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Research Progress on Pathogenesis and Treatment of Primary Dysmenorrhea

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Abstract: Primary dysmenorrhea is one of the common gynecological diseases of women of childbearing age, which can affect the work, study, and life of patients in severe cases. From the perspective of Western medicine, primary dysmenorrhea is caused by excessive secretion of prostaglandin and contraction of uterine smooth muscle, so the treatment focus of Western medicine is oral non-steroidal anti-inflammatory drugs or contraceptives, but its side effects cannot be ignored. From the perspective of Chinese medicine, primary dysmenorrhea is caused by qi-blood stagnation, so the focus of Chinese medication is dialectical treatment, which can improve qi-blood stagnation by acupuncture, decoction, moxibustion, etc., with fewer side effects and long-term clinical significance. The purpose of this paper is to analyze the relevant literature about the pathogenesis and treatment of primary dysmenorrhea in recent years, and to understand the research progress of primary dysmenorrhea in Western medicine and traditional Chinese medicine, so as to provide a reference for clinical treatment of primary dysmenorrhea.

Keywords: Primary dysmenorrhea; Pathogenesis; Treatment

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1. Dysmenorrhea

Dysmenorrhea refers to the pain and heaving in the lower abdomen of women before and after menstruation or during the menstrual period. Some patients may be accompanied by headache, dizziness, fatigue, backache, and in severe cases, nausea, vomiting, pallor, and even fainting [1]. It is divided into primary dysmenorrhea and secondary dysmenorrhea. Primary dysmenorrhea (PD) refers to the pain that occurs during or before menstrual cramps, mainly in the lower abdomen, often accompanied by waist pain, abdominal or anal distension, and other discomfort symptoms, without pelvic organic lesions [2]. Secondary dysmenorrhea refers to menstrual abdominal pain caused by organic pathological changes in pelvic organs, such as endometriosis, adenomyosis, hysteromyoma, uterine malformation, and chronic pelvic inflammatory disease [3].

Primary dysmenorrhea is the most common gynecological disease among women of childbearing age. About 75% of women of childbearing age are troubled by primary dysmenorrhea, which seriously affects their

normal work, study, and life [3,4].

2. Pathogenesis of primary dysmenorrhea

2.1. Pathogenesis of primary dysmenorrhea in Western medicine

2.1.1. Prostaglandin (PG)

Western medicine believes that primary dysmenorrhea is caused by increased synthesis and release of prostaglandin in the endometrium [5]. Excessive release of prostaglandin leads to strong contraction of uterine smooth muscle and uterine blood vessels, and finally leads to endometrial ischemia and hypoxia, causing pain. Prostaglandins are derived from long-chain unsaturated fatty acids such as arachidonic acid. Arachidonic acid, a component of cell membrane phospholipids, is released from cell membrane phospholipids under the action of phospholipase (PLA2), and then metabolized into prostaglandin G2 (PGG2) and prostaglandin H2 (PGH2) under the action of cyclooxygenase (COX). The two can be further synthesized into prostaglandin F2α (PGF2α) and prostaglandin E2 (PGE2) under the action of different synthetases. PGFs synthesized and secreted by endometrium during non-pregnancy are mainly PGF2α and PGE2, which relaxes uterine smooth muscle and makes it contract. High concentration of PGF2α acts on the PGF2α receptor on the wall of spiral arteriole, causing spasmodic contraction of uterine smooth muscle, resulting in the decrease of uterine blood flow, uterine ischemia, uterine hypoxia, deposition of acid metabolites, and reduction of pain threshold of pelvic nerve endings to chemical and physical stimulation, which leads to dysmenorrhea [6-8]. In a mouse experiment conducted by Yu *et al.*, it was found that the serum PGF2α concentration of the dysmenorrhea mice model was significantly higher than that of the control group, and the serum PGF2α concentration of dysmenorrhea mice decreased after Chinese medicine treatment [9].

Another metabolic pathway of arachidonic acid is that under the action of 5-lipoxygenase, 5-hydroxytryptamine (5-HT) is generated, then leukotriene A4 is further synthesized, and finally leukotriene B4 and leukotriene C4 are synthesized. Among them, leukotriene C4, PGF2α, and PGE2 act together on the uterus, causing uterine smooth muscle contraction and vascular contraction, and pain (**Figure 1**) [10-13]. Liu *et al.* found that the content of 5-hydroxyindoleacetic acid (5-HIAA), the final product of 5-HT in dysmenorrhea model rats, was significantly higher than that in the control group, and the number and degree of body twisting were higher than that in the control group [14].

