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Mechanisms of Recurrence in Sequelae of Pelvic Inflammatory Disease: A Review Based on the Theory of Damp-Heat Latent Pathogen

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Abstract: ***Sequelae of pelvic inflammatory disease (SPID) refers to the condition that develops when pelvic inflammatory disease (PID) is not effectively treated. In Western medicine, antibiotics are the primary treatment; however, long-term use tends to induce drug resistance and is associated with significant adverse effects. Therefore, Traditional Chinese Medicine (TCM) offers unique advantages in the prevention and treatment of SPID. Clinical observations indicate that its recurrent nature is closely related to the concealment of pathogenic factors within the body, which remain dormant until triggered by the decline of vital qi or re-infection with exogenous pathogens—a pattern consistent with the characteristics of "latent pathogen-induced disease." TCM posits that the core pathogenesis of this condition is blood stasis, often complicated by dampness, heat, cold, or deficiency, with the damp-heat stasis pattern being the most common clinical syndrome. The latent damp-heat pathogen harbors within, and over time, transgresses from the qi level to the blood level, leading to qi-blood disharmony and damage to the uterine vessels, which constitutes the core pathogenic mechanism of SPID recurrence. This article aims to explore SPID through the lens of the "damp-heat latent pathogen" theory, with the goal of providing a reference for clinical management.***

Keywords: Sequelae of Pelvic Inflammatory Disease, Damp-Heat Latent Pathogen, Recurrence, Research Progress.

1. Introduction

Pelvic inflammatory disease (PID) refers to a group of infectious conditions affecting the female upper reproductive tract, primarily including endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis. If PID is not diagnosed and treated promptly and appropriately, it can progress to sequelae of pelvic inflammatory disease (SPID), which may lead to infertility, ectopic pregnancy, chronic pelvic pain, and recurrent inflammatory episodes, thereby severely impacting women's reproductive health [1]. Epidemiological data indicate that the disease predominantly affects women of reproductive age, particularly those between 26 and 35 years old [2]. SPID poses a serious threat to female reproductive health, as persistent inflammation involves the fallopian tubes, uterus, and ovaries, causing endometrial damage and disrupting the protective mechanisms of the fallopian tubes, which ultimately increases the risk of infertility and ectopic pregnancy. Furthermore, it may lead to severe complications such as peritonitis, pelvic abscess, and even septic shock. The prolonged course of the disease, characterized by chronic pain and reproductive dysfunction, often imposes a significant physical and psychological burden on patients [3, 4].

2. TCM Understanding of Sequelae of Pelvic Inflammatory Disease

There is no direct record of the disease entity "SPID" in classical TCM literature. However, based on its clinical manifestations, it can be categorized under the traditional diagnostic terms such as "women's abdominal pain," "leukorrheal diseases," "irregular menstruation," "abdominal masses," and "infertility" [5]. A description that closely matches the etiology, pathogenesis, and clinical presentation of SPID can be found in the Complete Compendium of Women's Diseases (Furen Daquan Liangfang), which states: "When a woman's menstruation is obstructed, or when residual lochia remains postpartum and she is exposed to wind and cold, the blood becomes congealed due to cold, resulting in blood stasis. Blood stasis within the body causes intermittent fever and a sallow complexion. If stasis persists without resolution, it accumulates to form abdominal masses." This passage illustrates that the pathogenesis involves invasion by exogenous pathogens leading to blood stasis in the uterus, which disrupts the thoroughfare and conception vessels, impairs qi movement, and damages the channels, manifesting as lower abdominal pain, lumbosacral soreness, abnormal vaginal discharge, and secondary dysmenorrhea — symptoms commonly observed in clinical practice. Contemporary TCM practitioners recognize that its etiology is complex and can be summarized by factors such as cold, heat, phlegm, deficiency, depression, stasis, and dampness [6]. Among these, dampness and blood stasis are considered the primary pathogenic factors. As recorded in Fu Qingzhu's Gynecology (Fu Qingzhu Nüke): "Leukorrhea is invariably a dampness disorder." Regarding blood stasis, the distinguished TCM master Professor Xia Guicheng [7] pointed out that in PID, damp-turbidity and heat-toxin are the predominant factors, with stasis being secondary; however, in SPID, stasis becomes dominant, with damp-heat as a secondary factor, and deficiency patterns gradually become more pronounced. Clinical evidence confirms that SPID predominantly presents with damp-heat and blood stasis patterns. Damp-heat and stasis-toxin pathogens are densely distributed within the thoroughfare and conception vessels and the uterus, where they conflict with qi and blood, condensing to form blood stasis, which is characteristic of this condition.

