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Immunothrombosis-Related Recurrent Spontaneous Abortion: Mechanisms and Traditional Chinese Medicine Intervention

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Abstract: ***Recurrent spontaneous abortion (RSA) is a perplexing condition affecting couples of reproductive age, with a complex etiology and approximately half of cases remaining unexplained. Recent studies have revealed that the pathogenesis of RSA is not simply isolated immune dysregulation or a prethrombotic state, but rather a deeply intertwined pathological process involving both systems. The concept of "immunothrombosis" provides a novel framework for understanding this coupled mechanism. This review systematically summarizes the mechanisms underlying immunothrombosis in RSA, including immune cell imbalance at the maternal-fetal interface (dNK cells, dMφ, Treg/Th17 imbalance), excessive complement activation, neutrophil extracellular trap (NET) release, anti-β2GPI antibody-mediated immunopathology, and the pivotal role of core signaling pathways such as TLR4/NF-κB. On this basis, we explore the scientific alignment between the traditional Chinese medicine (TCM) pathogenesis of "intertwined heat and blood stasis" and the immunothrombosis theory, and summarize the research progress on TCM herbs and formulas with dual "heat-clearing and blood-activating" effects in intervening in immunothrombosis. Finally, in view of the limitations of current research, we propose that future studies should focus on key pathological links of immunothrombosis and systematically validate the synergistic blocking effects and mechanisms of TCM herbs and formulas with "heat-clearing and blood-activating" properties on the vicious cycle of immune activation and coagulation, thereby providing new insights for the precise prevention and treatment of RSA with TCM.***

Keywords: Recurrent spontaneous abortion, Immunothrombosis, Intertwined heat and blood stasis, Traditional Chinese medicine.

1. Introduction

Recurrent spontaneous abortion (RSA) is generally defined clinically as two or more consecutive spontaneous pregnancy losses with the same partner, affecting approximately 5% of couples of reproductive age worldwide [1]. Its incidence is increasing annually, causing not only severe physical and psychological harm to patients but also imposing a heavy burden on families and society. The etiology of RSA is highly heterogeneous, involving uterine anatomical abnormalities, endocrine disorders, immune dysfunction, prethrombotic state (PTS), and infectious factors [2]. However, the etiology remains unexplained in approximately 50% of cases, posing a significant challenge for precise prevention and treatment. For a long time, immune mechanisms and prethrombotic state have been regarded as two independent etiological factors in RSA. Immune factors mainly manifest as disrupted maternal-fetal immune tolerance, characterized by abnormal activation of immune cells such as natural killer (NK) cells, macrophages, and T cells [3]. In contrast, PTS is characterized by excessive coagulation and defective anticoagulant mechanisms, leading to placental microthrombi formation and resultant embryonic ischemia and hypoxia [4]. Nevertheless, clinical practice has demonstrated that single-target therapies directed solely at immune or coagulation pathways cannot completely improve pregnancy outcomes in all patients, suggesting a profound pathological link between the two [5].

Engelmann and Massberg first proposed the concept of "immunothrombosis," viewing coagulation as an intrinsic effector of the innate immune response and revealing the functional coupling of the immune and coagulation systems at the microcirculatory level [6]. This concept provides a new theoretical framework for understanding the complex relationship between immunity and thrombosis in RSA. At the maternal-fetal interface in RSA, excessive activation of immunothrombosis manifests as aberrant immune cell activation releasing pro-inflammatory cytokines, concurrently triggering the coagulation cascade and forming local microthrombi, ultimately leading to inadequate placental perfusion, trophoblast injury, and embryo loss [2]. Although TCM has a long history of preventing and treating RSA with proven efficacy, the underlying mechanisms have mostly been interpreted from the single perspectives of "reinforcing kidney and consolidating Chong meridian" or "activating blood and resolving stasis," lacking a systematic understanding of the "immune-thrombosis" coupling network. This review aims to systematically summarize the mechanisms of immunothrombosis in RSA, explore its correlation with the TCM pathogenesis of "intertwined heat and blood stasis," and review current research progress on TCM interventions targeting immunothrombosis, so as to provide a theoretical basis and new research directions for the precise TCM treatment of RSA.

