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Alternative Approaches for Treatment of Uterine Leiomyomas

By Karlee Ausk, BS, and Susan D. Reed, MD, MPH

UTERINE LEIOMYOMAS, OR FIBROIDS, ARE BENIGN SMOOTH MUSCLE tumors diagnosed in approximately 25% of symptomatic women in the United States.^{1,2} Using routine ultrasound examination, uterine leiomyomas are observed in nearly 50% of white women and 73% of black women in the fifth decade of life.³ Leiomyomas are the most common indication for hysterectomy in the United States, account for one in five visits to a gynecologist, and are associated with health expenditures of more than \$1.2 billion annually.⁴

Most women with symptomatic leiomyomas present in their 30s and 40s. The main symptoms are abnormal uterine bleeding, pelvic pain, dysmenorrhea, and pressure.⁵ Abnormal vaginal bleeding manifests as menorrhagia, metrorrhagia, or both. Symptomatic leiomyomas can lead to significant problems with iron-deficiency anemia, social embarrassment, and diminished work productivity. As a fibroid expands, it causes an increasing girth and sense of fullness. Its irregular shape can cause urinary frequency, constipation, and dyspareunia. Leiomyomas may reduce reproductive capability.

Women's desire for nonsurgical intervention has prompted both allopathic and naturopathic physicians to consider and develop nonsurgical treatments for leiomyomas. Disenchantment with allopathic medicine and traditional medical approaches⁶ has led many women to question the use of hysterectomy, the most common allopathic therapy for uterine leiomyomas.⁷ Because of the number of women with symptomatic uterine leiomyomas, an effective treatment that minimizes risk and also maximizes satisfaction would have great social impact. Complementary and alternative medicine (CAM) therapies for uterine leiomyomas are designed to minimize risk and to treat symptomatology, but are not necessarily aimed at diminishing leiomyoma size.⁸ Unfortunately, there is little research on CAM therapies for symptomatic uterine leiomyomas. Therefore, women are using these therapies with little information as to safety and efficacy. This review discusses the theoretical rationale for choosing CAM therapies for the relief of dysmenorrhea and menorrhagia in women with uterine leiomyomas and reviews information from the existing literature in this area.

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Risk Factors Affecting Incidence and Growth

Multiple reproductive characteristics, including early menarche,⁹ may be associated with the development of uterine leiomyomas. The risk of developing leiomyomas decreases with each pregnancy beyond 20 weeks gestation, but increases as time passes since the last birth.^{10,11} There may be a small decrease in risk associated with medroxyprogesterone acetate, especially with increased length of use,¹⁰ and with oral contraceptive use, except when that use is at an early age (13-16 years).¹¹ Smoking is associated with a 20-50% decreased risk of developing uterine leiomyomas.^{9,12}

Other risk factors for leiomyomas, not linked to reproduction, include increasing body mass index,⁹ diabetes mellitus, hypertension, Black race, and a family history of leiomyomas.¹²

Leiomyoma Pathophysiology

An understanding of the pathophysiology of leiomyoma growth and development is important as we attempt to evaluate the potential value of CAM therapies. Leiomyomas grow and become symptomatic because of smooth muscle cell proliferation and apoptosis inhibi-

tion, as well as by increased angiogenesis occurring within the leiomyoma and in surrounding myocytes. Leiomyomatous tissues upregulate extracellular matrix components, mainly type I and type III collagen, as compared to adjacent normal myometrium, and increase water content of tissues. Leiomyomatous tissue has an increased number of estrogen and progesterone receptors and expresses more aromatase P450 enzyme than normal surrounding smooth muscle cells. Consequently, a leiomyoma has the potential to produce endogenous estradiol from androgens.¹³

It is postulated that smooth muscle cell proliferation is mediated by a number of different growth factors found in cells destined to become leiomyomas. The leiomyomatous smooth muscle cells show an abnormal balance in the expression of transforming growth factor β (TGF- β) mRNA.¹⁴ This imbalance in TGF- β leads to increased extracellular matrix production and decreased collagenase. There is a 60% decrease in the number of TGF- β 2 receptors, which normally act to control cell proliferation, and an increase in TGF- β 3 receptors.¹⁵ In addition, insulin-like growth factors (IGF-1 and IGF-2) are enhanced in leiomyomatous tissue and promote cell proliferation. Menopause and GnRH-agonist therapy are associated with diminished leiomyoma growth and are also associated with decreased IGF-1 levels.¹⁵ Uterine leiomyomas are well-vascularized tumors with abnormal blood vessel structure and function, and secrete increased levels of many heparin-binding growth factors. Heparin-binding growth factors are implicated not only for their mitogenic activity on smooth muscle cells, but also for their angiogenic activity.¹⁵

