

## Uterine leiomyoma and traditional Chinese medicine

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**[ Abstract ] Objective** To review the recent research progress of traditional Chinese medicine in treating uterine leiomyoma and to evaluate its clinical effects. **Methods** Data sources information included in this article was identified by searching of PUBMED(2003 ~ 2008) and WANFANG DATA(1999 ~ 2008) online resources using the key terms “uterine leiomyoma” and “Chinese traditional medicine”. Study selection overview of the past 10 years of traditional Chinese medicine treatment on uterine leiomyoma literature, with information on the forefront of all areas of large sample studies, and author of many years of clinical experience as a professional doctor of Chinese medicine. **Results** Through the past 10 years in traditional Chinese medicine on the treatment of uterine leiomyoma to be outlined in the literature and found that traditional Chinese medicine treatment of small uterine leiomyoma (Diameter < 4 cm) are more efficient rate as high as 85%, the cure rate can be as high as 30%, no more efficiency is only 4%. **Conclusion** There is some clinical effect of traditional Chinese medicine on treating the uterine leiomyoma, especially for small leiomyoma. It is effective for the vast majority of patients if applied reasonably and is expected to waive the side effects brought about by hormone therapy and surgery.

**[ Key words ]** uterine leiomyoma; traditional Chinese medicine; treatment

### INTRODUCTION

Uterine leiomyoma (UL) is a benign substance and the most common gynecological tumour, which is formed by the proliferation of uterine smooth muscle cells and small amount of connective tissue fibers. The incidence rate of women in childbearing ages is from 20% to 25%<sup>[1]</sup>. Among 40-to 50-year-old women, its incidence rate became the maximum which was ranging from 52.2% to 60.0%<sup>[2]</sup>. The latest epidemiological data show that the incidence of uterine leiomyoma has a upward trend in recent years and the patients become much younger than before, resulting in clinical hysterectomy rate as high as 84% because of UL<sup>[3]</sup>. So how to control small leiomyoma has become a hotspot issues for the gynecological academics. And traditional Chinese medicine has a unique effect in controlling growth of leiomyoma with irreplaceable role. In this paper,

combining the basic theory of traditional Chinese medicine treatment to uterine leiomyoma, we summarized nearly 10 years clinical experiences about traditional Chinese medicine treatments on uterine leiomyoma and made evaluation on its role.

### BASIC RESEARCH PROGRESS OF UTERINE LEIOMYOMA

In the earlier research results, it was shown that the uterine leiomyoma was a kind of hormone-dependent disease. Estrogen and progesterone played an important role on its occurrence and development. In the latest research results, it was indicated that the uterine leiomyoma was caused by the activation of oncogenes and inactivation of tumor suppressor factor which led to the imbalance of apoptosis and proliferation<sup>[4,5]</sup>. But so far the pathogenesis of the leiomyoma is still not very clear.

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Nowadays, it is thought that the estrogen and progesterone are the start components for the growth of leiomyoma, as well as other factors such as age, race, maternal, obesity and other factors associated with them. Estrogen (E<sub>s</sub>), progesterone (P), growth factor (GF) could promote the growth of leiomyoma. Gonadotropin-releasing hormone (GnRH) is the controlling-factor for the growth of leiomyoma. Abnormal apoptosis, particularly in excessive inhibit of apoptosis is also related to the development of the leiomyoma. Local formation of the abnormal high E and ER environment may be the main factor which induced the UL. P is an important factor for growth of UL. High-dose P may reverse the role of GnRH in the dose-dependent manner. The common role of E<sub>2</sub>, P and ER, PR could not be separated. The cells growth and the maintenance of UL depends on the environment synergies between E<sub>2</sub> and P. E<sub>2</sub>, P have different roles on cell proliferation and apoptosis, which reveals there is the causal relationship among the hormone, proliferation apoptosis and UL. The changes of hormone adjustment process results in the increasing of proliferation rate and decreasing apoptosis rate<sup>[6]</sup>.

It was also noticed by the research that the compound of traditional Chinese medicine (consisted of astragalus, vitex health spider, water frog) which had the effects of invigorating Qi and dissolving stasis could significantly reduced the expression of leiomyoma cell proliferation-related proteins (PCNA) and apoptosis-related proteins (bcl-2, Fas/Fas-L) ( $P < 0.001$ ). By reducing the expression of PCNA, cell proliferation of uterine leiomyoma could be inhibited directly. Cells Apoptosis of uterine leiomyoma could be induced by conditioning bcl-2, Fas-L protein expression<sup>[7]</sup>.