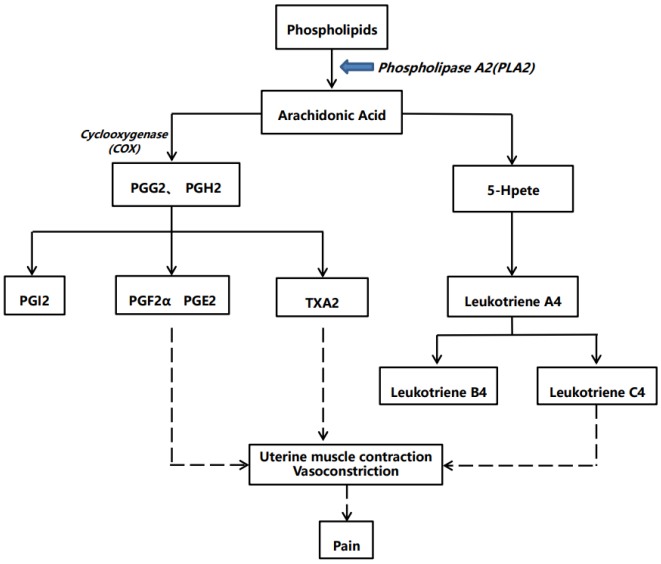

Figure 1. Prostaglandin synthesis process, pain-causing factors of dysmenorrhea.

2.1.2. Oxytocin (OT)

Oxytocin (OT) is the strongest uterine contractile agent known at present. When it binds to the oxytocin receptor (OTR), it can cause the contraction of the non-pregnant uterus. The content of OTR in the normal non-pregnant uterus is very small, but under pathological conditions, the stimulation of OT can make OTR highly expressed, increase the sensitivity of the uterus to OTR, and cause abnormal contraction of the uterus, leading to uterine ischemia and dysmenorrhea [15,16]. Oxytocin not only directly acts on uterine muscle cells to cause uterine contraction, but also stimulates endometrial cells to release PGF2α that causes dysmenorrhea, and the increase of PGF2α will stimulate the release of OT, forming a positive feedback cycle, which will jointly lead to uterine contraction and aggravate pain [17]. In addition, Liedman *et al.* confirmed that oxytocin plays a more important role in the non-pregnant uterus, especially in patients with dysmenorrhea [18].

2.1.3. Vasopressin (AVP)

In non-pregnant women, the effect of vasopressin (AVP) on uterine smooth muscle is much higher than oxytocin [19]. AVP acts on vasopressin receptors in the uterus, enhances myometrium activity, promotes uterine vasoconstriction, and makes the uterus ischemic, thus aggravating dysmenorrhea symptoms [20]; In addition, AVP directly promotes the production of PG, which causes uterine blood vessels to contract, resulting in decreased uterine blood flow and dysmenorrhea [21,22].

2.1.4. Others

The occurrence of primary dysmenorrhea is also related to estrogen, progesterone, Ca^{2+}, NO, etc. The level of PGF2α increased during dysmenorrhea, and the changes in prostaglandin were also related to the changes in estrogen and progesterone in the body. Due to uterine ischemia and hypoxia, the uterus will suffer from ischemia-reperfusion injury, and a large number of extracellular Ca^{2+} will enter the smooth muscle cells, resulting in intracellular Ca^{2+} overload, which will cause cell energy depletion and cell membrane damage. The uterine tissue cells will produce more oxygen free radicals to make the uterine smooth muscle spasm and cause dysmenorrhea [23,24]. It has been found that the content of NO in the uterus tissue of rats with primary dysmenorrhea increased and the content of Ca^{2+} decreased after treatment with traditional Chinese medicine, which inhibited the transmission of harmful information, which may be one of the mechanisms of treating primary dysmenorrhea [25].

