

Review Article

Research overview of Guanyuan acupoint (CV4) for treating primary dysmenorrhea

Paphawarin Asawadethmetakul, Thidarat Ongsritrakul

Huachiew Traditional Chinese Medicine Clinic, Thailand

Abstract: Primary dysmenorrhea (PD) is a prevalent gynecological disorder that significantly impacts women's quality of life and productivity. The Guanyuan (关元, CV4) acupoint, a key point in traditional Chinese medicine, has been widely used for centuries to alleviate menstrual pain. This article provides a comprehensive review of the commonly used combinations, treatment methods, and underlying mechanisms of CV4 in treating PD. By systematically reviewing relevant research from PubMed and CNKI databases, we aim to provide evidence-based insights to guide clinical practice.

Keywords: primary dysmenorrhea; Guanyuan; traditional Chinese medicine; review article

Corresponding author: Paphawarin Asawadethmetakul: cake.paphawarin@gmail.com

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Introduction

Primary dysmenorrhea (PD) is one of the most prevalent gynecological disorders, with rates ranging from 50% to 90%.^[1] PD is defined as menstrual pain without an underlying etiology, characterized by painful cramps in the lower abdomen that may extend to the area of the lower back, with associated physical symptoms including headache, dizziness, fatigue, tender breasts, nausea, vomiting, constipation or diarrhea, increased urination, sweating, and psychological symptoms including anxiety, depression, and irritability.^[2] Nonsteroidal anti-inflammatory medications (NSAIDs) and hormonal contraceptives are commonly used to treat PD.^[3] However, these medications are

unsatisfactory owing to their long-term side effects and do not result in a permanent cure.^[4,5] Scientific evidence demonstrates that complementary or alternative therapies are effective for managing PD symptoms, including traditional Chinese medicine (TCM).^[6-8] TCM uses the concept of balancing yin and yang by promoting the natural flow of Qi, in order to prevent or treat disease.^[9] Acupoints are specific points along the body's meridians. These invisible meridians are associated with specific organs.^[10] Acupoint selection plays a key role in curing illness, whether by acupuncture, moxibustion, Tuina massage, cupping, acupoint application, or heat therapy. Guanyuan (关元, CV4) is one of the most

frequently used acupoints for treating PD, either alone or in combination with others.^[11,12] CV4 has the ability to prevent disease by promoting health, supplementing Qi, replenishing yang, warming and regulating local area blood (uterus), and separating clear and excreting turbid. Previous studies have shown that stimulating CV4 is beneficial in modulating the levels of the hypothalamic-pituitary-adrenal axis, adjusting endocrine function, regulating hormone levels, improving ovarian function, inhibiting prostaglandins, normalizing uterine contraction, and having a therapeutic effect in PD.^[13,14] This article provides a comprehensive review of the commonly used combinations, treatment methods, and underlying mechanisms associated with CV4 in the treatment of PD.

1. Pathogenesis of primary dysmenorrhea

The symptoms of PD are caused by the excessive release of prostaglandins, especially PGF2 α .^[15] The increased prostaglandins cause excessive uterine smooth muscle contraction. This leads to insufficient blood flow to provide adequate oxygenation to the uterine muscle, which results in pain.^[16] In addition to the change in prostaglandins, behavioral, psychological, and physical impacts have also been attributed to PD.^[17,18]

As part of TCM, PD is generally classified into two types: excess or deficiency syndrome.^[19] The cause of PD mainly contains Qi stagnation, blood stasis, damp-heat, or cold accumulation, while the latter contains Qi and blood deficiency, liver and kidney deficiency, etc.^[20] TCM syndrome differentiation provides details such as the incidence cause, pathological location, characteristics and conditions of the disease, etc.^[21] Excess syndrome is based on the theory that “if there is blockage, there will be pain”, whereas deficiency syndrome is based on the theory that “if there is weakness, there will be pain”.^[22]

According to TCM’s meridians, PD is closely related to the Penetrating and Conception Vessel (冲任脉); these two vessels are among The Eight Extra Meridians (奇经八脉), run through the uterus, and aid in menstruation, fertilization, and pregnancy. Conception Vessel (冲脉) originate from the uterus, work on receiving and transporting Qi from the yin meridians to the uterus, provide yin substances for all women's physiological activities, and thus are called the “sea of yin (阴脉之海)”. Penetrating Vessel (任脉) work on supplying and controlling blood in the uterus and are called the “sea of blood (血海)”.^[23]

