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Research Advances on Chinese Herbal Enema for Thin Endometrial Receptivity Based on the Theory of "Chong Meridian as the Sea of Blood"

Hooi Ying OY YONG, Qian ZENG*

Affiliated Hospital of Chengdu University of TCM, Chengdu 610072, Sichuan, China
Correspondence Author

Abstract: ***Thin endometrium (TE) is one of the key factors leading to impaired endometrial receptivity (ER) and failure of assisted reproductive technology (ART). The theory of "Chong Meridian as the Sea of Blood" is a core concept in traditional Chinese medicine (TCM) reproductive health, which posits that deficiency of the Chong Meridian and insufficiency of the Sea of Blood are the central pathological mechanisms underlying TE. As an external treatment method in TCM, Chinese herbal retention enema allows herbal components to be absorbed via the rectum and directly delivered to the pelvic cavity and uterus. This approach offers unique advantages in promoting blood circulation, removing stasis, tonifying the kidney and essence, and regulating the Chong and Ren Meridians. Modern research suggests that this therapy may comprehensively improve ER through multiple pathways and targets, including enhancing endometrial blood perfusion, promoting angiogenesis, regulating sex hormone receptor expression, and exerting anti-inflammatory and immunomodulatory effects. This article systematically reviews the theoretical basis and modern mechanistic research progress on Chinese herbal enema for TE under the guidance of the "Chong Meridian as the Sea of Blood" theory, aiming to provide new insights and a theoretical foundation for clinical practice.***

Keywords: Chong Meridian as the Sea of Blood, Thin endometrium, Endometrial receptivity, Chinese herbal enema, Integrated traditional Chinese and Western medicine**.**

1. Introduction

With the rising incidence of infertility and the trend of delayed childbearing, the demand for assisted reproductive technology (ART) continues to grow. However, the clinical pregnancy rate remains around 40% [1]. Embryo quality and endometrial receptivity (ER) are two critical factors determining the success of assisted reproductive technology (ART), with endometrial factors accounting for over 60% of implantation failures. ER refers to the state of the endometrium during a specific period known as the "window of implantation", when it allows embryo positioning, adhesion, invasion, and successful bidirectional communication. A thin endometrium has been widely recognized as a key cause of infertility, recurrent miscarriage, and placental abnormalities. Modern medicine often employs high-dose estrogen, vasodilators, intrauterine perfusion of granulocyte colony-stimulating factor (G-CSF), or human chorionic gonadotropin (HCG) to address this issue. However, treatment efficacy varies significantly among individuals, and standardized protocols are lacking [2]. Although traditional Chinese medicine (TCM) does not explicitly use the term "endometrial receptivity", its understanding has long been embedded within theories of "menstruation" and "reproduction". The concept of "Chong Mai as the Sea of Blood", originating from The Yellow Emperor's Classic of Internal Medicine, is central to explaining menstrual and reproductive physiology. According to this theory, a robust Chong Mai and a full Sea of Blood ensure regular menstruation and fertility. Thin endometrium can be categorized under TCM patterns such as "scanty menstruation" and "infertility".

Its core pathogenesis involves kidney essence deficiency, dysfunction of the Chong and Ren Meridians, and insufficiency of the Sea of Blood, often accompanied by blood stasis. These factors lead to inadequate nourishment of the uterus, resulting in failure to sustain pregnancy.

Chinese herbal enema therapy, a quintessential external treatment in TCM, leverages its advantage of "acting locally and targeting the affected site directly" and is widely used in gynecological pelvic disorders. Meanwhile, the gut microbiota, regarded as the "second genome", communicates with distant organs through immune, metabolic, and neuroendocrine pathways—a concept known as the "gut-X axis", which has become a cutting-edge area in life sciences. Emerging evidence suggests that dysbiosis of the gut microbiota is associated with female reproductive disorders, particularly impaired endometrial receptivity, giving rise to the "gut-uterine axis" hypothesis. This article aims to explore the theoretical foundations of Chinese herbal enema in improving thin endometrium and ER from the perspective of the "Chong Mai as the Sea of Blood" theory, while elucidating its modern mechanisms of action to provide academic support for clinical application.

