



# Clinical Efficacy and Experimental Research Progress on Traditional Chinese Medicine Moxibustion Therapy in Ovarian Injury

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## Abstract

This review summarizes the clinical efficacy and experimental research of traditional Chinese medicine (TCM) moxibustion in the intervention of ovarian injury. Clinical and experimental research results have shown that as a nonpharmacological treatment method, Chinese medical moxibustion therapy is of great significance in the treatment of ovarian injuries such as diminished ovarian reserve, polycystic ovarian syndrome, premature ovarian failure, and premature ovarian insufficiency. Moxibustion, heat-sensitive moxibustion, and electroacupuncture have significant effects in improving ovarian function, overall treatment efficacy, pregnancy rate, ovulation rate, and sex hormone levels and have higher safety. Their therapeutic mechanisms have also been demonstrated. In conclusion, TCM moxibustion therapy has a significant effect in the treatment of ovarian injury, providing a new option for the treatment of the ovarian injury.

## Keywords

- ▶ TCM moxibustion
- ▶ ovarian damage
- ▶ heat-sensitive moxibustion
- ▶ electroacupuncture

## Introduction

In the female reproductive system, ovaries play a vital role. However, ovarian injury often brings great trouble to the female and health threat. Clinically, diminished ovarian reserve (DOR), polycystic ovary syndrome (PCOS), premature ovarian failure (POF), and premature ovarian insufficiency (POI) are relatively common ovarian injury problems. Studies have shown that increase in the incidence of DOR has affected approximately 10% of women causing infertility.<sup>1</sup> And the prevalence of PCOS in women of reproductive age is as high as 15%.<sup>2</sup> Therefore, approximately 1 to 3% of adult women worldwide are diagnosed with POF.<sup>3</sup> All of these diseases can damage the ovaries. Traditional Chinese medicine (TCM) moxibustion, as a natural therapy with a long history, is a unique health resource in China. It plays an important role in moxibustion therapy, and its application in

the treatment of ovarian injury has gradually attracted people's attention.<sup>4</sup>

Some literature research shows that TCM moxibustion has significant effects on improving ovarian function,<sup>5</sup> increasing ovulation rate and pregnancy rate,<sup>6</sup> and regulating endocrine level.<sup>6,7</sup> This review will comprehensively analyze the types of common moxibustion methods, the intervention period of moxibustion and the types of ovarian injury, covering the relevant literature in the field of clinical efficacy and experimental research of TCM moxibustion on ovarian injury in recent years, and explore the efficacy and potential mechanism of TCM moxibustion in the treatment of ovarian injury. In addition, we will also pay attention to the comparative research on the efficacy and safety of TCM moxibustion and other treatment methods, such as Western medicine, Chinese medicine, and combination drugs, to provide more basis for clinical practice.

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## Clinical Study on the Application of Moxibustion Therapy in Ovarian Injury

### Acupuncture

Acupuncture is a unique means of treating diseases in China. In recent years, acupuncture, as a treatment method of treating from the outside to the inside, plays an important role in the treatment of ovarian injury.

Clinically, acupuncture has a significant effect in the treatment of PCOS.<sup>8</sup> Compared with conventional drug treatment, acupuncture in the treatment of PCOS combined with infertility can significantly improve the total effective rate of clinical treatment, ovulation rate, and pregnancy rate.<sup>6</sup> And there were also marked reductions in serum levels of luteinizing hormone (LH), testosterone (T), and follicle-stimulating hormone (FSH).<sup>9</sup> For obese patients with PCOS, acupuncture can not only achieve ideal results but also obtain high satisfaction.<sup>10</sup> In addition, acupuncture also has significant effects in the treatment of POF and reduction of ovarian reserve function. Niu et al<sup>7</sup> founded that acupuncture could significantly reduce the serum levels of FSH and LH, increase the level of antimullerian hormone (AMH), increase the number of basal antral follicles, and increase the maximum ovarian plane diameter in patients with decreased ovarian reserve. In the treatment of patients with decreased ovarian reserve function with kidney deficiency and liver depression syndrome, Liang<sup>11</sup> showed that compared with the sequential treatment of estrogen and progesterone cycles, acupuncture and moxibustion can also significantly increase the serum AMH level, improve ovarian reserve function, and improve the clinical syndrome of TCM in patients with kidney deficiency and liver depression syndrome. This is of great significance for improving ovarian reserve function and preventing and delaying the occurrence of POF.