Many studies have implicated that numerous hormones, growth factors, cytokines and other signal transduction molecules also played important roles in the pathogenesis of uterine leiomyoma. Through the comparative and comprehensive analysis of DNA chips, protein interactions, RNA interaction and immunohistochemical studies, Swartz and so on's study<sup>[8]</sup> presumed an initial estrogen-primed signal transduction tunnel and based on the abnormal expression, it was suggested that an increase of E<sub>2</sub> → (Possible) up-regulated IGF-I

→ (may) up-regulated the A-myb and MAPK-P of cell nuclear; or, E<sub>2</sub> may be directly up-regulated the MAPK-P of the cytoplasm, then up-regulated MAPK-P through transferring from cytoplasm to the nuclear, and eventually leading to gene transcription, so as to promoting cell proliferation.

Epidemiological investigation concluded that the occurrence of uterine leiomyoma was related to the heredity. And the incidence of cervical erosion, pelvic inflammatory disease, family history of gynecological cancer and other factors were related to the uterine leiomyoma. In recent years, it was also found that the incidence of uterine leiomyoma was related to the genic mutation. Skubitz, etc<sup>[6]</sup> used gene chips to detect uterine leiomyoma as well as the normal uterine muscle tissue and found the main difference between the expression of genes were involved in cell signaling, transmission of protein, protein synthesis translation category, cytoskeleton and its exercise, ion channel and protein metabolism and transport, etc. At the same time, Litovkin, etc<sup>[9]</sup> found that gene on leiomyoma FN1 cell proliferation has obvious leading increase effects on the growth of uterine leiomyoma. Therefore, FN1 genetic had great significance on leiomyoma diagnosis, prognosis and treatment guide.

In short, it was believed by modern medical research that the incidence of uterine leiomyoma factors included (1) long-term and excessive stimulation of estrogen; (2) the important role of progesterone during the course of myomagenesis; (3) and growth factors, cytokines, the relevant gene mutation; (4) immune hypofrontality and (5) the factors related to genetic or infection.

## THEORETICAL FOUNDATION OF TRADITIONAL CHINESE MEDICINE IN TREATMENT OF UTERINE LEIOMYOMA

According to the pathogenesis of uterine leiomyoma, the treatment principles for uterine leiomyoma through using traditional Chinese medicine are as follows, (1) regulating hypothalamus-pituitary-ovarian gonadal function; (2) promoting blood circulation dissolving stasis; (3) anti-inflammatory; (4) improve immune function and (5) Giving drugs according to the dialectical situa-

tion of patients, that is: mainly cutting if healthy atmosphere is prosperous, or both attack and nourish if healthy atmosphere is fall off.

Traditional Chinese medicine believes that the uterine leiomyoma belongs to the category of indurated mass in the uterus or stasis syndrome. Its occurrence has close relation with liver, spleen, kidney and uterus. The main interpretation of the cause includes yin yang disharmony, depression of hepatic *qi*, less activity of spleen and kidney *qi* and the subsequent functional activity of *qi* being not smooth or *qi*-stagnancy and blood stasis. The methods of activating blood circulation to dissipate blood stasis or soft lump loosen knot are adopted as the main treatment approaches by the traditional Chinese medicine and the ancient pellet prescription of cassiabarktree twig with poria cocos (*Guizhi Fuling Wan*) is mostly used as the efficient formula. The capsule of cassiabarktree twig with poria cocos is its pellets' new dosage form and it can cure the uterine leiomyoma by oral use. Its key components include cassiabarktree twig, poria cocos, and tree peony root-bark, etc with the function of activating blood circulation to dissipate blood stasis and dissolving stasis. The anti-hyperplasia and contra-tumors mechanism of cassiabarktree twig with poria cocos is possibly related with its function to lower the internal female or progesterone as well as the content of smooth muscle cell receptor. As the progesterone possesses the important role on promoting leiomyoma development and it can bring the biological effect into play through combining the PR, one of the factors that the capsule of cassiabarktree twig with poria cocos's mechanism is possibly to lower the content of PR<sup>[10]</sup>. In short, traditional Chinese medicine treatment on uterine leiomyoma was conducted mainly through the following components.

### Impacts of Sex Hormone and its Receptor

Wang Yonglin, etc<sup>[11]</sup> used the traditional Chinese medicine in their estrogens crest-time. Five days before menstruation, the patients were given the treatment of justifications-decoction and drug withdrawal during menstrual period. Five days after menstruation, the treatment continued as using the powder of single-masted (*Xiaoyao San and Shixiao San*) with 6 circles as 1

course of treatment. The control group was treated through using the pellet of cassiabarktree twig with poria cocos (*Guizhi Fuling Wan*). The result manifested that the effects of treatment group were better than control group. This result confirmed that the theories of activating blood circulation to dissipate blood stasis through soup washing in luteal phase and soothing liver or strengthening spleen through plus or minus using the powder of single-masted (*Xiaoyao San and Shixiao San*) had certain curative effect and the post-treatment E<sub>2</sub> level decreased obviously comparing with the pretherapy condition.

