

# Research Progress on the Mechanism of Acupuncture in Treating Dysmenorrhea Caused by Endometriosis

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**Abstract:** *The incidence of endometriosis (EMS) has increased significantly in recent years. As a common gynecological disease, its incidence rate among women of reproductive age can reach 10%-15% and shows a gradual upward trend. Dysmenorrhea is the most typical clinical manifestation of endometriosis; recurrent and progressive pain seriously affects women's health and quality of life. Western medicine mainly relies on non-steroidal anti-inflammatory drugs, which have significant side effects. In contrast, there have been numerous studies on acupuncture for treating EMS-related dysmenorrhea, with remarkable efficacy. This article summarizes the clinical applications and relevant mechanisms of acupuncture, aiming to provide a reference for the promotion of acupuncture in the treatment of EMS-related dysmenorrhea.*

**Keywords:** Acupuncture, Endometriosis, Dysmenorrhea, Relevant Mechanisms, Review.

## 1. Introduction

Endometriosis (EMS) refers to the implantation and growth of active endometrial tissue in parts other than the uterine body. It is a common chronic inflammatory endometrial disease and tumor-like disease in the field of gynecology [1]. Its main clinical features include progressive dysmenorrhea, infertility, and pelvic masses, with an increasing incidence rate year by year [2]. Research data show that more than 80% of EMS patients have pain symptoms [3]. Although EMS is a benign disease, it is prone to recurrence, which seriously affects women's work and quality of life. In recent years, EMS has been a hot topic in medical research. The pathogenesis of EMS in Western medicine remains unclear, and the main theories include the implantation theory, coelomic metaplasia theory, and induction theory. In addition, it may be related to factors such as genetics, immunity, and inflammation [4]. Studies have shown that dysmenorrhea caused by EMS is associated with the production of inflammatory factors, such as prostaglandins, vascular endothelial growth factor, tumor necrosis factor, and nerve growth factor [5,6]. This article reviews the relevant mechanisms of acupuncture in treating EMS-related dysmenorrhea.

## 2. The mechanism of acupuncture in the treatment of dysmenorrhea caused by endometriosis

### 2.1 Regulation of Immune Inflammatory Factors by Acupuncture

#### 2.1.1 Tumor Necrosis Factor

Qi Z Y et al. [7] found that tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is involved in neuropathic and mechanical pain; the higher its content in the body, the more severe the pain response, which is positively correlated with the severity of the disease. At the same time, it is one of the vasoactive factors; high concentrations of TNF- $\alpha$  can induce neovascularization,

accelerate the growth rate of ectopic endometrium, and eventually lead to the formation of ectopic lesions.

Li P L et al. [8] explored the efficacy and mechanism of traditional Chinese medicine (TCM) combined with acupoint catgut embedding and gestrinone in the treatment of dysmenorrhea caused by EMS of damp-heat stagnation and blood stasis type. The conclusion showed that this combined therapy had a significant effect on dysmenorrhea caused by EMS of damp-heat stagnation and blood stasis type, and inhibiting the serum TNF- $\alpha$  level might be its mechanism of action.

#### 2.1.2 Interleukins

Interleukin-6 (IL-6) can promote the proliferation and activation of lymphocytes, cause autoimmune inflammatory damage, and also induce the proliferation of endometrial epithelial cells and epithelial-mesenchymal transition, thereby promoting the invasion of ectopic endometrial cells [9]. Research evidence shows that factors such as IL-6 can induce pain, and their contents in the peritoneal fluid, blood, and ectopic lesions of EMS patients are significantly different from those in normal people. Interleukin-32 (IL-32) can not only induce T cell apoptosis but also promote the release of other inflammatory mediators. Among them, the induction of PGE2 release is the most prominent feature of IL-32. It can stimulate the metabolism of arachidonic acid in peripheral blood cells and participate in regulating the normal function of natural killer cells. Abnormal function of natural killer cells is related to the dysregulation of IL-32 [10].