3. Origins of the "Damp-Heat Latent Pathogen" Theory

A latent pathogen refers to a pathogenic factor or pathological

state that, after invading the human body, does not immediately cause disease but remains concealed within, only to become active when the body's vital qi is weakened or upon re-exposure to exogenous pathogens [8]. The concept of latent pathogens can be understood in both narrow and broad senses. In the narrow sense, it refers to warm diseases (wenbing) that arise from pathogens that have been hidden and then manifest after a period of time—commonly known as "latent warm diseases." In the broad sense, it encompasses all pathogenic factors that do not cause immediate disease, including exogenous six excesses (liuyin), internal injuries from seven emotions (qiqing), phlegm-turbidity, blood stasis, fluid retention, qi stagnation, and other pathogenic influences. Such latent pathogens not only trigger warm diseases but also serve as an important pathological basis for various internal miscellaneous disorders [9, 10].

The concept of latent pathogens originates from the Yellow Emperor's Inner Classic – Plain Questions (Huangdi Neijing – Suwen), specifically from the chapter Discourse on the Correspondences of Yin and Yang (Yin Yang Ying Xiang Da Lun), which states: "Cold injury in winter will inevitably lead to warm disease in spring; wind injury in spring will inevitably lead to summer diarrhea; summerheat injury in summer will inevitably lead to malaria in autumn; dampness injury in autumn will inevitably lead to cough in winter." However, the specific term "latent pathogen" had not yet been coined at this point. The principles "When vital qi is stored within, pathogens cannot invade" and "Where pathogens accumulate, vital qi must be deficient" articulate the relationship between vital qi and latent pathogenic activity [11]. The concept of latent pathogens was first explicitly proposed by Wu Youke in the late Ming dynasty, in his work Treatise on Warm-Heat Epidemics (Wen Yi Lun), where he stated: "The epidemic pathogen is hidden in the pleurodiaphragmatic membrane, like birds nesting or beasts burrowing, beyond the reach of the defensive and nutritive qi, and inaccessible to ordinary medicines" [12]. He described how epidemic pathogens conceal themselves in the half-exterior and half-interior membrane source (moyuan), a location so concealed that conventional medications are powerless to reach it. In the Qing dynasty, Ye Tianshi, in his Treatise on Seasonal Latent Qi and Exogenous Diseases (San Shi Fu Qi Wai Gan Pian), wrote: "Spring warmth is a condition that arises from insufficient consolidation during winter storage; the cold pathogen is hidden in the lesser yin channel during winter and emerges in the lesser yang channel in spring," thereby clearly outlining the transmission pattern of latent warm diseases and expanding the application of latent pathogen theory from epidemics to a broader range of seasonal warm diseases, laying the theoretical groundwork for its subsequent generalization [13]. Wang Yanchang of the Qing dynasty, in his Wang's Medical Records (Wang Shi Yi Cun), stated: "All hidden and dormant diseases may involve the six excesses, various types of depression, dietary factors, blood stasis, phlegm accumulation, qi stagnation, fluid retention, and parasitic infestations." This reveals that the concept of latent pathogens had evolved beyond its original warm disease framework to encompass a broad definition, implying that latent pathogens include not only the six excesses but also emotional disturbances, phlegm stasis, toxins, water retention, and other factors that lead to diseases with a delayed onset [14].