2. Epidemiology and Diagnosis of Recurrent Spontaneous Abortion

The epidemiological characteristics of RSA vary depending on the diagnostic criteria applied. The "Chinese Expert Consensus on Clinical Practice of Graded Screening for Etiologies of Recurrent Spontaneous Abortion (2025 Edition)" clearly defines RSA as "two or more consecutive embryonic or fetal losses before 28 weeks of gestation with the same partner, including consecutive biochemical pregnancies" [7]. This criterion reflects the emphasis of Chinese scholars on

early intervention for reproductive health, contrasting with the "three-loss" criterion still used in some international regions. Epidemiological data indicate that RSA affects approximately 5% of couples attempting conception worldwide [1]. A U. S. study based on electronic health records from a large medical center showed that approximately 5-6% of individuals with a history of pregnancy met the diagnostic criteria for RSA, and the median age of patients was significantly higher than that of controls. Notably, age-stratified analysis revealed that many associated etiologies exhibited higher odds ratios in patients aged <35 years, suggesting that younger RSA patients may have a different etiological profile [8]. A prospective cohort study from Denmark also confirmed that the live birth rate is significantly reduced in older RSA patients [9]. In addition to age, the number of previous miscarriages is another important prognostic indicator. International data show that the risk of subsequent miscarriage is 12-20% after one loss, increases to 29% after two losses, and reaches as high as 36% after three losses [10].

3. The Pathological Mechanisms of Immunothrombosis in RSA

The formation of immunothrombosis involves a complex network of multiple immune cells, the complement system, inflammatory cytokines, coagulation factors, and signaling pathways. At the maternal-fetal interface in RSA, these factors interact, forming a vicious cycle of "immune activation -coagulation initiation -sustained amplification of immunothrombosis."

3.1 Immune Cell Imbalance at the Maternal-Fetal Interface

Immune cells at the maternal-fetal interface play a crucial role in maintaining pregnancy. Uterine natural killer (uNK) cells are the most abundant immune cells at this interface and normally maintain pregnancy by inducing local immune tolerance and promoting uterine vascular remodeling [11]. However, in RSA patients, decidual natural killer (dNK) cells become excessively activated, upregulating pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), thereby inhibiting trophoblast function [12]. Decidual macrophages (dMφ) in RSA patients exhibit preferential polarization toward the M1 phenotype, releasing inflammatory mediators like TNF-α and IL-1β, creating an inflammatory microenvironment that suppresses trophoblast invasion [13]. The balance between regulatory T cells (Treg) and T helper 17 (Th17) cells is critical for maintaining maternal-fetal tolerance. An imbalance in the Th17/Treg ratio can induce the recruitment of neutrophils [14], subsequently damaging vascular endothelial cells. Animal experiments have shown that high-dose IFN-γ disrupts maternal-fetal immune balance and promotes abortion by inhibiting the polarization of Treg and Th17 cells [15].

3.2 Excessive Activation of the Complement System

Excessive activation of the complement system is one of the key immunopathological mechanisms in RSA. Clinical studies have demonstrated that plasma levels of C5a and C5b-9 are significantly elevated in patients with pregnancy complications related to antiphospholipid syndrome (APS), and deposition of C4d, C3b, and C5b-9 can be observed in placental tissues [16]. The membrane attack complex (MAC, i.e., C5b-9), as the terminal product of complement activation, can directly insert into the trophoblast cell membrane, causing cellular injury or death [17]. Agostinis et al. found that in C6-deficient rats incapable of forming MAC, neither thrombosis nor fetal loss could be induced, directly demonstrating the central pathogenic role of MAC [18]. Excessive complement activation not only directly damages trophoblasts but also recruits neutrophils and promotes NET release via the C5a-C5aR axis, serving as a critical bridge linking immune recognition to coagulation initiation.

