

Phytotherapy for Uterine Fibroids

by Kerry Bone

Uterine fibroids, more correctly known as uterine myomas or uterine leiomyomas, are said to be among the most frequently encountered gynecological problems.¹ They are the most common solid pelvic tumor in women, occurring in 20 to 40% of women during their reproductive years. Approximately 600,000 hysterectomies are performed per year in the United States, about one third of these are because of fibroids.^{1,2}

Fibroids are benign tumors that originate from the smooth muscle cells of the uterus, although in some cases the smooth muscle tissue of uterine blood vessels may be their source.¹ One distinctive feature of the tumors is the presence of abundant fibrous connective tissue, hence the name "fibroids".³ This overexpression of collagen and extracellular matrix not only contributes to the growth of the bulk of the tumor, but is also considered to play a dynamic role in supporting the tumor growth. This is thought to be by influencing cellular proliferation and differentiation as well as serving as a repository for growth factors and cytokines.³

The tumors range in size and may be solitary or multiple. They can be found within the muscular layer of the uterus (intramural), externally extending into the abdominal cavity (subserous) or internally impinging on the uterine cavity (submucous).¹

Although their exact cause or causes remains unknown, there is now abundant information pertaining to the epidemiology, genetics, hormonal aspects and molecular biology of these tumors.² This information can help to inform a rational approach to their management using herbs and so is briefly reviewed below.²

Risk Factors

Reproductive History

Recently, a significant inverse association between risk of fibroids and age at menarche was reported. Compared with women who were 12 years of age at menarche, those who were ≤ 10 years of age at menarche were at increased risk (relative risk, RR, 1.24), whereas women

who were age ≤ 16 years of age at menarche were at lower risk (RR 0.68).^{2,4}

Several studies have shown an inverse relationship between the number of pregnancies and the risk of fibroids.² One explanation is that pregnancy reduces the time of exposure to unopposed estrogens. The reduced risk of fibroids requiring surgery in postmenopausal patients is probably due to tumor shrinkage in the reduced estrogen environment following menopause.²

The role of the use of oral contraceptives is controversial and may depend on the actual components of the pill used.² A significantly elevated risk of fibroids has been reported among women who first used oral contraceptives in their early teenage years (13-16 years of age) compared with those who had never used them.^{2,4}

In contrast, hormone replacement therapy (HRT) may not only prevent the shrinkage of fibroids after menopause, it may even stimulate their growth (or at least the growth of some of the tumors in women with multiple tumors).²

While tamoxifen is antiestrogenic in breast tissue it probably exerts estrogenic effects on the uterus. Hence it has been linked to promoting fibroid growth in a percentage of women in several clinical studies.²

Obesity

Several studies have found a marked association between obesity and an increased incidence of fibroids.² This may be related to hormonal factors, especially excess estrogen. In obese premenopausal women, decreased metabolism of estradiol by the 2-hydroxylation route reduces the conversion of estradiol to inactive metabolites, which could result in a relatively hyperestrogenic state.^{2,5} (See the studies cited later in this article on how flaxseed can help to correct this effect.)

A prospective study from the UK found that the risk of fibroids increased approximately 21% for each 10-kg (22-lb) increase in body weight.⁶ A large US study found a correlation between BMI and fibroid risk.⁷

Diet

One study has addressed the question of dietary influences on the prevalence of fibroids. In an Italian population, 843 women with fibroids were compared with 1557 women without. A diet weighted toward green vegetables was protective (RR 0.5), whereas a higher intake of meats was associated with a greater incidence of fibroids (RR 1.7).^{8,9}

It is known that vegetarians have lower plasma estrogen levels compared to non-vegetarians, so this fact could explain this observation. Also low fat diets are known to reduce estrogen levels.²

Smoking, Alcohol and Caffeine

Several studies have shown a reduced risk of fibroids associated with current smoking, but not past smoking.² Again this has been attributed to the reputed antiestrogenic effect of cigarette smoking.

One study found no change in risk for caffeine consumption and an increased risk for more than 7 drinks of beer per week.¹⁰

Infection

A case-control study of 318 women found, after adjustment for other known risk factors, that the incidence of uterine fibroids was positively correlated with a history of pelvic infection.^{8,11} A history of 3 separate episodes of pelvic inflammatory disease conferred a relative risk of 3.7. Similarly a history of infection with chlamydia gave a relative risk of 3.2.

Hypertension

High blood pressure is known to damage the smooth muscle lining of the arteries, and atherosclerosis is in part a proliferative condition of blood vessel walls. A prospective study of hypertension and risk of uterine fibroids found that diastolic blood pressure was an independent risk factor.^{8,12} Hypertensive women were 24% more likely to report fibroids, and for every 10-mg Hg increase in diastolic blood pressure the risk for fibroids increased 8 to 10%.