The damp-heat latent pathogen is a specific pathological concept refined from the latent pathogen framework to explain the recurrent nature of SPID. Specifically, dampness, classified as a yin pathogen, tends to obstruct qi movement and damage yang qi, and is characterized by its lingering and stubborn nature. Heat, classified as a yang pathogen, rises and flares upward, easily consuming body fluids and even generating wind and moving blood. These two factors combine, with dampness restraining heat and heat steaming dampness, creating a situation where dampness and heat bind together. This creates a pattern of difficult diffusion and blocked descent, causing the pathogen to lodge deeply within the body, making it difficult to expel. Once entrenched, the damp-heat latent pathogen not only obstructs qi movement but also tends to invade the nutritive and blood levels, disrupting the harmonious movement of defensive and nutritive qi. The retention of defensive qi empties the channels, while the stagnation of nutritive qi generates heat from stasis. The longer the damp-heat pathogen lurks, the more severe the qi stagnation and blood stasis become, affecting a broader range of tissues and forming the root cause of SPID recurrence and chronicity [15].

4. The Damp-Heat Latent Pathogen Theory and Mechanisms of SPID Recurrence

Recent research has investigated the pathogenesis and therapeutic strategies for SPID based on the theory of damp-heat latent pathogens, suggesting that damp-heat pathogens lurk within the pelvic membrane source and the uterine collateral vessels. When vital qi is deficient or triggered by exogenous factors, the latent pathogen is activated, forming a pathological pattern characterized by "deficiency of vital qi and lingering of pathogen" [15]. The modern biological implications of the damp-heat latent pathogen theory can be understood through the interplay between chronic inflammation and tissue fibrosis. Studies on SPID rat models have shown that persistent inflammatory stimulation can activate the transforming growth factor-beta 1 (TGF-β1)/Smads signaling pathway, which drives fibroblast activation and extracellular matrix deposition, ultimately leading to tubal and pelvic tissue fibrosis and adhesion formation [16, 17]. The "latent and unresolved" nature of the damp-heat pathogen closely parallels this state of low-grade, persistent inflammation, while the "fibrotic scar" serves as the pathological soil for the latent pathogen, creating a vicious cycle of "inflammation-fibrosis-re-injury." Clinical studies have confirmed that herbal formulas targeting damp-heat latent pathogens can regulate this pathological process through multiple targets. For instance, combining Erdan Hongteng Baijiang Decoction with conventional Western medicine in SPID patients not only reduced serum levels of inflammatory cytokines such as IL-6 and TNF-α but also upregulated the proportion of $CD3^+$ and $CD4^+$ T lymphocyte subsets, thereby improving immune function [18]. Further studies on electroacupuncture at acupoints combined with Yinqiao Hongjiang Mixture demonstrated that the combined regimen could reduce serum TGF-β1 and monocyte chemoattractant protein-1 (MCP-1) levels, resulting in a 3-month follow-up recurrence rate of 5.00%, significantly lower than the 20.00% observed in the control group ($P < 0.05$) [19]. Another study indicated that Hongteng Baijiang Erdan Decoction combined with microwave therapy for SPID with

damp-heat stasis pattern not only improved hemorheological parameters but also achieved a 3-month recurrence rate of only 4.17%, far lower than the 17.02% for antibiotic treatment alone [20]. These findings suggest that therapeutic strategies based on "clearing and expelling latent pathogens while strengthening vital qi" may inhibit the activation of the TGF-β1/Smads pathway and modulate the immune microenvironment, thereby interrupting the SPID inflammation-fibrosis cycle and effectively reducing the risk of recurrence.