2. Role of Guanyuan acupoint (CV4)

In ancient times CV4 was known as Xiaji (下纪), Dantian (丹田), and Cimen (次门).^[24] CV4, located on the anterior midline of the lower abdomen, 3 cun (寸) or 4 fingers spacing below the umbilicus, belongs to the Conception Vessel (冲脉) and is called the “gate of origin”. CV4 is a meeting point of the Conception Vessel (冲脉) with the three yin meridians of the foot (the spleen, liver, and kidney meridians), as well as where Penetrating Vessel (任脉) converges with the kidney meridian in the abdomen, and also a front-mu point of the small intestine meridian.^[25] The Acupuncture and moxibustion points out that “CV4 has the functions of warming and tonifying yang, regulating the Vessel (冲任脉), promoting Qi and blood circulation, resolving blood stasis and pain, and benefiting the kidneys for health care”.^[26] CV4 is highly nourishing and strengthening acupoint; it is useful for gynecological disease,^[27] as it connects to many organs; it’s also helpful with urination, digestive, kidney, and hepatobiliary problems, or even with pain and weakness of the limbs and back.^[28,29] Previous animal experiments found that there is a convergence of afferent nerve fibers between the uterus and CV4 in the L3–L6 of the lumbar spinal cord

regions; this could be the neural basis for the connection pathway between the uterus and CV4.^[30]

3. Guanyuan acupoint clinical application in treating primary dysmenorrhea

3.1 Single acupoint therapy

3.1.1 Acupuncture

The study of single acupuncture at CV4 for treating PD during the menstrual period Kong Yi, et al^[31] found that the pain began to be alleviated in 5 minutes after retaining the needle; the analgesic effect was rapid, and as time went by, the degree of pain gradually improved. Wang Hui, et al^[32] observed and recorded the visual analog scale (VAS) pain score at 11 different time points before and after acupuncture at CV4. As a result, the VAS pain score obviously decreased 30 minutes after retaining the needle and 180 minutes after removing the needle. Zhu Futing^[33] studied the change in pain before and after acupuncture at CV4 for 30 minutes in PD patients. After 3 menstrual cycles of treatment, the pain score was a significant decrease ($p < 0.05$). Their mechanism may be related to the change in high-resistance and low-velocity blood flow of the uterine, improving blood perfusion of the uterine, and inhibiting spastic contraction of the uterine. But somehow, in clinical practice, multi-acupoint acupuncture or other composite methods are often used to enhance therapeutic effects.

3.1.2 Moxibustion

Moxibustion for treating PD is commonly selected at CV4. First, single-point moxibustion at CV4 is a simple treatment with high safety, low economic cost, and easy acceptance by patients. Second, moxibustion delivers heat and moxa percutaneous absorption to stimulate Qi and blood circulation, unblock meridians, and regulate internal organs. Previous studies have indicated that moxibustion for PD can improve endocrine hormones, nerve factors,

immunological function, and uterine microcirculation.^[34,35] Huang Qianru, et al^[36] studied the effects of moxibustion at CV4 and utilized an infrared thermal imager to monitor the Conception Vessel (冲脉) temperature before and after moxibustion for 30 minutes. The findings revealed that there is a significant increase in the temperature of the Conception Vessel (冲脉) which can promote the flow of Qi and blood to alleviate the symptoms of PD. The duration of moxibustion has an influence on the moxibustion effect. Lin Sensen, et al^[37] compared the effects of moxibustion at CV4 at different times. Group A treated 5 times/cycle; Group B treated 7 times/cycle; both groups treated three menstrual cycles. Both groups have a curative effect, which is probably associated with their effects on decreasing PGE2/PGF2 α levels in PD patients; however, there were no significant differences between the groups. Zhang Bingyue^[38] utilized fMRI scans to explore the brain regions of PD patients before and after intervention. This study performed the moxibustion at CV4 seven days before menstruation, once every other day, to continuously treat three menstrual cycles. Resulting in moxibustion at CV4 can elicit local consistency in several pain-related brain regions as well as an increase or decrease in cerebral blood flow. Those altered brain regions may be the targets of moxibustion's analgesic effect at CV4. Xiong Jun, et al^[39] performed heat-sensitive moxibustion at CV4 on PD patients, and rs-fMRI was used to explore the change in regional homogeneity (ReHo) before and after intervention. The result showed that heat-sensitive moxibustion at CV4 has a significant immediate effect, and the prefrontal cortex may play a key role in analgesic sensation and emotion. The functional connectivity change between the prefrontal cortex and the default mode network might be the key core mechanism for analgesic effects.

