for the prevention and treatment of intrauterine adhesions (IUA)

5.1. Microbiota regulation

The persistent inflammatory state caused by the dysbiosis of the reproductive tract microecosystem may exacerbate the degree of endometrial fibrosis, forming a vicious cycle. Currently, problems such as the high recurrence rate after intrauterine adhesion (IUA) surgery and difficulties in pregnancy indicate that there are still limitations in clinical treatment. However, the crucial role of microecological dysregulation in this provides new ideas for clinical prevention and treatment. The animal experiment by Wu Fei et al. [34] showed that Lactobacillus crispatus can effectively alleviate uterine fibrosis in mice, reduce the levels of IL-1β and TNF-α in serum, and inhibit the TGF-β1/SMADs signaling pathway. Clinical research has shown that compared with the estrogen treatment group, the recurrence rate of intrauterine adhesions in patients in the Lactobacillus crispatus treatment group is lower after surgery, which proves the effectiveness of microecological regulation in the prevention and treatment of IUA. In addition, the genetically engineered "Lactobacillus crispatus - pMG36 - mCXCL12" has a better therapeutic effect than the unmodified Lactobacillus crispatus [35]. Recent studies have found that unsaturated long-chain fatty acids selectively inhibit Lactobacillus iners, promote the growth of beneficial lactobacilli, and improve the ecological balance of the reproductive tract [36]. Combining different ways of microbiota regulation with traditional clinical treatment methods may provide a more comprehensive treatment strategy for the prevention and treatment of IUA.

5.2. Modern biological therapies

In recent years, stem cells have become an important direction in exploring new strategies for the prevention and treatment of intrauterine adhesions (IUA) due to their characteristics such as self-renewal, multi-lineage differentiation, immunomodulation, and promotion of angiogenesis. Mesenchymal stem cells can promote angiogenesis, inhibit the occurrence of fibrosis by downregulating the expression levels of transforming growth factor-β (TGF-β) and connective tissue growth factor (CTGF), etc. They can effectively increase the menstrual volume of patients, enhance the thickness of the endometrium, and improve the pregnancy rate and live birth rate [37]. However, more rigorous research protocols are still needed for its clinical translation to gradually become an effective prevention and treatment strategy. In addition, platelet-rich plasma (PRP) can also promote the regeneration of damaged tissues, angiogenesis, as well as the migration, differentiation, and proliferation of cells. It helps to improve endometrial receptivity and thus promote the repair of the endometrium. Autologous PRP intrauterine perfusion has a significant effect in the treatment of patients with moderate to severe IUA [38].

5.3. Intervention of traditional Chinese medicine

In recent years, with the rapid development of traditional Chinese medicine (TCM), it has also demonstrated unique value in the prevention and treatment of intrauterine adhesions (IUA). Berberine, an extract from the Chinese herb Coptis chinensis, can effectively inhibit the expression of TNF-α, IL-1β, and IL-6 in the serum of IUA rats, restore the diversity of the vaginal flora, reduce the relative abundance of conditional pathogenic bacteria such as Staphylococcus aureus and Escherichia coli, and at the same time increase the abundance of beneficial bacteria such as Lactobacillus and Bifidobacterium [39]. The "Tiaoshen Tongluo Prescription" can significantly reduce the phosphorylation level of Smad2/3 in the endometrium and upregulate the expression of Smad7 by regulating the TGF-β1/Smad signaling pathway in IUA model rats, thereby alleviating the degree of fibrosis and promoting endometrial reconstruction [40]. The Chinese herbal medicine Yangmo Prescription can promote the repair of the endometrium after transcervical resection of adhesions (TCRA), effectively prevent the recurrence of IUA, and significantly improve the postoperative fertility rate. Its curative effect is superior to that of combined estrogen and progesterone therapy. The multi-target regulatory characteristics of TCM can synergize with stem cells, platelet-rich plasma (PRP), etc. to achieve more comprehensive repair and regulation. However, the specific mechanism and optimization plan of this synergistic strategy still need to be further studied and verified, which may provide a more effective combined intervention approach for the prevention and treatment of IUA.

6. Summary and Prospect

The occurrence and development of intrauterine adhesion (IUA) are closely related to the dysregulation of the reproductive tract microbiota. The two form a vicious cycle by altering the microenvironment of the reproductive tract, leading to immune dysregulation, and further triggering inflammatory and fibrotic reactions. Basic research needs to further optimize the experimental protocol, focus on the pathogenesis of IUA and the dynamic changes of the microbiota, and more deeply analyze the interaction mechanisms among the microbiota, immunity, and fibrosis. Among the existing clinical treatment options, microbiota regulation can improve the balance of the microbiota, modern biotherapies can promote repair and inhibit fibrosis, and traditional Chinese medicine can achieve synergistic effects through multi-target regulation. However, all of them have limitations in treatment. Future clinical research needs to clarify the synergistic targets of each therapy, optimize the protocol through rigorous clinical research, promote the transformation from basic research to clinical practice, and provide more precise and efficient solutions for the prevention and treatment of IUA.

Acknowledgements

Science Foundation of Xi'an International Medical Center Hospital (No. 2023MS05 and No.2024MS06).

Natural Science Basic Research Program of Shaanxi Province (No. 2025JC-YBQN-1218).

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