Genetic Factors

The higher incidence of clinically significant fibroids among African-American women in the United States suggests that a genetic predisposition to fibroids may exist.² There is a two-fold higher correlation of hysterectomy in identical female twins compared to non-identical female twins.¹³ This has been confirmed in other studies, although the effects of phenotype are thought to be at least as important as genotype.²

Hormonal Influences

It is widely accepted that estrogen and the interaction with estrogen receptors in the nucleus of the smooth muscle cell influence the growth of uterine fibroids. At menopause, fibroids begin to shrink in most patients, hence ovarian hormones are thought to play a key role in fibroid growth.¹⁴

While there are a considerable amount of both experimental results and clinical findings to support this connection, not the least being the recent use of gonadotropin-releasing hormone (GnRH) agonists as treatments for fibroids, the mechanism remains poorly understood.¹⁴ Estrogen may directly increase proliferation of leiomyoma cells or might indirectly increase growth by augmenting the effects of progesterone.¹⁴

The enzyme aromatase is present in fibroids. This enzyme governs the conversion of androstenedione into estrone and testosterone into estradiol. Also 17beta-hydroxysteroid dehydrogenase (17beta-HSD), which converts estrone into estradiol (the active form of estrogen) is overexpressed.¹⁵ This has led to speculation that aromatase inhibitors may be therapeutically useful in the management of fibroids.^{14,16}

Growth Factors

The growth promoting effects of estrogen and progesterone on the uterine smooth muscle cells is probably mediated via various locally produced growth factors.² In particular, transforming growth factor-beta (TGF-beta) appears to be the only factor overexpressed in fibroid cells which is hormonally regulated.³ Other growth factors have also been extensively investigated, but their role remains unclear.²

One interesting observation is the connection with prolactin.² Prolactin is produced by uterine tissues as well as the pituitary gland, and is a known growth promoter for vascular smooth muscle.² While this is speculative at this stage, it does provide further support for the use of chaste tree, which has been shown to decrease circulating prolactin levels in clinical trials.¹⁷

Clinical Features

Most patients with fibroids are symptom-free. When symptoms do occur, they usually correlate with the size and location of the tumor. Malignant transformation of fibroids is extremely rare. Excessive menstrual bleeding, presumably due to the vascular changes in the lining of the uterus is the most common symptom.¹ This can lead to severe fatigue and anemia over time. The reason why fibroids cause menorrhagia is not fully understood.¹⁸ However it is the submucosal fibroids that are most commonly linked to this problem.

The role of fibroids as a possible cause of infertility is debated.¹⁸ They can grow larger during pregnancy, but not in all women,¹⁸ and may increase the risk of spontaneous miscarriage during the early stages of pregnancy.¹⁸ For patients undergoing *in vitro* fertilization, distortion of the endometrial cavity by fibroids is associated with decreased pregnancy rates and increased spontaneous abortion rates in up to 50% of cases.¹⁹

Conventional Medical Treatments

Historically, symptomatic fibroids have been treated surgically, usually by hysterectomy. However, there are now less invasive options which include uterine artery embolization, myomectomy (fibroid removal) and GnRH analogues (often in conjunction with myomectomy).^{20,21} All these treatments carry the risk of side effects, which suggests a role for more gentle agents such as herbs in milder cases.

Herbal Treatment of Fibroids

The aim of herbal treatment for uterine fibroids is to minimize any further growth of the tumors and to manage any associated symptoms, especially the menorrhagia. It is unlikely that herbal treatments will substantially shrink fibroids (although see the study cited below). Treatment needs to be trialled for at least 3 months and combined with attention to those lifestyle issues identified by the risk factors listed earlier in this article. In particular, attention should be given to achieving a healthy body weight and diet.

A recent review observed that no controlled trials of complementary treatments for uterine fibroids could be found in the literature.²² However, a traditional Chinese herbal formula also used in Kampo was found by Japanese medical scientists to shrink uterine myomas.²³ The formula, known in Japanese as Keishi-bukuryo-gan (KBG) and in Mandarin as Kuei-chih-fui-ling-wan, contains *Cinnamomum cassia*, *Paeonia lactiflora*, *Prunus persica* seeds, *Poria cocos* and *Paeonia suffruticosa*. In English it is known as Cinnamon and Hoelen combination. This formula is frequently used in gynecological disorders such as pelvic inflammatory disease, menopausal symptoms, and menorrhagia and dysmenorrhea related to venous congestion of the pelvic region.