He M R et al. [11] conducted a clinical observation on acupuncture combined with Tongbin in the treatment of dysmenorrhea caused by EMS of cold coagulation and blood stasis type, and detected changes in serum IL-6 and interferon- $\alpha$  (INF- $\alpha$ ). The results showed that electroacupuncture could effectively down-regulate the expression levels of IL-6 and INF- $\alpha$  in peripheral serum, thereby effectively improving dysmenorrhea in EMS patients

of cold coagulation and blood stasis type.

Sun K F et al. [12] observed the effects of electroacupuncture combined with Tongbining on the expression levels of serum inflammatory mediators (IL-32 and PGE2) in EMS patients with dysmenorrhea. After treatment, the conclusion was drawn that electroacupuncture combined with Tongbining could have a positive impact on the expression levels of serum IL-32 and PGE2 in EMS patients with dysmenorrhea.

## 2.2 Regulation of Estrogen by Acupuncture and Moxibustion

In terms of pathogenic nature, endometriosis is an estrogen-dependent disease. There is an increase in local estrogen receptor expression in ectopic endometrium, and the increase in local estrogen levels can stimulate the growth of ectopic endometrium. One of the pathogenic mechanisms of EMS is mediated by various enzymes involved in estrogen metabolism, as well as estrogen receptors, progesterone receptors, and their related gene polymorphisms [13].

Yan Hong et al. [14] used acupuncture and moxibustion to treat adenomyosis and observed and compared estrogen levels before and after acupuncture and moxibustion treatment. The results showed that estrogen levels decreased. The decrease in estradiol secretion may be due to acupuncture reducing the sensitivity of target cells in the uterus to estrogen.

## 2.3 Regulation of Nerve Growth Factors by Acupuncture and Moxibustion

Recent studies have found that NGF and BDNF can activate the mitogen-activated protein kinase (MAPK) signaling pathway after binding to their receptors. Currently, more and more evidence shows that the degree of dysmenorrhea in EMT patients is related to the density of nerve fiber distribution [15,16]. NGF is a nerve growth factor that plays an important role in regulating peripheral pain. It can promote the formation of neuropeptide substance P to increase local nerve fiber tissue in lesions and induce uterine contraction to cause dysmenorrhea.

Shen Guilin et al. [17] observed the clinical efficacy of warm acupuncture and moxibustion combined with Wenjing Decoction in the treatment of dysmenorrhea associated with endometriosis. The study concluded that the warm acupuncture and moxibustion group could significantly reduce serum NGF and ICAM-I and improve hemodynamics. Su Jiaru et al. [18] studied the efficacy of Zhentong Xiaozheng Formula combined with moxibustion in the treatment of dysmenorrhea associated with endometriosis and its effect on pain-related factors. The study concluded that Zhentong Xiaozheng Formula combined with moxibustion can regulate NGF secretion and improve the efficacy of endometriosis.

## 2.4 Inhibition of Angiogenesis by Acupuncture

Angiogenesis plays an irreplaceable role in the occurrence and development of EMS. This process is affected by the joint participation of multiple signaling pathways, among which the vascular endothelial growth factor (VEGF)/VEGF

receptor (VEGFR) signaling pathway is the most important. The high expression of VEGF also endows the ectopic endometrium with a strong ability of angiogenesis, ensuring the survival of the ectopic endometrium, leading to continuous bleeding, congestion, and edema. The accumulation of blood stasis in the abdominal cavity causes symptoms such as pelvic pain, progressive dysmenorrhea, infertility, and menstrual abnormalities [19].

Sun K F et al. [20] observed the effects of acupuncture on dysmenorrhea and serum levels of VEGF and matrix metalloproteinase-9 (MMP-9) in EMS patients, thereby exploring the role and possible mechanism of acupuncture in the treatment of EMS-related dysmenorrhea. The study found that the occurrence of EMS-related dysmenorrhea may be closely related to the up-regulation of VEGF and MMP-9. Electroacupuncture can effectively down-regulate the expression levels of VEGF and MMP-9 in peripheral serum, thereby effectively improving EMS-related dysmenorrhea in patients and achieving a therapeutic effect.