Fuping, etc<sup>[12]</sup> observed the clinical effects of daemonorops draco tumour particle treatment on uterine leiomyoma and its impacts on E<sub>2</sub>, P, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). According to the syndrome of hypermenorrhea, they divided the patients in 2 groups with the treatment group of 78 cases and the control group of 45 cases. These 2 groups were given the treatment of daemonorops draco tumor particle and capsule of cassiabarktree twig separately, and the total effective rate of treatment group and control group was 96.2% and 71.1% respectively. In the treatment group, the content of P and E<sub>2</sub> was lowered and the level of LH and FSH increased obviously and it had great difference with the condition of control group. It was believed that one of its action mechanisms was to reduce the patients' E<sub>2</sub> and P level. And they made further observation on patients which were younger than 45 years old and found that the daemonorops draco tumor particle only had impacts on blood serum P level. The P level had significant deviation between prior treatment and post treatment. It had no obvious impacts on the content of E<sub>2</sub>, LH and FSH. For those patients who were older than 45 years, all of the contents, such as the E<sub>2</sub>, P, LH and FSH had significant deviation between prior treatment and post treatment. The results demonstrated that the decrease of progesterone level had associativity with uterine leiomyoma diminution.

After adopting the treatments of tripterygium glycosides, Gao Yu-ping<sup>[13]</sup> made further measurements on the levels of FSH, LH, pituitary prolactin (PRL), E<sub>2</sub>, P and testosterone (T). It was found that the P level de-

creased and FSH and LH level increased obviously. The ER, PR protein expression decreased significantly and the size of uterine leiomyoma zoomed out. This result confirmed that the treatments of tripterygium glycosides to gonads axis not only had reversible depressant effects, but also could restrain uterine leiomyoma and muscle tissues' ER, PR expression on protein level. Possibly, this was the main therapeutic action mechanism.

### **Adjustments to Uterine Shape and its Activities**

It was shown by the uterine histomorphology that under the role of estrogen on uterine leiomyoma, the muscle fibers in myometrium had the syndrome of hyperplasia and hypertrophy with some regional disorder or cross-shuttle. The uterine cavity was out of shape as the results of compression. After treatments, there were some improvements on uterine histomorphology with different degrees. Liu Hong, etc.<sup>[14]</sup> carried out the treatments through using the traditional Chinese medicine which could activate blood circulation and soft lump loosen knot, such as salvia miltiorrhiza bunge, red peony root, trogopteris, health pollen and anteaters, etc. It was shown that the activating blood circulation or dissipating blood stasis treatment can change the connective tissue's hyperplasia and lower the size of uterine leiomyoma in different degrees ranging from 3% to 100%. Chen Xilin, etc.<sup>[15]</sup> observed the function of the capsule of cassia bark twig and tuckahoe which was used to treat the uterine leiomyoma and found it could play the anti-bacterial and anti-platelet aggregation role as well as lowering the blood viscosity. This method could also improve the cavitas pelvis microcirculation, loosen the uterus smooth muscle and have strong analgesic effects.

### **Immune Modulations**

Li Ling, etc.<sup>[16]</sup> used the tumour-cleaning tablet as the treatment method and found patients' serum immune regulatory factor IL-2 level increased while TNF- $\alpha$  level decreased significantly. It was shown that the tumour-cleaning tablet could play the role of adjusting and boosting the immune function as well as the direct anti-tumor effects.

## **CLINICAL EFFECTS OF TRADITIONAL CHINESE MEDICINE TREATMENT TO UTERINE LEIOMYOMA**

### **Approaches of Traditional Chinese Medicine Treatment to Uterine Leiomyoma**

Starting from the overall concept, according to the syndrome to determine the curing methods and combining the cyclical nature of women, the traditional Chinese medicines was used to treat the uterine leiomyoma from multi-channel and multi-angle aspects and achieved good clinical experience and research fruits. In recent years, abiding by the principles of internal-disease external-treatments, many scholars have managed to use external treatment to cure the uterine leiomyoma patients and diversified its approaches. These kinds of treatments improved the patients' conditions and raised the curative effects. The detailed methods include external applyment of traditional Chinese medicine, sticking applyment on acupoints, medicine clyster, vaginal drug administration, acupuncture therapy, etc.

### **Clinical Effects of Traditional Chinese Medicine Treatment to Uterine Leiomyoma**

In recent 10 more years, there had been many reports that the traditional Chinese medicine was used to treat uterine leiomyoma. The treatment approaches were diversified but the main way was to use the traditional Chinese medicine. As these kinds of treatments had obvious clinical effects, it was shown that the approaches which were treating uterine leiomyoma with activating blood circulation and dissipating blood stasis medicines had been generally accepted and become the consensus.