3.3 Neutrophil Extracellular Traps (NETs)

NETs are web-like structures released by neutrophils through a process called NETosis, consisting of a DNA scaffold and granule proteins such as myeloperoxidase (MPO) and neutrophil elastase (ELANE) [19, 20]. Studies have shown that NETs can impair trophoblast proliferation through elastase activity [21]and directly damage trophoblasts and endothelial cells, disrupting placentation and vascular function [22]. Recent mechanistic studies have revealed that NETs can aggravate placental injury by activating BNIP3-mediated mitophagy in trophoblasts, leading to mitochondrial dysfunction, ROS accumulation, and apoptosis [23]. Additionally, mitochondrial ROS released by NETs can induce trophoblast pyroptosis [24]. Regarding coagulation regulation, the histone component of NETs can activate platelets via TLR2 and TLR4 [25], while the DNA scaffold provides a platform for platelet adhesion and aggregation [26, 27]. NETs can also bind and activate coagulation factor XII [28], induce tissue factor (TF) expression, and inhibit the fibrinolytic system [29]. Grossi et al. revealed that β2GPI is present on the surface of NETs and can stimulate CD4+ β2GPI-specific T cells, linking innate and adaptive immunity and creating a sustained positive inflammatory feedback loop [30]. Thus, through their dual "pro-inflammatory and pro-coagulant" activities, NETs serve as a central node connecting immune activation and thrombus formation.

3.4 Anti-β2GPI Antibody-Mediated Immunopathology

Anti-β2GPI antibodies are the core pathogenic antibodies in APS, which is one of the most common treatable causes of RSA [16]. Upon binding to β2GPI on the trophoblast surface, anti-β2GPI antibodies can decrease the synthesis of human chorionic gonadotropin (hCG) and weaken trophoblast invasiveness [31]. They can also enter syncytiotrophoblasts, inducing aberrant cell death [32], and inhibit the proliferation, differentiation, and invasion of extravillous trophoblasts, leading to impaired spiral artery remodeling [33]. Studies have confirmed that anti-β2GPI antibodies can activate the complement system via the classical pathway, inducing C5b-9 deposition [34], and can also activate the alternative pathway by inhibiting complement factor H (CFH) [35]. Furthermore, anti-β2GPI antibodies trigger local placental inflammation through the TLR4/MyD88 pathway [36], and induce trophoblast pyroptosis via the TLR4/NLRP3/GSDMD axis. At the immune cell level, anti-β2GPI antibodies can directly activate dNK cells to produce IFN-γ and TNF-α [37], upregulate tissue factor (TF) expression on monocytes [38], and increase TF expression on the surface of dMφ by

activating the NF-κB signaling pathway [39].

3.5 Core Signaling Pathways and Immune Cell-Platelet Interactions

The TLR4/NF-κB signaling pathway serves as a central hub linking immune recognition to coagulation activation. Various immune stimuli can initiate the downstream NF-κB signaling cascade via TLR4 [40]. Crucially, NF-κB competes with the transcription factors KLF2 and KLF4, which maintain the vascular anticoagulant phenotype, for the common co-activator CBP/p300. When the TLR4/NF-κB pathway is persistently activated, KLF expression is downregulated, leading to the loss of anticoagulant protection and amplification of pro-inflammatory and pro-thrombotic effects [41].