2. The Theory of "Chong Meridian as the Sea of Blood" and the TCM Perspective on Thin Endometrial Receptivity

2.1 Theoretical Connotation of "Chong Meridian as the Sea of Blood"

The Chong Meridian, also known as the "Sea of Blood", is regarded as the "sea of the twelve regular meridians" for its role in regulating qi and blood throughout the meridian

system. As stated in Su Wen · Shang Gu Tian Zhen Lun (Plain Questions · Ancient Ideas on Innate Truth): At the age of fourteen, the Tiān Guǐ (reproductive essence) arrives, the Rèn Meridian becomes free-flowing, and the Tài Chōng Meridian becomes abundant; then menstruation begins regularly, thus enabling pregnancy".

This passage clearly emphasizes the direct correlation between the abundance or decline of the Chong Meridian and menstrual and reproductive functions. Originating from the uterus, the Chong Meridian shares a common source with the Ren Meridian. Along its pathway, it extensively connects with organs such as the liver, kidney, and stomach, gathering both innate essence and acquired essence derived from food and water. Together, these nourish the uterus. The cyclical proliferation and shedding of the endometrium are considered a direct reflection of the periodic "filling" and "emptying" of the "Sea of Blood" [3].

2.2 Thin Endometrium from the Perspective of "Insufficiency of the Sea of Blood"

The fundamental pathogenesis of thin endometrium (TE) in traditional Chinese medicine (TCM) lies in the insufficiency of the Sea of Blood, which can be specifically categorized into the following patterns:

(1) Kidney Deficiency and Essence Depletion: The kidney governs reproduction and stores essence, which can transform into blood. Congenital inadequacy or excessive sexual activity may impair the kidney, leading to deficiency of kidney essence. This results in failure to transform essence into blood, leaving the Sea of Blood without sufficient source for replenishment, and thus preventing endometrial growth.

(2) Qi and Blood Deficiency: The spleen and stomach are the sources of qi and blood generation. If the production of qi and blood is insufficient, the Chong and Ren Meridians will lack nourishment, causing the Sea of Blood to remain deficient and the uterus to be inadequately nourished.

(3) Blood Stasis Obstructing the Uterus: Multiple intrauterine procedures, pelvic inflammatory conditions, or emotional distress can lead to blood stasis. This obstructs the Chong and Ren Meridians as well as the uterine collaterals, hindering the arrival of fresh blood to the uterus while allowing stagnant blood to accumulate—a condition described as "blood stasis occupying the Sea of Blood". This impedes endometrial proliferation.

These mechanisms coincide with those recognized in modern medicine—such as intrauterine adhesions (IUA), uterine fibroids, and endometritis—which are known to contribute to decreased endometrial receptivity (ER) [4].

3. Advances in Western Medical Research on Endometrial Receptivity

3.1 Factors Influencing Endometrial Receptivity in Western Medicine

Endometrial receptivity (ER) refers to a specific state of the endometrium during the "window of implantation" when it permits embryo positioning, adhesion, invasion, and ultimately successful implantation. The achievement of this process relies on the precise coordination of morphological structure, molecular biological microenvironment, and immune status of the endometrium. Modern medical research indicates that any factor disrupting this delicate balance can directly or indirectly lead to impaired ER, thereby becoming a critical cause of embryo implantation failure and female infertility. These influencing factors can be systematically categorized into three major classes: abnormal uterine anatomical structure, pelvic pathologies and inflammatory microenvironment, as well as endocrine and iatrogenic factors [5].

First, abnormal intrauterine anatomy is one of the most direct factors impairing ER. Uterine fibroids—particularly submucosal fibroids and intramural fibroids encroaching on the endometrial cavity—not only physically occupy uterine space and disrupt endometrial integrity but also interfere with ER by altering the local microenvironment. Studies have shown that such fibroids can reduce the expression of key endometrial receptivity markers such as Homeobox A10 (HOXA10) and E-cadherin, thereby impairing the dialogue between the embryo and the endometrium [6].