Acupuncture inhibits angiogenesis in ectopic endometrial tissue by reducing the level of matrix metalloproteinase (MMP). MMP is involved in the degradation and formation of the basement membrane of endothelial cells in blood vessels, stimulates the sprouting of endothelial cells in blood vessels, and thus promotes angiogenesis. Zuo D D et al. [21] found that acupoint catgut embedding can reduce the serum levels of VEGF and MMP-2 in EMS patients by inhibiting the expression of the PI3K/Akt/mTOR signaling pathway, thereby inhibiting angiogenesis in ectopic endometrial tissue.

## 2.5 Alleviation of Pain by Acupuncture

Pain is a common complaint of EMS; approximately 70%-80% of patients experience varying degrees of pelvic pain, including dysmenorrhea and chronic pelvic pain, which shows a progressive aggravating trend [22]. The pain-related mechanisms are related to processes such as nerve neogenesis and increased prostaglandin levels [23].

Abnormally increased nerve fiber density is the primary link in the occurrence of EMS lesions and pain. The ectopic endometrium stimulates the formation of nerves and blood vessels in the lesion and its surrounding tissues. The newly formed nerve fibers amplify the pain signals of the central nervous system and increase the patient's pain sensation. Zhang X Z et al. [24] found that the levels of protein gene product 9.5 (PGP9.5), brain-derived neurotrophic factor (BDNF), tyrosine receptor kinase B (TrkB), VEGF, and angiopoietin-2 (Ang-2) in the nerve fibers of EMS model rats were all increased. Different intervention methods were applied to the rats; among them, in the group treated with brain acupuncture combined with TCM, the pain symptoms of the rats were relieved, and the serum levels of PGP9.5, BDNF, TrkB, VEGF, and Ang-2 decreased significantly. This study confirmed that brain acupuncture can alleviate pain by inhibiting abnormal neurovascular formation.

PGE2 can inhibit cell death and apoptosis [25]. The proliferation and invasion levels of human endometrial epithelial stromal cells are positively correlated with PGE2 levels, indicating that PGE2 can promote the implantation of

ectopic endometrium. This is consistent with the research finding that PGE2 levels are highly expressed in EMS patients. PGE2 directly interferes with the invasion and proliferation of ectopic endometrial cells by regulating steroid hormone synthesis. Prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>) is a pain-causing substance. Endometriosis stimulates its massive secretion, induces aseptic inflammatory response, and aggravates local pain. Both PGE2 and PGF<sub>2α</sub> can inhibit uterine smooth muscle contraction, reduce uterine blood flow, induce uterine hypoxia and ischemia, promote the accumulation of acidic metabolites, mediate the excitation of peripheral sensitive neurons, and stimulate the release of substances such as substance P, thereby leading to symptoms such as dysmenorrhea [26].

Sun K F et al. [27] explored the effect of acupuncture combined with medication on the expressions of serum interleukin-32 (IL-32) and prostaglandin 2 (PGE2) in EMS patients with dysmenorrhea. The results showed that electroacupuncture could significantly reduce PGE2 levels, effectively relieve dysmenorrhea symptoms in EMS patients, improve their immune function, and enhance their quality of life, demonstrating good clinical efficacy. Li Q Y [28] observed the clinical effect of Wenbao Decoction combined with acupoint catgut embedding in the treatment of dysmenorrhea caused by EMS of kidney deficiency and blood stasis type. The study found that combined with acupoint catgut embedding, the high expression of inflammatory factors was inhibited, and PGF<sub>2α</sub> decreased significantly, which was conducive to the recovery of patients and worthy of reference.

### 3. Summary

A large number of studies have shown that acupuncture has a definite effect in the treatment of EMS-related dysmenorrhea, which can effectively relieve dysmenorrhea symptoms, and the research on its mechanism is becoming more and more in-depth. The mechanisms mainly include four aspects: regulating the body's immune function, inhibiting the expression of estrogen and its receptors, regulating nerve growth factors, and inhibiting angiogenesis. However, there are still the following problems to be solved urgently: there are relatively few scientific studies on the mechanisms of acupuncture in treating EMS-related dysmenorrhea, and some mechanisms still need further research. At the same time, it is necessary to further explore the exact mechanism of acupuncture in treating EMS-related dysmenorrhea from multiple aspects such as physiology, pathology, and neuroscience, so as to guide scientific research and clinical application more accurately.

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