Methods

We conducted a systematic literature search utilizing the CONSORT¹⁶ and MOOSE guidelines.¹⁷ We searched Medline, Embase, Cinahl, and Cochrane Library, attempting to retrieve all relevant randomized or controlled comparisons related to CAM therapy of symptomatic leiomyomas. The search terms were "leiomyoma," "complementary therapies," "dysmenorrhea," "menorrhagia," "acupuncture," or "traditional Chinese medicine" (TCM), and the search was limited to the English language. The citation lists of relevant publications, review articles, abstracts of scientific meetings, and included studies also were searched. Only randomized or controlled clinical studies were included. Search results showed: Medline—12 English-language controlled clinical trials; Cochrane Library—nine reviews, three relevant to this paper; Embase—10 citations but none were controlled clinical trials; Cinahl—28 citations with two controlled clinical trials.

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Table 1

Effects of CAM therapies on leiomyomas

First author, year	Sample size (age range)	Therapy	Inclusion Criteria	Findings
Chiaffarino, ¹⁸ 1999 Case control	2,400 (21-54 yrs)	1) Diet rich in red meat 2) Diet rich in green vegetables	Cases—Histologically confirmed leiomyomas Controls—No history of leiomyomas	Beef and ham consumption OR = 1.7 (95% CI 1.4-2.2) Green vegetable consumption OR = 0.5 (95% CI 0.4-0.6)
Mehl-Madrona, ¹⁹ 2002 Case control	74 (24-45 yrs)	1) Weekly traditional Chinese medicine, body therapy (somatic therapy, bodywork), and guided imagery x 6 months 2) Traditional allopathic treatment	Cases and controls— Ultrasound confirmed leiomyomas	Fibroids shrank or stopped growing in 22/37 (P < 0.01) with greater patient satisfaction in the intervention group (P < 0.05)

Findings from the Review

The studies on CAM therapies for leiomyoma treatment are extremely limited. Only two observational studies directly related to diet or CAM therapies and leiomyoma were found. (See Table 1.) The first, a nutrition case control study, did not investigate nutritional CAM therapy of leiomyoma, but rather assessed the development of leiomyoma based on dietary intake.¹⁸ A standardized, previously validated questionnaire to evaluate the consumption frequency of selected dietary items was administered among women with histologically confirmed leiomyomas (cases) and women without leiomyomas (controls) with a 98% response rate. The results suggest that women whose diet is rich in green leafy vegetables are less likely to be diagnosed with leiomyoma, odds ratio (OR) = 0.5 (95% confidence interval [CI] 0.4-0.6). Women with diets high in red meat had an increased risk of a leiomyoma diagnosis, OR = 1.7 (95% CI 1.4-2.2).¹⁸ The findings of this study are potentially biased because of the possibility of misclassification in the identification of women with and without leiomyomas and because questionnaires were administered up to two years after the clinical diagnosis of uterine fibroids had been made.

A second case control study evaluated a weekly treatment program of TCM, somatic therapy, body therapy, and guided imagery.¹⁹ TCM is based on the tenet that disease is caused by an imbalance in vital energy or *qi*.²⁰ Symptoms associated with leiomyoma are related to stagnant *qi* (vital energy) and cold damp, deficient blood; therefore, TCM modalities aim to correct an imbalance of *qi* and relieve pelvic congestion. In this study, the diagnosis of leiomyoma was confirmed by ultrasound among 37 cases, recruited by word of mouth. The control group consisted of patients with ultrasound confirmed leiomyomas identified from records of emergency department visits matched to cases by age, presenting symptoms, fibroid size, health insurance status, and who underwent standard therapy leiomyoma therapy. Leiomyoma had growth

cessation or shrinkage in nearly 60% of the CAM-treated cases compared to 8% of nontreated controls (P = < 0.01). There was not a significant difference in symptom relief between groups. However, the treatment group had higher satisfaction with care despite an increased cost to the patient above the traditional allopathic medicine approach (P = < 0.05). Bias due to misclassification could have confounded results. Cases were potentially of higher socioeconomic status (SES); treatments were paid for out of pocket. Although controls were matched to cases by health insurance status, one might question whether a comparison between individuals presenting to an emergency room for care (controls) to otherwise healthy outpatient women recruited by word of mouth (cases) is appropriate. Unfortunately, the complex therapeutic approach that was studied, including TCM, somatic therapy, body therapy, and guided imagery is potentially difficult to replicate, and although Chinese medicines usually are safe, an increasing number of significant and even fatal outcomes due to contaminants in Chinese herbal preparations have been reported.²¹ Thus, quality of products is an ongoing concern.