The interaction between immune cells and platelets constitutes a positive feedback mechanism that sustains the amplification of immunothrombosis. NETs can activate platelets and serve as a scaffold to promote platelet adhesion and aggregation; conversely, activated platelets can stimulate neutrophils to undergo NETosis [27], forming a NETs-platelet positive feedback loop. In the decidual microenvironment, activated dMφ, dNK cells, and the imbalanced Th17/Treg ratio collectively participate in this process, creating a vicious cycle of "immune activation → coagulation initiation → further amplification of immunothrombosis. "

4. Understanding of RSA and Immunothrombosis Mechanisms in Traditional Chinese Medicine

4.1 TCM Etiology and Pathogenesis of RSA

Recurrent spontaneous abortion falls under the TCM categories of "habitual miscarriage" (hua tai) and "repeated fetal loss" (shu duo tai). Zhang Jingyue of the Ming Dynasty stated in Jingyue Quanshu: Furen Gui: "In all cases of repeated miscarriage during pregnancy, it must be due to deficiency and depletion of qi and vessels." Modern TCM holds that the core pathogenesis of habitual miscarriage is injury to the Chong and Ren meridians, leading to an unconsolidated fetal origin. Specifically, this can be summarized as: kidney deficiency and unconsolidated Chong and Ren as the root, causing the fetus to lose its anchor; blood stasis obstructing the uterus as the branch, depriving the fetus of nourishment; combined with disharmony of qi and blood and liver constraint disturbing the Chong meridian. These four factors interact to cause repeated conception followed by repeated loss.

4.2 Alignment of "Intertwined Heat and Blood Stasis" Pathogenesis with Immunothrombosis

The core feature of immunothrombosis is immune activation as the initiating factor and the coagulation system as the effector, forming a pathological positive feedback loop at the microcirculatory level. This process aligns remarkably well with the TCM pathogenesis of "intertwined heat and blood stasis." The Suwen: Zhizhenyao Dalun states: "All conditions characterized by swelling, pain, soreness, and fright belong to fire." The inflammatory response triggered by immune activation exhibits pathological features consistent with the concept of "heat." The immune-inflammatory cascade initiated at the maternal-fetal interface and placenta is a microscopic manifestation of "heat generated internally." Ye Tianshi's Wenre Lun points out: "When heat enters the blood aspect, one must fear consumption of blood and stirring of blood, and directly cool the blood and disperse stasis." Here, "heat entering the blood aspect" reveals the critical pathogenesis wherein heat pathogen directly disturbs blood circulation, which aligns closely with the modern medical understanding of "inflammation triggering coagulation. "

In the context of immunothrombosis, "heat pathogen blazes and scorches, refining blood into stasis; static blood accumulates internally, stagnating and generating heat," with the two acting as both cause and effect, forming a vicious cycle. Applying this pathogenesis to RSA, it can be summarized as "intertwined heat and blood stasis damaging the fetal origin." The series of inflammatory responses triggered by immune activation represent "heat generated internally, blazing and scorching the blood aspect," while the destruction of the internal environment and the generation of coagulation activity caused by this inflammatory response are a modern interpretation of "heat scorching ying-nutrient and yin, refining blood into stasis." The interaction between immunity and thrombosis creates a pathological state of "intertwined heat and blood stasis, congealing in the uterus," obstructing the uterine collaterals, depriving the fetus of nourishment, and ultimately leading to the pathological chain of "heat-stasis-thrombosis-fetal malnourishment- miscarriage. "

5. Research Progress on TCM Intervention in Immunothrombosis

5.1 Single Herbs and Their Active Components

Many TCM herbs with the dual functions of clearing heat and resolving toxins as well as activating blood and resolving stasis have active components that show potential for simultaneously intervening in both immune activation and coagulation initiation.

Chishao (Paeoniae Radix Rubra) is a classic heat-clearing, blood-cooling, stasis-dispersing, and pain-relieving herb. Paeoniflorin, a component of total paeony glycoside (TPG), can inhibit the upregulation of pro-inflammatory mediators TNF-α and IL-1β, and suppress the activation of JNK and p38 MAPK [42-44]. Simultaneously, TPG can significantly reduce platelet aggregation, prolong prothrombin time, and decrease whole blood viscosity, thereby reducing thrombus formation [45].