Zhou Xingchen^[40] also confirmed that heat-sensitive moxibustion at CV4 can significantly activate the prefrontal cortex, and may be closely related to the key emotional analgesia.

3.1.3 Acupoint application

Acupoint application is based on acupuncture and herbal medicine theories and is used to treat and prevent disease by applying to certain acupoints. Applications with different herbal formulations exert varying therapeutic effects. Qi Jinling^[41] confirmed that the combination of menstrual-warming, cold-dissipating, blood stasis-dispelling, and pain-relieving effects of Chinese herbs on CV4-treated PD with cold coagulation and blood stasis type have a satisfactory effect, with a total effective rate of 92.5%. Huang Qun, et al^[42] compared the effect of hospital formula Tongjing patch at CV4 with ibuprofen capsules in treating PD in cold coagulation and blood stasis syndrome. The therapeutic effect and dysmenorrhea symptom score of the Tongjing patch were significantly better than those of ibuprofen capsules ($p < 0.01$). Huang Heqing^[43] observed the effect of CV4 single application and multi-acupoint applications in the treatment of PD in adolescence. Both groups showed therapeutic effects and can improve the symptoms of PD, but the improvement of dizziness and insomnia in multi-acupoint applications is better than in CV4 single applications.

3.2 Combination acupoints

3.2.1 Two-acupoint combination therapy

(1) Guanyuan (关元, CV4) combined with Sanyinjiao (三阴交, SP6), located on the inside of the lower leg, with 3 cun (寸) or 4 fingers widths directly above the tip of the medial malleolus, posterior to the medial border of the tibia, is commonly used to treat gynecological disease, including dysmenorrhea.^[44] Zheng Min,

et al^[45] found that during periods of pain, the combination of acupuncture at CV4-SP6 tends to have better analgesic effects than single acupuncture CV4. Liu Qun^[46] applied mild moxibustion at CV4-SP6 with PD patients and found that mild moxibustion could improve uterine microcirculation disorder by increasing blood velocity and reducing vascular resistance. Wang Hongbin, et al^[47] confirmed that the combination of CV4-SP6 and neither acupuncture nor moxibustion treatment has a good analgesic effect for PD.

(2) Guanyuan (关元, CV4) combined with Shenque (神阙, CV8): CV8, located in the umbilicus, where Qi in the body joins and connects to the internal organs, including the uterus. Several studies have shown that the combination of CV4-CV8 with normal moxibustion, ginger moxibustion, or Chinese herbal application not only maintains the analgesic effect after treatment but also improves patients quality of life, relieves the symptoms of cold and blood stagnation syndrome in PD, and reduces the use of painkillers.^[48-50]

3.2.2 Multi-acupoint combination therapy

(1) Acupuncture/Acupuncture combined with other treatment: Xue Xiao, et al^[51] selected Guanyuan (关元, CV4), Sanyinjiao (三阴交, SP6), and Zusanli (足三里, ST36) for acupuncture in treating PD patients for different durations: 15 minutes, 30 minutes, and 45 minutes. As a result, 30 minutes of acupuncture was the most effective duration for treating PD. Chen Weiwei^[52] evaluates the difference between local distal compatibility and local compatibility in acupuncture treating PD with cold coagulation and blood stasis types. The local distal compatibility group performed at Guanyuan (关元, CV4), Zhongji (中极, CV3), and Sanyinjiao (三阴交, SP6); the local compatibility group performed at CV4, Zhongji (中极, CV3), and Zigong (子宫, EX-CA1).