### Moxa-moxibustion

Moxa-moxibustion is a TCM therapy in which folium artemisiae argyi is used to make moxibustion materials, where they burnt to generate heat and stimulate acupoints or specific body surface areas, and thus, the goal of disease prevention and treatment is achieved. Most studies have shown that moxibustion combined therapy can be used to treat patients with ovarian injury.

Similar to acupuncture and moxibustion therapy, moxa-moxibustion can also be used for patients with ovarian insufficiency such as PCOS, POF, and decreased ovarian reserve function. For the treatment of patients with PCOS, moxa-moxibustion combined with Western medicine and Chinese medicine can significantly improve the overall effective rate, ovulation rate, and pregnancy rate than Western medicine or Chinese medicine alone, and the regulation of hormone levels such as FSH, LH, and AMH is also significantly improved than with single therapy alone.<sup>12,13</sup> This type of combination therapy also has a similar therapeutic effect on patients with reduced ovarian reserve, which can improve ovarian function by increasing the total response rate and maintaining the stability of sex hormones such as FSH and

estradiol (E<sub>2</sub>), thus improving ovarian function.<sup>5,14</sup> Wu and Shu<sup>15</sup> also showed that massotherapy and moxa-moxibustion combined with Yougui Pills can significantly improve the efficacy of POF with the syndrome of spleen and kidney yang deficiency, and its effect on regulating FSH, LH, and E<sub>2</sub> levels has also been proved. At the same time, this therapy can also improve the safety of treatment.

### Heat-Sensitive Moxibustion

Heat-sensitive moxibustion is a new type of therapy developed on the basis of moxa-moxibustion, which is to find heat-sensitive acupoints through suspension moxibustion and apply specific techniques to stimulate moxibustion to achieve individualized desensitization of acupoints, which can significantly improve the effect of moxibustion.<sup>4</sup> With the clinical application of thermosensitive moxibustion, the effectiveness of this technology in treating ovarian injury has also been developed.

Li and Fan<sup>16</sup> showed that self-made Yiqi Huoxue decoction combined with heat-sensitive moxibustion on the basis of conventional Western medicine could significantly improve the total effective rate, ovulation rate, and pregnancy rate of PCOS patients and also improve the serum sex hormone levels of patients. For PCOS patients with the syndrome of kidney yang deficiency, heat-sensitive moxibustion combined with letrozole can significantly improve follicular development and endometrial thickness compared with letrozole alone. Unlike the study conducted by Li and Fan 2019,<sup>16</sup> no significant advantage was found in improving pregnancy and ovulation rates with this combination therapy,<sup>17</sup> which may be related to the type of combination or the type and severity of patients. In the treatment of PCOS infertility patients, the therapeutic effect of acupuncture combined with heat-sensitive moxibustion is significantly better than that of acupuncture combined with mild-warm moxibustion. It can not only significantly improve the condition of polycystic ovary, but also regulate the levels of LH and FSH, which is significantly better than acupuncture combined with mild-warm moxibustion.<sup>18</sup> Similar to the above, heat-sensitive moxibustion can also be used to treat patients with POF or POI. A study has shown that heat-sensitive moxibustion combined with Bushen Shugan prescription has a higher clinical efficiency in the treatment of patients with POI than Bushen Shugan prescription alone, and its regulation of hormone levels and ovarian function is significantly better than Bushen Shugan prescription alone.<sup>19</sup> For patients with POF, electroacupuncture combined with heat-sensitive moxibustion is more effective than taking Climen orally.<sup>20</sup> Under the same condition of taking Climen orally in the control group, the overall efficacy of acupuncture combined with heat-sensitive moxibustion showed no significant advantage, but it had fewer side effects and was more easily accepted by the patients. Yang et al<sup>21</sup> showed that the effect of heat-sensitive moxibustion combined with artificial cycle therapy in the treatment of POF with spleen-kidney yang deficiency syndrome was significantly better than that of artificial cycle therapy and speculated that its efficacy may be related to the improvement of

serum prefibrin and vascular endothelial growth factor levels. For the treatment of POF with kidney yin deficiency syndrome, heat-sensitive moxibustion combined with meridian ebb acupoint application is not only superior to single meridian ebb acupoint application but also has higher safety.<sup>22</sup>