According to the clinical criteria established by the Ministry of Health<sup>[17]</sup>, the assessment standards for clinical effects are as follows, (1) cure, leiomyoma and clinical symptoms disappeared; (2) markedly effective, leiomyoma size lowering more than 1/2 and the symptoms severity integral points fell 2/3 comparing with prior treatment; (3) effective, leiomyoma size lowering more than 1/3 and the symptoms severity integral points fell 1/3 ~ 2/3 comparing with prior treatment; (4) invalid, no leiomyoma size lowering obviously and the symptoms severity integral points fell less than 1/3

**Table 1 The clinical effects of treatment of uterine leiomyoma with traditional Chinese medicine**

Time	Author	Number of cases	Average size of leiomyoma	Total off ective	The clinical effect ( % )			
					Cure rate	Significant efficiency	Efficient	Inefficient
2001	YANG JL <sup>[18]</sup>	300	<6 cm in diameter	86.7	7	40.7	39	13.3
2003	SANG HL <sup>[19]</sup>	120	* 96.45 cm <sup>3</sup> involume	95.8	30	37.5	28.3	4.2
2004	WANG YX <sup>[20]</sup>	45	<5.6cm in diameter	95.9	26.7	40	28.9	4.4
2005	WANG P <sup>[21]</sup>	74	2.0 cm × 3.5cm	95.9	16.2	50	29.7	4.1
2006	SONG SM <sup>[10]</sup>	504	4.0 cm × 3.8 cm × 3.5 cm	77.1	0	14.8	6.2	30.0
2007	WANG HY <sup>[22]</sup>	38	<6.2cm in diameter	89	16	47	26	11
2008	ZHAO H <sup>[23]</sup>	200	4.1 cm × 3.5 cm × 3.8 cm	94	0	52	42	6

Note: \* Gross tumor volume:  $4/3\pi abc$

comparing with prior treatment. In this respect, we summed up recent years' large sample clinical data of traditional Chinese medicine treatment to uterine leiomyoma, see Table 1.

As it was shown in the table, the effective rate of treating uterine leiomyoma by traditional Chinese medicine was more than 85% and the cure rate was as high as 30%. Mehl-Madrona<sup>[2,4]</sup> used the traditional Chinese medicine treatment which was involved 37 cases of uterine leiomyoma in clinical data. The time range was 180 days, and sizes of 22 leiomyoma cases zoomed out or ceased growing. All of the cases' syndrome were relieved and received a fairly high degree of satisfaction. Comparing with other medicine and surgery operation, the author believed that the treatment with traditional Chinese medicine was value for money and worth a try. In recent years, the multi-approach treatment with traditional Chinese medicines had made new achievements and their clinical effect was obvious which were better than treatment with Western medicine (Mifepristone)<sup>[25]</sup>.

Taking an clinical literature overview of traditional Chinese medicine treatment to uterine leiomyoma, here are the common features as follows, (1) relatively smaller leiomyoma, the largest diameter <6.2 cm, the vast majority ranging from 3 cm to 4 cm, and the smaller leiomyoma, the better clinical effect and the higher cure rate; (2) either oral or enema, the main approach was to take Chinese traditional medicine orally combined with other assistance means; (3) the shortest time range was 90 days, and most cases were 180 days.

**ASSESSMENT AND PROSPECTS OF TRADITIONAL CHINESE MEDICINE TREATMENT ON UTERINE LEIOMYOMA**

With long-term efficacy and stability, there were many advantages of traditional Chinese medicine treatment to uterine leiomyoma, such as improving symptoms, reducing bleeding, correcting anemia and physical restoration, etc. But the course of these kinds' treatments lasted long time and the leiomyoma sizes reduced slowly. Also, there were no reports about recurrence after drug withdraws. Nevertheless, for small leiomyoma, especially for those patients whose leiomyoma's diameter was less than 4 cm, this treatment was still a good policy to avoid the passive embarrassing situation of awaiting its doom and it is a positive attitude to contain the leiomyoma in the "embryonic" state. It could improve the patients' syndrome as well as their life quality which was consistent with the 21<sup>st</sup> century concept and had great prospects.

In short, traditional Chinese medicine treatment to uterine leiomyoma had diverse methods and greatly noticeable clinical effects. It could keep the patients away from trauma surgery and after operation pelvic adhesions, genital mutilation, bad blood circulation or small residual issues, etc. It also can avoid ovarian function suppression caused by hormone therapy or hormone absence as well as recurrence after drug withdraws. For uterine leiomyoma, the performances of traditional Chinese medicine treatment have unique advantages, broad development prospects and great potentials.

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