2.2. Pathogenesis of primary dysmenorrhea in traditional Chinese medicine

Traditional Chinese medicine holds that “if obstructed, then painful,” and “if not vibrant, then painful.” Because of exogenous wind-cold, consuming cold diets, and living in cold places for a long time, it is easy to cause the cold pathogens to stagnate in the uterus, and blood stasis accumulates in the uterus, causing cold coagulation and blood stasis; Because of emotional depression and stagnation of *liver-qi*, *qi* movement is unfavorable, *chong* and *ren* are blocked, and blood circulation is not smooth, resulting in *qi* stagnation and blood stasis [26]. Overly hot constitution, improper recuperation during the menstrual period and postpartum, pathogenic damp-heat, and the stagnation of *qi* and blood will lead to the stagnation of damp-heat and blood stasis. The stagnation of *qi* and blood stasis, cold coagulation and blood stasis, and stagnation of damp-heat and blood stasis can all lead to stagnation of excess pathogen in *chong* and *ren* of the uterus and poor circulation of *qi* and blood, which fits the saying of “if obstructed, then painful” [27]. Deficiency of essence, deficiency of *kidney-qi*, excessive consumption of bad habits, long-term injury due to serious illness or early pregnancy and prolificacy, resulting in the deficiency of *kidney-qi*; The spleen loses its healthy movement, and the acquired source is insufficient, so it cannot nourish *Chong Ren* and uterus, resulting in *qi* and blood weakness [28]. The uterus is out of nourishment

due to the deficiency of *qi* and blood and a deficiency of *kidney-qi*, which fits the saying of "if not vibrant, then painful." There are many causes of dysmenorrhea, which are divided into deficiency and excess, such as cold coagulation, dampness resistance, blood stasis, and *qi* stagnation, deficiency is divided into *qi* deficiency and blood weakness, and there are also differences between liver, spleen and kidney deficiency. Due to physical differences, cold and heat coagulations are often mixed with deficiency and excess, which are mutually harmful [29-31]. The key to dysmenorrhea is "blood stasis." Primary dysmenorrhea can be divided into four types: *qi* stagnation and blood stasis, cold coagulation and blood stasis, *qi* and blood weakness, and liver and kidney loss, with cold-dampness stagnation being the most common type [32,33].

3. Treatment of primary dysmenorrhea

There are various treatment methods for primary dysmenorrhea. Because there are no organic pelvic lesions, its treatment principle is mainly to relieve pain and improve the quality of life of patients.

3.1. Western medicine treatment method

3.1.1. NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are often used as first-line drugs for primary dysmenorrhea and are widely used in the world. Primary dysmenorrhea is characterized by excessive synthesis and release of prostaglandin in the endometrium, so blocking the COX pathway can reduce the synthesis and release of prostaglandin, thus reducing the contraction of the uterus and blood vessels and achieving the purpose of relieving pain [34]. However, due to its non-selectivity, it will damage the gastric mucosa and cause adverse reactions such as nausea, vomiting, and stomach discomfort. It is worth noting that arachidonic acid can not only synthesize prostaglandin through the COX pathway to cause dysmenorrhea but also produce leukotrienes through the 5-lipoxygenase pathway to cause pain, so some patients are not sensitive to NSAIDs because of the 5-lipoxygenase pathway [35].

3.1.2. Oral hormonal contraceptives

At present, hormonal contraceptives are recognized as the second-line drugs for primary dysmenorrhea, mainly by inhibiting ovulation and endometrial growth, or causing endometrial atrophy, reducing menstrual flow. It can also relieve primary dysmenorrhea by prolonging the menstrual cycle [13]. However, such drugs which may affect reproductive function should not be taken for a long time, especially for women who have fertility requirements [36].

3.1.3. Vitamin

Vitamin E can relieve primary dysmenorrhea, which is metabolized into tocopherol after entering the body. By regulating female estrogen, it can also inhibit the activities of phospholipase A2 and COX, thus inhibiting the production of prostaglandin, promoting the action of prostacyclin, dilating peripheral blood vessels, improving blood circulation, and alleviating female dysmenorrhea signs, thus playing a role in relieving dysmenorrhea [37]. Vitamin B1 supplementation can improve dysmenorrhea by reversing the common symptoms of vitamin B1 deficiency, such as muscle spasms, fatigue, and decreased pain tolerance. Vitamin B6 can promote the inflow of magnesium ions into cells, activate ATPase, consume a lot of ATP, and relieve dysmenorrhea [11].

3.1.4. Drugs for inhibiting uterine contraction

One of the characteristics of primary dysmenorrhea is the intense contraction of the uterus, so the purpose

of relieving pain can be achieved by inhibiting the contraction of smooth muscle. For example, calcium channel blockers (CCBs) can be used as a potential drug to treat primary dysmenorrhea. CCBs can prevent the release of calcium ions from cells, relax smooth muscle, dilate blood vessels, relieve uterine myometrium contraction spasm, and relieve pain [38]. In Li's research [39], Xintongding was used to treat patients with primary dysmenorrhea, and the effective rate was 76.6%.