Furthermore, even non-cavity-distorting intramural fibroids may adversely affect pregnancy outcomes by interfering with endometrial decidualization and increasing apoptosis. A meta-analysis demonstrated that they significantly reduce live birth rates (RR = 0.79) and clinical pregnancy rates (RR = 0.85) in IVF [7]. Additionally, endometrial polyps (EP), as common benign lesions, impair ER through both mechanical and biochemical pathways—by occupying space, triggering chronic inflammation (e.g., upregulated NF-κB expression), and reducing the expression of critical receptivity markers such as IGFBP-1 and HOXA10. Intrauterine adhesions (IUA), a serious consequence of abnormal repair following damage to the endometrial basal layer, lead to endometrial fibrosis, gland reduction, impaired angiogenesis (e.g., aberrant VEGF expression), and resultant uterine cavity narrowing or occlusion, severely disrupting the structural and functional basis of ER [8]. Although hysteroscopic surgery remains the primary approach for restoring uterine anatomy, complete recovery of ER post-operation remains challenging and often requires adjuvant therapies such as estrogen to facilitate endometrial repair [9].

Secondly, pelvic disorders and a persistent inflammatory microenvironment represent another major dimension affecting ER. Endometriosis (EMs) and adenomyosis are typical examples. Although some controversy exists, most studies suggest that the chronic inflammatory state, progesterone resistance, impaired decidualization, and dysregulated expression of key molecules such as LIF and its receptor in EMs collectively contribute to a "defective endometrium," thereby reducing ER [2]. Adenomyosis, characterized by the invasion of endometrial tissue into the myometrium accompanied by an inflammatory response, may negatively impact ER through similar mechanisms. A meta-analysis indicated that it significantly lowers clinical pregnancy rates in IVF/ICSI (RR = 0.71) [10]. On the other hand, hydrosalpinx impairs embryo implantation through the reflux of fluid into the uterine cavity, which not only

mechanically flushes the endometrium but also directly exposes endometrial tissue to inflammatory cytokines (e.g., TNF-α, IL-2) and toxic substances. This process downregulates receptivity-related gene expression via activation of the NF-κB/miR-133b/SGK1/HOXA10 signaling pathway, ultimately leading to a substantial decline in implantation rates [10].

3.2 Western Medical Treatments for Endometrial Receptivity

Various therapeutic strategies for thin endometrium (TE) aim to improve endometrial thickness (EMT) and receptivity, thereby enhancing the success rate of assisted reproductive technology (ART). Current treatments can be broadly categorized into the following classes: pharmacological therapy, regenerative medicine, intrauterine perfusion therapy, and complementary and alternative medicine (CAM).

Pharmacological therapy serves as a foundational approach. Endocrine treatment seeks to mimic or enhance physiological hormonal support, including the use of estrogen to directly promote endometrial cell proliferation; growth hormone (GH) to improve endometrial quality by increasing blood perfusion and upregulating receptivity-related gene expression; and human chorionic gonadotropin (hCG) administered via intrauterine perfusion to upregulate key implantation factors such as VEGF and LIF. Gonadotropin-releasing hormone agonists (GnRH-a) are used to modulate the endogenous hormonal environment and enhance endometrial responsiveness to estrogen. Additionally, vasoactive agents such as low-dose aspirin, sildenafil, and vitamin E work through mechanisms such anticoagulation, vasodilation, and antioxidation to improve uterine arterial blood flow and endometrial microcirculation.

Regenerative medicine represents a cutting-edge direction. Stem cell therapy—utilizing mesenchymal stem cells derived from bone marrow, adipose tissue, menstrual blood, or umbilical cord—holds promise for repairing damaged endometrial tissue through their strong differentiation potential and paracrine effects, promoting angiogenesis, reducing fibrosis, and fundamentally regenerating the endometrium. Their cell-free derivatives, exosomes, which act as key mediators of intercellular communication, also demonstrate significant potential in promoting endometrial repair and regeneration while avoiding risks associated with cell transplantation.