Huangqin (Scutellariae Radix), a key herb for clearing heat and calming the fetus, contains the active component baicalin, which has been shown to exert both anti-inflammatory (reducing Hs-CRP and IL-6) and anticoagulant (prolonging APTT and reducing fibrinogen) effects [46]. Baizhu (Atractylodis Macrocephalae Rhizoma) can block the TLR4/NF-κB pathway by regulating multiple signaling cascades including TNF, IL-17, and PI3K-Akt, thereby reducing the release of pro-inflammatory cytokines such as

TNF-α and IL-6 [47]; Concurrently, it inhibits the phosphorylation of MAPK and PI3K-Akt pathways within platelets, significantly reducing platelet aggregation capacity.

The active component tetramethylpyrazine in Chuanxiong (Chuanxiong Rhizoma) can inhibit platelet aggregation while also possessing immunomodulatory effects [48]. Studies have shown that tetramethylpyrazine can downregulate the transcription factor GATA-3 and upregulate T-bet, thereby correcting Th2 dominance and restoring Th1/Th2 cytokine balance, as well as reducing infiltration of neutrophils and other inflammatory cells [49]. Its antiplatelet activity is achieved by blocking the phosphorylation of MAPK and PI3K-Akt signaling pathways within platelets [48].

Paeonol can ameliorate inflammatory responses by inhibiting pathways such as TLR4/NF-κB [50]and MAPKs, suppress TNF-α-induced endothelial cell adhesion function [51], and synergistically inhibit platelet aggregation with clopidogrel [52]. Danggui (Angelicae Sinensis Radix) and its active components (Angelica polysaccharide, ferulic acid, etc.) exert simultaneous intervention on both immune inflammation and the coagulation system through a network of multi-target, multi-pathway regulation [53]. In a rat model of lipopolysaccharide-induced gestational thrombophilia, Angelica polysaccharide was shown to significantly reduce serum IL-6 and TNF-α levels while reversing abnormal elevations in TF, D-dimer, and fibrinogen and the decrease in antithrombin-III, thereby reducing thrombus formation [54].

5.2 TCM Compound Formulas

Among compound formulas adhering to the principle of "simultaneously treating heat and stasis," kidney-tonifying and blood-activating formulas have been the most extensively studied. Ge et al. systematically reviewed the mechanisms of kidney-tonifying and blood-activating formulas in treating APS-related RSA, noting that they exert therapeutic effects through four pathways: regulating immunity, modulating coagulation function, improving vascular endothelial function, and enhancing endometrial receptivity [55]. Clinical studies have confirmed that Fuyuan Huoxue Gushen Decoction significantly downregulates peripheral blood TLR4/MyD88 mRNA expression in APS-related RSA patients, suppresses inflammatory responses, reduces platelet aggregation rate, prolongs APTT, and decreases ICAM-1 and VCAM-1 levels [56]. Basic research on the kidney-tonifying and blood-activating formula has also shown that it can activate the PI3K/AKT/HIF-1α/VEGF pathway and improve the prethrombotic state in a mouse model of RSA [57]. Furthermore, formulas such as Huoxue Jiedu Decoction, based on the theory of "stasis-toxin intermingling, " have demonstrated effects in regulating the PI3K/Akt/NF-κB inflammatory signaling pathway, reducing M1 macrophage infiltration, and downregulating the expression of pro-inflammatory cytokines such as TNF-α and IL-6 in the treatment of deep vein thrombosis [58], providing potential research avenues for the "simultaneous treatment of heat and stasis" approach in RSA.