3.1.5. Transcutaneous nerve electrical stimulation

It relieves pain through two mechanisms. The first is to send a series of afferent pulses through the large-diameter sensory fibers of the same nerve root, so as to increase the threshold of pain signals caused by uterine hypoxia and high contraction, thereby reducing pain perception. The second mechanism is that peripheral nerves and the spinal cord stimulate the release of endorphins, which provides another way of partial pain attenuation. This may be another option for women with contraindications to NSAIDs and their efficacy [11,40].

3.1.6. Surgery

Only a small number of patients with severe dysmenorrhea are ineffective in drug treatment, so they can choose surgical treatment and remove the uterosacral nerve. In Chen and Soong's clinical study [41], the pain relief rate of patients with primary dysmenorrhea after laparoscopic resection of the uterine presacral nerve was 77.1%, and severe cases could choose to remove the uterus [34].

3.1.7. Others

In addition to medical treatment and surgical treatment, environmental pain can be achieved by improving lifestyle, having a healthy diet, and local hot compress. Having a healthy lifestyle and good eating habits, exercising properly, and strengthening physical fitness, as well as choosing a local hot compress or massage to promote blood circulation and vasodilation when the pain is severe can relieve the pain [11,40].

3.2. Traditional Chinese medicine treatment method

3.2.1. Acupuncture

Acupuncture is one of the most commonly used methods to treat primary dysmenorrhea at present, and there are many acupoints to choose from, such as Guanyuan, Zhongji, Qihai, Xuehai, and Sanyinjiao [42]. In Guo's research [43], 180 patients with primary dysmenorrhea were investigated, and randomized controlled trials were conducted, in which the control group was treated with traditional Chinese medicine. The treatment group was treated by acupuncture with Shu Mu acupoints. Ganshu, Shenshu, Qihaishu, Guanyuanshu, Cixiu, Qimen, Guanyuan, Zhongji, Qihai, and Sanyinjiao acupoints were selected for three menstrual cycles. Finally, compared with the control group, the contents of serum PGF2α, of β-endorphin (β-EP) and the improvement of uterine blood flow in the treatment group were statistically significant ($P < 0.05$), which proved that acupuncture at Shumu acupoints can effectively treat primary dysmenorrhea by reducing serum PGF2α, increasing the content of β-EP and improving the hemorheology of patients' uterus. In a study by Lin *et al.* [44], 60 patients with primary dysmenorrhea were randomly divided into an acupuncture group and a control group. The acupuncture group selected Guanyuan, Sanyinjiao, and Diji acupoints, while the control group took painkillers and monitored the serum PGF2α content. The results confirmed that there was a significant difference in the serum PGF2α content between the acupuncture group and the oral painkiller group ($P < 0.05$), and its mechanism may be related to reducing the level of prostaglandin PGF2α in patients' menstrual blood. Tang and Liu randomly divided 60 patients with primary dysmenorrhea into an acupuncture treatment group and an oral Western medicine control group and found that acupuncture treatment had a more obvious effect on patients with primary dysmenorrhea [45].

In addition to ordinary acupuncture therapy, a new acupuncture therapy-buccal acupuncture therapy has appeared in recent years. Professor Wang Yongzhou's team found that there was a miniature holographic system on the face. Animal experiments proved that buccal acupuncture could relieve pain from the central nervous system by increasing the content of β-EP in cerebrospinal fluid and inhibiting the release of cholecystokinin octapeptide (CCK-8) [46,47]. According to the foregoing study, common acupuncture can achieve the purpose of relieving dysmenorrhea by acupuncture at different acupoints, such as Guanyuan, Sanyinjiao, Xuehai, and Qihai. These mechanisms are also based on the theory of Big Triple Jiao, so it can be speculated that dysmenorrhea can also be treated by acupuncture at the corresponding acupoints on the cheek.

In Guan's research [48], the research object is patients with dysmenorrhea caused by endometriosis, and the acupoints of the waist, sacrum, and lower jiao are selected, and then the acupoints are added according to the abdominal physical examination. Buccal acupuncture has been used for three menstrual cycles, and statistical difference analysis between the visual analog scale (VAS) before and after treatment was carried out. It is concluded that after three menstrual cycles of buccal acupuncture treatment, the patients' pain symptoms have been effectively alleviated, and the VAS has decreased significantly. This study proves that buccal acupuncture therapy is effective in treating dysmenorrhea and has long-term clinical significance. This provides a basis for the clinical treatment of primary dysmenorrhea with buccal acupuncture.