In an open study, 110 premenopausal women, average age 43.2 years (ranging from 27 to 52 years) were treated with the equivalent of 22.5 g/day of the dried herb formula administered as a freeze-dried decoction (1.5 g) for 12 weeks or more. These women had symptomatic uterine myomas all less than 10 cm in diameter. Clinical symptoms of menorrhagia and dysmenorrhea were improved in more than 90% of cases, with shrinkage of the fibroids in about 60% of patients.

The authors concluded that in young women who wished to remain fertile, and in women just before menopause, KBG treatment might be the first choice. The mechanism of action of the formula is not known, but the authors of the study suggested that it may act as a GnRH antagonist and could be weakly anti-estrogenic in the presence of estrogen. If this is the case, then the most important herbs in the formula are probably the two *Paeonia* species.

There is evidence to suggest that flaxseed supplementation causes change in estrogen metabolism that may be favorable for inhibition of uterine fibroids. Estradiol is the biologically active estrogen that drives the tumor growth. It is metabolized in the liver by the CYP450 enzymes 2-hydroxylase and 16alpha-hydroxylase into 2-hydroxyestrone and 16alpha-hydroxyestrone, respectively. The latter is still potently estrogenic, with uterotrophic activity similar to estradiol. Hence excessive formation of 16alpha-hydroxyestrone contributes to estrogen excess. Controlled clinical studies have shown that supplementation with flaxseed (10-25 g per day) significantly reduced the relative formation of 16alpha-hydroxyestrone in both pre- and postmenopausal women.^{24,25}

Treatment Strategy: Goals, Actions and Herbs

- Chaste tree is a major part of treatment and can be given in high doses (to depress estrogen production) if the fibroids are severe
- Liver herbs such as Schisandra and rosemary may help to reduce the enterohepatic recycling of estrogen by increasing its breakdown
- Antihemorrhagic herbs are indicated for the menorrhagia. The best uterine antihemorrhagic herb is shepherd's purse. Others include horsetail, yarrow and Tienchi ginseng
- Herbs that have been traditionally used to control benign growths include Echinacea root, Thuja and greater celandine. Recent research suggests that Echinacea root increases NK cell number and activity²⁶
- Typically, estrogen-modulating herbs such as false unicorn and wild yam would not be used. However, they may be needed to encourage ovulation in older women who tend to ovulate less frequently. They should only be used in conjunction with chaste tree for fibroids and not in high doses
- To modify the effects of estrogen and its metabolism, the dietary intake of phyto-estrogens, especially the lignans as found in flaxseed, should be increased
- *Paeonia* has been used in traditional Chinese formulations to shrink fibroids

Case Histories

Case History 1

A patient aged 43 presented with uterine fibroids characterized by menorrhagia and pain, especially with menstruation. She did not want surgery and asked for herbs to control her symptoms.

Treatment was as follows (based on 1 week).

<i>Capsella bursa-pastoris</i>	1:2	20 mL
<i>Achillea millefolium</i>	1:2	25 mL
<i>Thuja occidentalis</i>	1:5	20 mL
<i>Echinacea angustifolia</i>	1:2	20 mL
<i>Panax notoginseng</i>	1:2	<u>15 mL</u> 100 mL

Dosage: 5ml with water three times a day.

She was also prescribed chaste tree (*Vitex agnus castus*) 1:2, 2.5 mL with water twice a day, with the first dose on rising in the morning.

Ginkgo biloba 50:1 standardized extract, 40 mg per tablet, two tablets per day, was also prescribed for the pain.

After 10 weeks of treatment there was considerable improvement in the menorrhagia and pain. Herbal treatment was maintained for continued symptom control.

Case History 2

A female patient aged 41 presented with multiple uterine fibroids and heavy bleeding. A few of the tumors were quite large (>8 cm). She was placed on the following treatment:

a)

<i>Astragalus membranaceus</i>	1:2	20 mL
<i>Paeonia lactiflora</i>	1:2	30 mL
<i>Hypericum perforatum</i>	1:2	25 mL
<i>Withania somnifera</i>	1:2	<u>35 mL</u> 110 mL

Dosage: 5 mL with water twice a day

b) Chaste Tree 1:2 liquid. Dosage: 4 mL with water on rising.

This patient also regularly took Echinacea root 1:2 liquid at 5 mL per day.

Over the ensuing 5 years of treatment her fibroids grew slightly (but not rapidly) but she now experiences normal uterine bleeding. Her gynecologist cannot understand why this is so. Note that unlike the previous case, this patient received no uterine antihemorrhagic herbs.

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