Many of the studies of CAM modalities for the treatment of dysmenorrhea, the second most frequent clinical complaint among women with fibroids, are of marginal quality and have not been replicated, but met inclusion criteria for review. (See Table 2.) Successful therapies may include: topical heat,²² vitamin and dietary intervention,²³ relaxation training,²⁴ high frequency TENS,²⁵⁻²⁸ acupuncture/acupressure,²⁹⁻³¹ and herbal therapies.³² Acupuncture may be the most promising.³³ It has long been used in the treatment of gynecological problems and appears to activate endogenous opioid systems.²⁹ There is currently poor evidence to suggest that spinal manipulation improves dysmenorrhea.^{34,35}

Potential for CAM Treatment Modalities

CAM modalities that potentially affect smooth

Table 2

Effects of CAM therapies on dysmenorrhea

First author, year	Sample size (age range)	Therapy	Findings
Akin, ²² 2001 RCT (double dummy, 4 arms)	84 (21-50 yrs)	1) Topical heat/NSAID, 2) Topical heat/placebo, 3) Unheated patch/ NSAID, 4) Unheated patch/ placebo	Decreased pain in groups 1, 2, 3 compared to group 4 ($P \leq 0.001$), placebo shortened time to pain relief in group 1 compared with group 3 ($P = 0.01$)
Barnard, ²³ 2000 randomized crossover design	33 (22-48 yrs)	1) Low-fat vegetarian diet, 2) Usual diet with placebo supplement	Decreased pain duration ($P < 0.01$), decreased body weight ($P < 0.001$), increased SHBG ($P < 0.001$) in group 1 compared with group 2
Bennink, ²⁴ 1982 RCT (3 arms)	15 (19.2 yrs)	1) Relaxation training with EMG biofeedback, 2) Relaxation training with no feedback, 3) No treatment	Reduced EMG activity ($P < 0.05$), reduction of cramps ($P < 0.05$) in group 1 compared with groups 2 and 3
Dawood, ²⁵ 1990 Randomized 4-way crossover study	32 (28.5 yrs)	1) High frequency TENS for 2 cycles, 2) Placebo-TENS, 3) NSAIDs	Less pain rescue medication requirement for group 1 compared with groups 2 and 3 ($P < 0.01$), delayed time to need for pain rescue medication with group 1 compared with group 3 ($P < 0.05$)
Helms, ²⁹ 1987 RCT (4 arms)	43 (28 yrs)	1) Real acupuncture, 2) Placebo acupuncture, 3) No medical or acupuncture intervention, 4) Visitation control with monthly non-acupuncture visits	Decreased dysmenorrhea pain scores in group 1 compared with groups 2, 3, and 4 ($P < 0.001$)
Hondras, ³⁴ 1999 RCT (2 arms)	138 (18-45 yrs)	1) Spinal manipulative therapy, 2) Low-frequency manipulation (LFM)	NSS difference in reduction of pain scores between groups 1 and 2 ($P = 0.44$), NSS difference in reduction of plasma prostaglandins between groups 1 and 2 ($P = 0.15$)
Kotani, ³² 1997 RCT, double-blind (2 arms)	40 (14-45 yrs)	1) Toki-shakuyaku-san, 2) Placebo pill	Significantly decreased pain in group 1 compared with group 2 ($P < 0.005$)
Lewers, ³⁷ 1989 RCT (2 arms)	21 (20-38 yrs)	1) Acupuncture-like TENS, 2) Placebo pill	Pain relief between groups 1 and 2 NSS
Lundeberg, ²⁶ 1985 Randomized crossover trial (3 arms)	21 (15-29 yrs)	1) High-frequency TENS, 2) Low-frequency TENS, 3) Placebo TENS	Improved pain relief in group 1 compared to groups 2 and 3, NSS difference between group 2 and group 3
Mannheimer, ²⁷ 1985 RCT (3 arms)*	27 (19-27 yrs)	1) High-frequency TENS, 2) Acupuncture-like TENS, 3) Placebo TENS	Decreased pain duration and severity in group 1 compared with group 3 ($P = 0.05$)
Milsom, ²⁸ 1994 Randomized, open crossover trial	12 (23.8 yrs)	1) High-frequency and intensity TENS, 2) NSAID	Equivalent pain relief in groups 1 and 2 with time to pain relief 30-60 min for group 1 ($P < 0.001$) and 90-120 min for group 2 ($P < 0.001$)
Neighbors, ³⁰ 1987 RCT (2 arms)	20 (19-38 yrs)	1) Acupuncture-like TENS, 2) Placebo pill	Significant pain relief in group 1 compared to group 2 ($P < 0.05$)
Taylor, ³¹ 2002 RCT (2 arms)	61 (31.6 yrs)	1) Acupressure device, 2) Standard treatment control	Improved menstrual pain relief in group 1 compared to group 2 ($P < 0.0001$) Decreased use of pain medication in group 1 compared to group 2 ($P < 0.05$)
Thomason, ³⁵ 1979 RCT (3 arms)	11 (17-35 yrs)	1) Spinal manipulative therapy, 2) "Sham" activator contact tip, 3) Interview alone	Decreased pain severity in group 1 compared to groups 2 and 3