In clinical research by Li *et al.* [2], the patients with moderate and severe primary dysmenorrhea were randomly assigned by selecting the acupoints of the waist, sacrum, and lower jiao for buccal acupuncture treatment, and the buccal acupuncture treatment was compared with oral painkillers to observe whether the differences in VAS, dysmenorrhea symptom score and health survey brief form between the two groups before and after treatment were statistically significant. It is finalized that the VAS scores and other items in the two groups decreased compared with those before treatment, and the difference between the two groups was statistically significant after the treatment ($P < 0.05$). Buccal acupuncture can effectively relieve the clinical symptoms of moderate and severe primary dysmenorrhea, alleviate the symptoms associated with good dysmenorrhea and improve the quality of life.

3.2.2. Traditional Chinese medicine decoction

The most classic therapy of Chinese medicine is Chinese medicine decoction, which has been passed down since ancient times. Yuan *et al.* used Shaofu Zhuyu decoction to treat patients with primary dysmenorrhea [49]. According to Wang *et al.* [50], acupoint application of traditional Chinese medicine based on Jinkui Wenjing decoction has a significant effect on treating primary dysmenorrhea of cold coagulation and blood stasis type, which can effectively improve the symptoms of menstrual abdominal pain and improve the quality of life of patients and is suitable for popularization among students and even wider groups. In Zhao's research [51], the observation group was treated with modified Shaoyao Gancao decoction, and its overall effective rate and VAS score were significantly better than those of the control group ($P < 0.05$). It shows that the modified Shaoyao Gancao decoction can improve the clinical efficacy of primary dysmenorrhea and relieve the pain of patients. In Wang and Shi's clinical research [52], Wenjing Huayu decoction combined with Guizhi Fuling capsule has an obvious analgesic effect on patients with primary dysmenorrhea, and its mechanism may be related to regulating the expression of PGF2α and PGE2 in serum, and the medication safety is high.

3.2.3. Moxibustion

Moxibustion has a penetrating and diffusing effect. Through the stimulation of nerve endings and the conduction of the nervous system, it can promote local and systemic effects on the body, promote changes in nerves, endocrine, immunity, and metabolism, and relieve dysmenorrhea. Liao *et al.* [53], as well as Liu and

Wang [54], found that moxibustion at Shenque acupoint combined with warm acupuncture at Guanyuan and Sanyinjiao acupoints has a better clinical effect than warm acupuncture at Guanyuan and Sanyinjiao acupoints alone, and is safe and reliable, which is worthy of clinical reference. The studies from Li, Ma, and Wei [55], as well as Hou and Zhang [56], also concluded that although both the ibuprofen group and the moxibustion group can improve VAS, shorten the duration of dysmenorrhea, and reduce the severity of dysmenorrhea, the moxibustion group has more advantages, can achieve better clinical efficacy in treating primary dysmenorrhea, and the recurrence rate of dysmenorrhea is lower.

4. Summary

Primary dysmenorrhea affects patients' daily life. In the exploration of the pathogenesis and treatment of primary dysmenorrhea, modern medicine believes that primary dysmenorrhea is caused by excessive secretion of prostaglandin and excessive contraction of uterine smooth muscle. The focus of treatment is oral non-steroidal anti-inflammatory drugs or contraceptives, but there are many side effects, so the use of medication should be cautious. From the perspective of traditional Chinese medicine, primary dysmenorrhea is caused by *qi* and blood stagnation, so the focus of traditional Chinese medicine treatment is dialectical, which emphasizes the overall concept and adopts milder methods for treatment, which has long-term significance despite requiring some time to take effect. In addition, the new buccal acupuncture therapy in recent years may provide a new direction for the treatment of primary dysmenorrhea. Therefore, if primary dysmenorrhea is treated by combining traditional Chinese and Western medicine, it can not only fully display the characteristics of traditional Chinese medicine, but also absorb the advanced modern medical experience, which has broad development prospects.

Author contributions

Ma H is responsible for data acquisition, analysis, and paper writing. Li L and Wang G are responsible for writing ideas and revising opinions of the paper. Zhang B, Chen J, and Yuan S participated in data collection and screening, and put forward opinions on the revision of the paper in time. Sun Y has contributed to project design and analysis and is one of the corresponding authors. All authors made great contributions to this article.

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Disclosure statement

The authors declare no conflict of interest.

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