Both groups are effective in treating PD with cold coagulation and blood stasis type, but in the long-term, local distal compatibility acupuncture tends to have a better effect in relieving PD syndrome. The total effective rate in local distal compatibility acupuncture was 87.8%, while for local compatibility acupuncture it was 81.3%, and there was no statistically significant difference between the two groups. Cheng Xingmin, et al^[53] performed acupuncture using the method of “tonifying the spleen and stomach, regulating the Conception Vessel (冲脉)” at Guanyuan (关元, CV4), Zusanli (足三里, ST36), Diji (地机, SP8), Sanyinjiao (三阴交, SP6), Zhongwan (中脘, CV12), and Guilai (归来, ST29). The result showed that this method can shorten the pain of PD in cold coagulation and blood stasis type; the mechanism is related to the changes in PGE2 and PGF2 α . Li Na^[54] treated PD by based on ordinary acupuncture at CV4, Zhongji (中极, CV3), Zigong (子宫, EX-CA1), Diji (地机, SP8), Sanyinjiao (三阴交, SP6), and added Baihui (百会, GV20) and Sishencong (四神聪, EX-HN1) to tonify the nerve and alleviate the pain, and confirmed that ordinary acupuncture adding Baihui (百会, GV20) and Zigong (子宫, EX-CA1) could better improve the symptoms of distension, nausea, and vomiting and could give analgesic effects than just ordinary acupuncture. Wu Liangyan^[55] compared with moxibustion at CV4 combined with acupuncture at Guanyuan (关元, CV4), Shenque (神阙, CV8), Zigong (子宫, EX-CA1), Zusanli (足三里, ST36), Sanyinjiao (三阴交, SP6), and Xuehai (血海, SP10) to ibuprofen capsules. The result showed that acupuncture combined moxibustion can improve the symptoms of PD in cold coagulation and blood stasis type, and neither in short-term nor long-term effect, acupuncture combined moxibustion treatment had a better effect than ibuprofen capsules. Jiang Bing, et al^[56] investigated the effect of

Dingtong Wenjing decoction combined with warming needles in treating PD in cold coagulation and blood stasis syndrome and discovered that it can improve uterine hemodynamics, reduce peripheral blood pain-related mediators in patients, and increase endogenous opioid peptide content, which gives an analgesic effect in PD.

(2) Moxibustion: Li Cong^[57] observed the dose and effect of herbal-cake-partitioned moxibustion (HCPM) for treating PD. Mingmen (命门, GV4), Yaoyangguan (腰阳关, GV3), Shenque (神阙, CV8), and Guanyuan (关元, CV4), on Penetrating and Conception Vessel (冲任脉) were selected for moxibustion in this study. The doses of moxa were divided into five, seven, and nine moxa cones. All HCPM with five, seven, and nine moxa cones was effective, and it has been found that higher doses can increase thermal energy. In this study, nine moxa-cones performed the most effectively. Their therapeutic mechanism is related to the regulation of estradiol and progesterone levels, as well as indirectly reducing the hypercontractility of the uterine smooth muscle.

(3) Abdominal acupuncture: is a form of acupuncture that uses acupoints around the abdominal area to treat conditions across the body. It's also commonly used to treat PD. Abdominal acupoints that are used to treat PD mainly consist of Guanyuan (关元, CV4), Qihai (气海, CV6), Xiawan (下脘, CV10), Zhongwan (中脘, CV12), and can be added to other abdominal acupoints. Previous studies indicated abdominal acupuncture has a reliable effect in relieving pain in PD, stabilizes the long-term analgesic effect, has an advantage in the benign regulation of systemic function, is painless, has high safety, and is worth promoting clinically.^[58-61]

(4) Fire needle acupuncture: is an acupuncture technique that involves heating

needle, and quickly piercing into acupoints to treat disease. In clinical practice, it is usually used for the cold-type syndrome of PD. The acupoints selected for fire needle acupuncture mostly including in CV4. Studies have confirmed that fire needle acupuncture was more effective than ibuprofen treatment; their therapeutic mechanism is related to the changes in serum levels of β -EP, ET-1, and PGE2/PGF2 α , which improve the clinical symptoms of the cold-type syndrome of PD.^[62-64]

(5) Acupuncture catgut embedding: is a special form of acupuncture based on ancient theory and modern materials that implants catgut into acupoints, thereby generating a long-term stimulation effect. In modern studies, acupuncture catgut embedding is mostly based on Guanyuan (关元, CV4), Sanyinjiao (三阴交, SP6), and Ciliao (次髎, BL32).^[8,9] Acupuncture catgut embedding therapy effectively improve uterine artery hemodynamics and alleviate the pain and symptoms of PD.^[65-67]