Intrauterine perfusion therapy offers a localized interventional approach. Granulocyte colony-stimulating factor (G-CSF) infusion stimulates endometrial proliferation and neovascularization, while autologous platelet-rich plasma (PRP) intrauterine perfusion releases high concentrations of various growth factors (e.g., VEGF, PDGF, EGF), strongly promoting endometrial cell proliferation, migration, and tissue repair [11].

4. Regulation of the “Sea of Blood” by Chinese Herbal Enema to Improve Endometrial Receptivity: Advantages and Mechanisms

4.1 Theoretical Basis of Enema Therapy in Traditional Chinese Medicine

The rectum (also referred to as the “Po Men” or “Soul Gate” in TCM) is considered a “hollow Organ that discharges without storing”. It is richly vascularized and closely adjacent to pelvic organs (uterus and adnexa), sharing extensive vascular and lymphatic networks. After rectal mucosal absorption, herbal compounds bypass the hepatic first-pass effect, directly reaching the affected site (i.e., the “Sea of Blood” and uterus) via the pelvic vascular plexus. This results in highly concentrated drug delivery, making it particularly effective for promoting blood circulation, resolving stasis, eliminating masses, clearing heat, and removing toxins. Its unique advantage lies in addressing pelvic pathologies characterized by blood stasis and heat, which aligns perfectly with the core pathogenesis of TE: insufficiency of the Sea of Blood accompanied by stasis obstruction in the uterine collaterals [12].

Chinese herbal enema therapy, also known as “rectal herbal administration” or “Dao Fa”, is a significant external treatment modality in TCM with a profound theoretical foundation and distinctive mechanisms of action [13]. According to TCM theory, the rectum and anus (“Po Men”) serve as the “envoy of the five zang organs”, responsible for discharging waste and functioning as an organ that “discharges without storing”. Due to its connection with the spleen, stomach, and intestines—collectively forming the pathway for transporting and transforming food and waste—it can absorb medicinal substances and regulate visceral functions. The core principles underpinning this method are “where the meridians pass, the treatment reaches” and “treating the affected area directly via the nearest accessible point” [13].

Anatomically, the rectum is located in the lower Jiao and is richly supplied with collateral vessels. It lies in close proximity to the uterus and adnexa (conceptualized as the “Uterus” and “Uterine Collaterals” in TCM), sharing pelvic vascular plexuses (such as the middle and inferior rectal venous plexuses and the uterovaginal venous plexus) and lymphatic networks, forming an interconnected communication system [10]. Drug absorption through the rectal mucosa effectively bypasses the hepatic first-pass effect, significantly enhancing bioavailability. Medicinal effects rapidly penetrate the intestinal wall into the pelvic venous plexus, acting with precision and speed on the “Sea of Blood” and uterus—akin to a “high-speed pathway”—achieving the TCM ideal of “medicine reaching the affected site with strong and specialized efficacy” [14].

Based on this physiological and pathological understanding, enema therapy demonstrates unique advantages in gynecological applications, particularly for pelvic disorders. Its concentrated therapeutic action is especially suited to countering the core pathological factors of stasis and heat. To address stasis, enema formulations often include herbs such as Salvia miltiorrhiza (Dan Shen), Paeonia lactiflora (Chi Shao), Prunus persica (Tao Ren), and Sargentodoxa cuneata (Hong Teng) to vigorously promote pelvic blood circulation, release adhesions, and dissipate masses. For heat, herbs like Patrinia scabiosifolia (Bai Jiang Cao), Taraxacum mongolicum (Pu Gong Ying), and Phellodendron amurense (Huang Bai) are

commonly used to directly suppress pelvic inflammation and clear damp-heat and toxins [15].