## Experimental Study on the Application of Moxibustion to Ovarian Injury

### Acupuncture

Studies have shown that acupuncture has a significant effect on regulating sex hormone levels in PCOS rats, which can significantly reduce the levels of serum LH, FSH, T, and AMH and significantly increase the level of E<sub>2</sub>.<sup>23</sup> And it can also improve the ovary morphology and function of PCOS model rats induced by dehydroepiandrosterone (DHEA). This regulation of acupuncture on sex hormone levels in female rats with PCOS was also demonstrated in a study.<sup>2</sup> Chen et al<sup>24</sup> also showed that acupuncture could regulate autophagy in ovarian granulosa cells through the PI3K/AKT/mTOR pathway mediated by LncMEG3. In addition, it was also demonstrated that LncMEG3 could target miR-21-3p to inhibit the early and late apoptosis of ovarian granulosa cells in PCOS rats,<sup>24</sup> which revealed the significance of acupuncture in the treatment of PCOS. For the study of acupuncture intervention in PCOS rat models, Xing et al<sup>25</sup> provide another insight into the mechanism of acupuncture in the treatment of PCOS, suggesting that acupuncture can improve endometrial angiogenesis by activating the PI3K/AKT pathway, thereby promoting endometrial receptibility and the number of implant sites in PCOS rats, providing a more theoretical basis for clinical application.

### Moxa-moxibustion

In recent years, experimental research on the effects of moxa-moxibustion on female reproductive health has also been developed. Jin et al<sup>26</sup> showed that moxa-moxibustion intervention before or in the early stage of DOR in Sprague-Dawley (SD) rats can improve ovarian function, and its protective effect is related to the androgen receptor mediated androgen balance. It is worth noting that the treatment course of moxibustion before DOR occurs needs to be longer than that of moxa-moxibustion in the early stage of DOR to achieve the same ovarian protection effect. As for the study of moxa-moxibustion intervention before the occurrence of the disease, Shen et al<sup>27</sup> found that moxibustion pretreatment can significantly improve the estrus cycle of rats with POI, regulate the levels of E<sub>2</sub>, AMH, FSH, and LH in serum, inhibit the apoptosis of ovarian granulosa cells, protect the ovarian function of POI rats, and thus improve the fertility of POI rats. When moxibustion intervention was performed during the occurrence of the disease, Li et al<sup>28</sup> demonstrated that moxibustion could improve tripterygium glycoside (TGS) suspension-induced ovarian function decline and inhibit ovarian granulosa cell apoptosis in DOR rats by regulating PI3K/AKT signaling pathway, which was consistent with the previous study.<sup>25</sup>

Similarly, the efficacy of moxibustion intervention after the occurrence of female reproductive system diseases in animals has been demonstrated. Moxa-moxibustion intervention can reduce the NLRP3 inflammasome activated by TGS-damaged ovarian tissue and follicular development in rats and improve the inflammatory microenvironment by activating Nrf2/HO-1 pathway.<sup>29</sup> However, whether NLRP3 over-activation is Nrf2/-HO-1 dose-dependent needs to be further studied. For the rat model of POI, moxibustion can improve the ovarian reserve function of cyclophosphamide (Cy)-induced POI rats by reducing mitochondrial dysfunction and NLRP3 inflammatory activation,<sup>29</sup> which may also be a new strategy for the treatment of POI.

### Electroacupuncture

Electroacupuncture is a treatment method that originated from TCM acupuncture and moxibustion. It plays an important role in the treatment of primary insomnia, anxiety, depression, and persistent pain<sup>30,31</sup> by combining traditional acupuncture procedures with electrical stimulation.<sup>32</sup> In recent years, electroacupuncture has made progress in the treatment of ovarian injury.