(6) Acupoint application: Previous clinical studies treated PD by selecting the Chinese herbal formula Shaofu Zhuyu tang (少腹逐瘀汤) for application to CV4, Qihai (气海, CV6), Shenque (神阙, CV8), etc. and found that it can shorten lower abdominal pain, reduce accompanying symptoms, and decrease PGF2 α levels, but no difference was observed in PGE2 and sex hormone levels.^[68,69] The mixture of Chinese herbs of Rou Gui (*Cinnamomum cassia*), Yan Hu Suo (*Corydalis Yanhusuo*), Xiao Hui Xiang (*Foeniculum vulgare* Mill), Wu Yao (*Lindera aggregate* Kosterm), and Wu Ju Yu (*Tetradium ruticarpum*), applied to CV4, Zhongji (中极, CV3), Qihai (气海, CV6), Shenque (神阙, CV8) and Zigong (子宫, EX-CA1), is also believed to be effective for PD in cold coagulation and blood stasis type.^[70,71]

4. Guanyuan acupoint experimental study in treating primary dysmenorrhea

Research on rats treating PD with cold coagulation syndrome using single acupuncture at CV4; Recent studies have shown that acupuncture at CV4 can relieve pain, reduce the writhing in PD, and at the same time can also control TXB2 and 6-keto-PGF1 α , which may be one of the significant substances in preventing and treating PD.^[72,73] Yang Jiamin, et al^[74] hypothesized that acupuncture at CV4 may affect uterine contractility by regulating the endogenous opioid peptide receptors in the uterus, resulting in an analgesic effect. The different levels of stimulation during acupuncture at CV4 affect the analgesic effect of PD; however, more stimulation does not necessarily lead a better effect, depending on the size of the needle, the depth of the acupuncture, and the duration of needling. Cui Xiao, et al^[75] found in an experiment that acupuncture at CV4 on cold coagulation syndrome in PD model rats with different stimulation levels had effects on myosin light chain kinase (MLCK). When using a thicker, deeper needle with the reinforcing technique, the frequency of uterine smooth muscle contraction was significantly reduced compared to a finer, shallower needle without any stimulation techniques. They believe that the frequency and intensity of needle stimulation are one of the factors determining the efficacy of acupuncture.

Moxibustion research on PD rats: Qin Zhongyin, et al^[76] compared the effects of herbal-cake-partitioned moxibustion and direct moxibustion at CV4 on rats with PD and found that herbal-cake-partitioned moxibustion at CV4 increased serum β -EP, uterine PGE2 levels, and splenic NK cell activity while reducing uterine PGE2 α levels. The analgesic effects of both herbal-cake-partitioned moxibustion and direct moxibustion at CV4 were similar, but the effect on splenic NK cell activity in herbal-cake-partitioned

moxibustion at CV4 group was more significant. Qi Shuangshuang, et al^[77] compared the effects of moxibustion at Guanyuan (关元, CV4) and Shenque (神阙, CV8) on rats with PD and investigated the immunological mechanisms of PD. A light microscope was used to observe histopathological changes in the spleen after treatment. The number of spleen nodules and spleen sizes in the Guanyuan (关元, CV4) and Shenque (神阙, CV8) groups significantly increased; however, the number of spleen nodules in CV4 group was slightly higher than Shenque (神阙, CV8) group. It can be seen that both moxibustion at Guanyuan (关元, CV4) and Shenque (神阙, CV8) increase splenic NK cell activity in PD and exert analgesic effects, but the effect at CV4 is more prominent. Liu Chao^[78] discovered that ginger moxibustion at Guanyuan (关元, CV4) and Shenque (神阙, CV8) on PD rats with cold and dampness stagnation syndrome can significantly reduce the writhing, improve the uterine edema, increase uterine smooth muscle relaxation substances PGE2 and P, reduce uterine smooth muscle contraction substances PGF2 α and E2, alleviated the level of PGF2R, E2R, and OTR receptors, increased the level of PGE2R, balance PD-related endocrine molecule receptor gene expression, and exert its analgesic effect. Chen Zhaoheng^[79] demonstrated that mild moxibustion at CV4 and Sanyinjiao (三阴交, SP6) can treat PD rats by improving the microcirculatory disturbance and reducing PGE2 and PGF2 α levels in the uterus. Elevated levels of interleukin-2 (IL-2), 5-hydroxytryptamine (5-HT), and substance P can cause inflammation in the uterus, leading to dysmenorrhea. Previous studies found that after electroacupuncture at Guanyuan (关元, CV4) and Sanyinjiao (三阴交, SP6), there was a significant decrease in the writhing and the levels of IL-2, 5-HT, and substance P. This

proves that electroacupuncture at CV4 can clearly alleviate PD.^[80,81]