4.2 Modern Pharmacological Mechanisms of Chinese Herbal Enema in Improving Endometrial Receptivity (ER)

4.2.1 Improving Endometrial Blood Perfusion

Herbs that activate blood circulation and resolve stasis (e.g., Salvia miltiorrhiza, Ligusticum chuanxiong, Paeonia lactiflora) are commonly used in enema formulations. Studies have shown that they can dilate blood vessels and reduce the uterine artery resistance index (RI) and pulsatility index (PI). This mechanism is similar to that of Western drugs such as aspirin and sildenafil — enhancing blood flow in the uterine spiral arteries to provide sufficient oxygen and nutrients for endometrial growth [16].

4.2.2 Promoting Angiogenesis and Repair

To address impaired angiogenesis caused by conditions such as intrauterine adhesions (IUA) and endometriosis (EMs), kidney-tonifying and blood-activating herbs have been shown to upregulate the expression of vascular endothelial growth factor (VEGF). This promotes the formation of new blood vessels in the endometrium, thereby improving endometrial blood supply and thickness, and facilitating the repair of damaged endometrial tissue [9].

4.2.3 Regulating Sex Hormones and Their Receptors

In addressing endocrine disturbances induced by controlled ovarian hyperstimulation (COH), kidney-tonifying and essence-replenishing herbs (such as Cuscuta chinensis, Epimedium brevicornum, and Placenta hominis) may modulate the expression of estrogen receptors (ER) and progesterone receptors (PR) in the endometrium. This enhances the endometrial responsiveness to circulating sex hormones, corrects hormonal imbalances, and promotes the proliferation and transformation of endometrial cells [17].

4.2.4 Anti-inflammatory and Immunomodulatory Effects

To counteract the inflammatory microenvironment associated with conditions such as endometriosis (EMs), hydrosalpinx, and endometritis, enema administration of heat-clearing, detoxifying, blood-activating, and stasis-resolving herbs (e.g., Sargentodoxa cuneata, Patrinia scabiosifolia, Salvia miltiorrhiza) can alleviate chronic intrauterine and pelvic inflammation. This therapy reduces levels of inflammatory factors such as TNF-α, modulates immune cell function, and fosters an immune microenvironment conducive to embryo implantation [18].

5. Conclusion

The analysis presented in this study demonstrates that Chinese herbal enema therapy, guided by the theory of "Chong Meridian as the Sea of Blood," exhibits promising potential for improving thin endometrium (TE) and enhancing endometrial receptivity (ER). Although there is still a lack of large-scale, multicenter randomized controlled trials (RCTs) providing high-level evidence-based medical support, existing clinical observations and case reports consistently indicate that Chinese herbal enema, as an adjunctive treatment, is particularly beneficial for patients with repeated implantation failure (RIF) or those presenting with pelvic blood stasis and heat patterns (such as endometriosis or chronic pelvic inflammatory disease). It effectively increases endometrial thickness, improves uterine blood perfusion, and enhances clinical pregnancy rates.

Commonly used enema formulations predominantly follow the therapeutic principles of "tonifying the kidney and replenishing essence" and "activating blood circulation and resolving stasis", as exemplified by prescriptions such as Shao Fu Zhu Yu Tang (Lower Abdomen Stasis-Expelling Decoction) and customized kidney-tonifying and blood-activating formulas. These approaches not only align with the TCM theoretical essence that "the Chong Meridian serves as the Sea of Blood and governs reproduction", but also leverage local rectal administration to achieve targeted drug delivery, avoid hepatic first-pass effects, and significantly enhance bioavailability.

This therapy not only macroscopically addresses conditions such as "insufficiency of the Sea of Blood" and "stasis obstruction in the uterine collaterals", but also exerts multifaceted regulatory effects at the microscopic level by promoting angiogenesis, suppressing inflammatory responses, modulating the immune microenvironment, and regulating the expression of receptivity-related molecular markers. These mechanisms collectively reflect its multi-pathway, multi-target integrative action.

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