6. Existing Problems and Development Trends

Although the immunothrombosis theory offers a new perspective for understanding the complex mechanisms of RSA and preliminary progress has been made in TCM intervention research, several issues remain to be addressed. First, current Western medical treatments for RSA are largely based on a "target-blockade" strategy directed at a single etiology, such as anticoagulation or immunomodulation. However, clinical practice reveals that anticoagulation or immunotherapy alone cannot completely improve pregnancy outcomes in all patients, indicating that RSA fundamentally involves a deeply coupled pathological process of immune activation and coagulation. Although existing mechanistic research has delved into individual pathways such as NETs, complement, and TLR4/NF-κB, it largely focuses on isolated links and lacks systematic integration of the "immune-thrombosis" positive feedback network [2]. Second, regarding TCM mechanistic research, although some herbs have been shown to possess individual anti-inflammatory (heat-clearing) or anticoagulant (blood-activating) effects, systematic screening targeting the integrative target of "immunothrombosis" remains largely unexplored. Research on many herbs with dual heat-clearing, detoxifying, and blood-activating, stasis-resolving properties and their active components in the context of RSA is still needed. Furthermore, existing studies often verify the "heat-clearing" or "blood-activating" effects of TCM separately, failing to systematically elucidate how they simultaneously intervene in multiple key nodes such as NET formation, complement activation, and platelet-neutrophil interactions to achieve synergistic blockade of the "immune-thrombosis" positive feedback loop.

In this context, it is imperative to adopt an integrative medical perspective to systematically analyze the core nodes and dynamic interaction patterns of the "immune-thrombosis" coupling network at the maternal-fetal interface in RSA patients. Future research should focus on key immunothrombosis links such as NET formation, complement activation, and platelet-neutrophil interactions, and delve deeper into the synergistic regulatory mechanisms of TCM herbs and formulas with dual "heat-clearing and blood-activating" effects on these links. By establishing animal and cellular models that can simulate the pathological state of "intertwined heat and blood stasis," combined with multi-parameter dynamic monitoring and key signaling pathway intervention validation, the blocking effects of TCM on the vicious cycle of "immune activation-coagulation initiation-thrombus amplification" can be systematically evaluated. This research paradigm will help elucidate the modern scientific connotation of the "intertwined heat and blood stasis" pathogenesis from a holistic perspective and provide direct experimental evidence for screening and optimizing TCM intervention strategies for RSA.

7. Summary and Outlook

In summary, the pathogenesis of recurrent spontaneous abortion is a complex pathological process involving the deep coupling of immune activation and coagulation initiation. The concept of "immunothrombosis" provides an integrative framework for understanding this process. Immune cell imbalance at the maternal-fetal interface, excessive complement activation, NET release, anti-β2GPI antibody-mediated immunopathology, and core signaling pathways

such as TLR4/NF-κB collectively constitute the molecular network of immunothrombosis, forming a vicious cycle of "immune activation-coagulation initiation-sustained amplification of immunothrombosis." This mechanism aligns remarkably well with the TCM pathogenesis of "intertwined heat and blood stasis," providing a modern scientific interpretation for the "heat-clearing and blood-activating" approach to treating RSA.

Currently, single TCM herbs and compound formulas with dual "heat-clearing and blood-activating" properties show great potential in intervening in immunothrombosis. However, existing research is often fragmented and lacks a systematic analysis of the "immune-thrombosis" coupling network. Future research should take key pathological links of immunothrombosis (such as NET release, trophoblast pyroptosis, excessive complement activation, and abnormal platelet activation) as entry points, and systematically validate the synergistic regulatory effects of TCM herbs and active components with dual "heat-clearing and blood-activating" properties on these links, with emphasis on elucidating their molecular mechanisms in disrupting the "immune-thrombosis" vicious cycle through the regulation of core signaling pathways such as TLR4/NF-κB and PI3K/Akt. Ultimately, combined with rigorously designed clinical studies and high-quality evidence-based data, we aim to advance TCM from traditional empirical practice toward precision-based mechanistic understanding, gradually establishing a new diagnostic and therapeutic framework targeting immunothrombosis-related RSA that reflects the precise correlation of "disease-syndrome-formula-efficacy."

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