Studies have shown that electroacupuncture plays an important role in the treatment of SD rats with PCOS. It can improve the disordered estrous cycle, ovarian tissue morphology, and hormone levels of FSH, LH, and E<sub>2</sub> in rats with PCOS.<sup>33-36</sup> Concurrently, it also has a similar therapeutic effect on the improvement of symptoms in PCOS mice such as C57BL/6J mice and female mice of the Institute for Cancer Research.<sup>37,38</sup> In addition, the mechanism of electroacupuncture improving the symptoms of PCOS rats has also been developed. Shen et al<sup>36</sup> found that electroacupuncture may improve the gonadal axis function of PCOS rats through the expression of hypothalamic Kisspeptin protein. Cong et al<sup>33</sup> also clarified the ability of electroacupuncture to resist the effects of PCOS by inhibiting endoplasmic reticulum stress-mediated apoptosis and autophagy of ovarian granulosa cells. In addition, electroacupuncture can also improve the reproductive characteristics of PCOS rats by regulating hypothalamic neuropeptide Y and growth hormone levels,<sup>34</sup> regulating Alas2-mediated apoptosis and mitochondrial function,<sup>39</sup> and regulating kisspeptin-GnRH/LH pathway through androgen activity attenuation.<sup>35</sup> Chen et al<sup>40</sup> showed that electroacupuncture also had a certain promoting effect on ovarian function and menstrual cycle of POF mice. For rats with DOR, the effect of electroacupuncture on improving ovarian function and hormone levels can be achieved by regulating the expression of GSH-related regulatory enzyme protein and mRNA in the ovary and improving the body's ability to resist oxidative stress.<sup>41</sup>

## Discussion

In the treatment of ovarian injury, TCM moxibustion has gradually attracted attention. However, there are still some controversies and inadequacies in this field.<sup>42</sup> This review summarizes the clinical efficacy and experimental research progress of TCM moxibustion in the treatment of ovarian

injury, aiming to provide reference and enlightenment for further research.

TCM theory believes that the ovary is an important organ of the female reproductive system, which is mainly responsible for the growth and development of eggs and the secretion of female hormones, and plays an important role in female fertility and health. When the ovary is affected by trauma or internal diseases, it may lead to abnormal ovarian function and even affect fertility. Therefore, treatment of ovarian damage is essential to maintain women's health and fertility. In terms of clinical efficacy, TCM moxibustion has shown significant effects in improving ovarian function,<sup>11,14</sup> increasing pregnancy rate,<sup>43</sup> and regulating hormone levels.<sup>13</sup> The clinical effect of its combination with Western medicine or TCM is more significant.<sup>16</sup> It should be noted that TCM moxibustion therapy for ovarian injury needs to comprehensively consider the specific conditions of the patient, such as age, etiology, course of disease, and other factors, and combine with other TCM treatment methods such as herbal medicine for comprehensive treatment to achieve better efficacy. At the same time, when receiving TCM moxibustion therapy, patients also need to cooperate with the guidance of doctors, pay attention to regulate diet, living habits, etc., so as to improve the therapeutic effect.

In terms of experimental research, the therapeutic effect of TCM moxibustion on ovarian injury is supported by experimental evidence. For example, moxibustion can improve the estrus cycle of mice,<sup>37</sup> inhibit apoptosis of rat ovarian granulosa cells,<sup>28</sup> and regulate hormone balance.<sup>44</sup> Interestingly, these studies covered moxibustion interventions before, during, and after the occurrence of ovarian damage, and all of them were able to obtain significant effects. These findings suggest that moxibustion intervention can be applied in the prevention, treatment, and recovery of ovarian injury.

## Conclusion

TCM moxibustion therapy has potential advantages and broad prospects in the treatment of ovarian injury, which can improve ovarian function, maintain the stability of endocrine level, and, combined with other treatment methods for comprehensive treatment, can achieve better therapeutic effects. However, there are still some controversies and insufficiencies in the existing research. Future research should focus on the following: (1) The mechanism and advantages of TCM moxibustion in the treatment of ovarian injury should be further explored. (2) The advantages and disadvantages of TCM moxibustion therapy and other treatment methods should be further explored in terms of efficacy and safety. (3) The influence of individual differences on the treatment effect should be paid attention to, so as to provide more accurate treatment for clinical practice. (4) At present, the experimental mechanism of heat-sensitive moxibustion on ovarian injury is lacking. At the same time, it is hoped that through further research, more possibilities of TCM moxibustion therapy in the treatment of ovarian injury

can be explored, so as to provide patients with a safer and more effective treatment method.

## CRedit Authorship Contribution Statement

Houpeng Wang: Data curation, methodology, and writing—original draft. Ning Zhang: Visualization, resources, and methodology. Liping Zheng: Conceptualization, methodology, and supervision. Liaoliao Hu: Writing—review and editing.

## Conflict of Interest

The authors declare no conflict of interest.

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