5. Therapeutic Principles and Methods for SPID Based on Damp-Heat Latent Pathogen Theory

Based on the "damp-heat latent pathogen" framework, contemporary TCM practitioners have developed a therapeutic approach that combines "clearing and expelling latent pathogens" with "strengthening vital qi and consolidating the foundation." This strategy aims to break the pathological cycle of "inflammatory damage – tissue fibrosis – latent pathogen reactivation" in SPID [15]. The rationale for this approach arises both from the pathological understanding of the latent characteristics of the pathogen and from clinical evidence. The strategy of "clearing and expelling latent pathogens" focuses on resolving the surface symptoms caused by the binding of dampness and heat. These pathogens are characterized by their stubborn and lingering nature, and simply using bitter and cold herbs to directly purge them is often ineffective and may even damage the spleen and stomach. Therefore, the therapeutic principle emphasizes the combined use of "clearing" and "expelling" approaches [15]. Clinical studies have shown that Hongteng Baijiang Erdan Decoction combined with microwave therapy in patients with SPID of damp-heat stasis pattern achieved a total effective rate of 95.83%, with a 3-month recurrence rate of only 4.17%, significantly lower than the 17.02% observed with azithromycin therapy alone ($P < 0.05$) [20]. Laboratory tests further indicated that this regimen significantly reduced serum levels of IL-6, TNF-α, and CRP, and improved hemorheological parameters such as whole-blood viscosity and plasma viscosity [18]. Another study confirmed that after treatment with modified Erdan Hongteng Baijiang Decoction in combination with antibiotics, the proportions of $CD3^+$ and $CD4^+$ T lymphocytes and the $CD4^+/CD8^+$ ratio in patients significantly increased compared with baseline, suggesting that the therapeutic efficacy may be associated with the regulation of T lymphocyte subsets and the alleviation of inflammatory responses [21].

The strategy of "strengthening vital qi and consolidating the foundation" aims to reverse the state of "vital qi deficiency with lingering pathogen." Prolonged SPID damages vital qi, rendering the body incapable of expelling the pathogen—a key internal factor underlying recurrence [22]. Chen Yingyi and colleagues believe that this condition is characterized by root deficiency and branch excess, and that the fundamental treatment principle should be to reinforce vital qi while eliminating residual pathogens [21]. Zhou Hui et al. treated SPID with Fuzheng Chufu Decoction combined with clindamycin phosphate tablets and found that the observation group showed superior outcomes in reducing TCM syndrome scores, shrinking inflammatory masses, and reducing pelvic effusion compared with the antibiotic-only group ($P < 0.05$). Furthermore, more pronounced decreases in serum TNF-α and IL-6 levels and improvements in blood viscosity were observed [21]. Additionally, a study combining electroacupuncture with Yinqiao Hongjiang Mixture reported that the combined treatment could downregulate TNF-α, TGF-β1, and MCP-1 levels, and reduce the 3-month recurrence rate to 5.00%, far lower than the 20.00% in the control group [19]. These results indicate that interventions targeting damp-heat latent pathogens should not only aim to expel the pathogen but also improve the local pelvic microenvironment and immune status to reduce long-term recurrence risk.

In summary, the therapeutic strategy for SPID based on the "damp-heat latent pathogen" pathogenesis embodies a dynamic integration of "expelling the pathogen" and "supporting vital qi." During the acute phase or when the pathogen is predominant, the emphasis should be on clearing and expelling damp-heat and promoting blood circulation to resolve stasis, rapidly eliminating the pathogen to halt disease progression. In the remission phase or when deficiency becomes more pronounced, the focus should shift to reinforcing vital qi, whether through benefiting qi, nourishing yin, or warming yang, allowing vital qi to recover so that the latent pathogen has no foothold. This phased, multi-targeted therapeutic strategy offers distinct clinical advantages over antibiotic monotherapy in improving clinical symptoms and reducing recurrence rates.

6. Conclusion

This article has examined the mechanisms of SPID recurrence from the perspective of the damp-heat latent pathogen theory, elucidating the core pathogenesis of "pathogen concealment with vital qi deficiency." The essence of this condition lies in the residual damp-heat pathogen lurking in the membrane source and collateral vessels, which, when triggered by predisposing factors, combines with external pathogens to precipitate recurrence. Modern research indicates that this process is intimately linked to the activation of TGF-β1/Smads and NF-κB pathways by persistent low-grade inflammation, which drives pelvic fibrosis. The fibrotic scar provides the pathological soil for the latent pathogen, establishing a vicious cycle of inflammation–fibrosis–re-injury. Clinical evidence confirms that the therapeutic principles of clearing and expelling latent pathogens while strengthening vital qi can downregulate factors such as TNF-α and TGF-β1, improve the immune microenvironment, and reduce recurrence rates to approximately 5%. However, current limitations include the lack of objective biomarkers for latent pathogens, small sample sizes, and short follow-up periods. Future research should employ systems biology approaches to construct a "latent pathogen–target–formula" association network, providing a more robust framework for TCM-based prevention and management of SPID recurrence.

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