Summary

Acupoint selection and combination play important roles in the effectiveness of PD treatments. Previous studies analyzing the data of acupoint selection in acupuncture and moxibustion treating PD have stated that CV4 was the most frequently used; the main meridian selections were the Conception Vessel (冲脉), Spleen Meridian, and Bladder Meridian. In association rule analysis, the combination with the most support was (关元, CV4) and Sanyinjiao (三阴交, SP6), whereas the combination with the highest confidence interval was Guanyuan (关元, CV4), Sanyinjiao (三阴交, SP6) and Zusanli (足三里, ST36).^[82,83] In PD with different types of syndrome, such as excess syndrome or deficiency syndrome, the acupoint selection also differs, which is all based on syndrome differentiation. TCM therapy could be viewed as an effective option for PD. Numerous studies have confirmed that the treatment of PD at CV4 can improve endocrine hormones, nerve factors, immunological function, and uterine microcirculation. In the view of TCM, the mechanism effects on treating PD are mostly based on promoting Qi and blood circulation, flowing the meridians, and regulating the inner organs. Most studies focus on the mechanisms of endocrine factors; while there are few investigations into other mechanisms, further investigation is needed. We hope this article can provide more ideas for research on the treatment of PD at CV4.

Future perspectives

Future studies should focus on brain imaging techniques to investigate the neural mechanisms of acupuncture and moxibustion in the treatment of PD. The sample size may

need to be larger to provide more accurate results. The low-frequency amplitude, local consistency, and brain function connectivity should all be considered when analyzing the data.

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บทความปริทัศน์

ความก้าวหน้าด้านงานวิจัยในการรักษาอาการปวดประจำเดือนชนิดปฐมภูมิด้วยจุดกวนหยวน

ปภาวรินทร์ อัสวเดชเมธากุล, อิดารัตน์ องค์กรีตระกูล
คลินิกการประกอบโรคศิลปะ สาขาการแพทย์แผนจีนหัวเฉียว

บทคัดย่อ: โรคปวดประจำเดือนชนิดปฐมภูมิ เป็นโรคที่พบบ่อยทางนรีเวช ซึ่งส่งผลกระทบต่อคุณภาพชีวิตและการทำงานของสตรี ในศาสตร์การแพทย์แผนจีน จุดกวนหยวน Guanyuan (关元, CV4) มีบันทึกมายาวนานในการใช้รักษาโรคทางนรีเวช รวมถึงอาการปวดประจำเดือน บทความนี้ได้รวบรวมและสรุปงานวิจัย วิธีการรักษาต่างๆ จุดฝังเข็มร่วมที่ใช้บ่อยคู่กับจุดกวนหยวน Guanyuan (关元, CV4) ตลอดจนสรุปกลไกของจุดกวนหยวน Guanyuan (关元, CV4) ในการรักษาโรคนี้ โดยอาศัยฐานข้อมูลจาก PubMed และ CNKI เพื่อเป็นแนวทางการรักษาทางคลินิก

คำสำคัญ: ปวดประจำเดือนชนิดปฐมภูมิ; จุดกวนหยวน; ศาสตร์การแพทย์แผนจีน; บทความปริทัศน์

ผู้รับผิดชอบบทความ: ปภาวรินทร์ อัสวเดชเมธากุล: cake.paphawarin@gmail.com



文献综述

关元治疗原发性痛经的研究进展

马惠敏，翁慧珍

泰国华侨中医院

摘要：原发性痛经是妇科常见疾病之一，发病日久会严重影响女性的生活与工作质量。关元穴是治疗原发性痛经的主要常用穴位，应用历史悠久。本文基于 PubMed 和 CNKI 数据库的相关研究，对关元穴的常用配伍、治疗方法及其治疗原发性痛经的有效机制进行综合评述并加以分析，旨在为临床提供可靠的循证依据。

关键词：原发性痛经；关元穴；中医；综述

通讯作者：马惠敏：cake.paphawarin@gmail.com