*Inclusion criterion was dysmenorrhea. For all others, the inclusion criterion was primary dysmenorrhea.

RCT = randomized controlled trial; NSAID = nonsteroidal anti-inflammatory drug; SHBG = Sex hormone binding globulin; NSS = not statistically significant; EMG = electromyogram; TENS = transcutaneous electrical nerve stimulation

muscle cell and collagen proliferation, angiogenesis, and steroid metabolism could be effective therapies. However, to our knowledge, no specific studies of the effect of CAM therapies on these physiologic processes have been reported. Naturopathic practitioners have justified treatment choices based on theoretical treatment effects.⁸

A principle CAM therapeutic focus is nutritional intervention. Patients are encouraged to adopt a diet high in fiber, low in dietary fat, and high in soy products and legumes. Poor nutrition is believed to inhibit the health of the liver, thereby slowing the metabolism of estrogen.

Nutritional supplements commonly used include lipotropic factors and pancreatic enzymes. The lipotropic factors (inositol and choline) promote removal of fat from liver, thereby speeding estrogen metabolism. Pancreatic enzyme use is controversial, but in theory, digests the fibrous and smooth muscle tissue surrounding the leiomyoma, dissolving it.

Herbal phytoestrogen use has been encouraged in women with leiomyomas. Phytoestrogens are selective estrogen receptor modulators and are hypothesized to act as antagonists at estrogen receptors in the myometrium and endometrium. Natural progesterone cream also is used in the treatment of leiomyomas. Progesterone therapy is reported to counteract the estrogen dominance that may lead to the development of leiomyomas. There is an important counter-argument, however, that in vitro, progesterone causes fibroid growth, so this therapy remains controversial.³⁶

Conclusion

This review highlights the need for further studies on CAM therapies for uterine leiomyoma. There are limited data to support a variety of alternative therapies to decrease uterine leiomyoma growth and symptoms including dietary modification, TENS, acupuncture/acupressure, and TCM. More rigorously designed studies are needed to clarify current recommendations regarding CAM modalities in the treatment of leiomyomas. Because of the high incidence of uterine leiomyoma, any further research on the use of CAM therapies for leiomyoma could have a dramatic impact. ❖

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Beating the Post-Baby Blues: Massage Can Help

Source: Field T, et al. Massage and relaxation therapies' effects on depressed adolescent mothers. *Adolescence* 1996;31:903-911.

Source: Onozawa K, et al. Infant massage improves mother-infant interaction for mothers with postnatal depression. *J Affect Disord* 2001;63:201-207.

■ COMMENTS BY MARY L. HARDY, MD

POST-PARTUM DEPRESSION (PPD) IS A RELATIVELY uncommon (10-15% of new mothers are affected) but serious outcome of pregnancy that can have adverse consequences for both the mother and the child. Research suggests that PPD can interfere with the establishment of mother-infant bonding and have negative impacts on children's cognitive and emotional development measurable even after 12 months.¹ Conventional therapy includes options such as medication, cognitive behavioral therapy, and social support.² Although conventional therapy can be very effective, experts are concerned that women may under-represent their symptoms and may be reluctant to seek care because of the risk and stigma of being labeled an unfit mother. Women also are concerned that if they continue to breastfeed while taking antidepressants, exposure of the infant to potent medication is inevitable. Women have been very willing to embrace complementary and alternative medicine (CAM) for other complaints of pregnancy³ and several recent articles have reviewed the evidence for CAM therapies and PPD.^{4,5} Recently, several interesting articles have examined the possibility of using massage therapy as an adjunctive treatment for PPD.

The first study looks at a group of high-risk patients: teenage mothers.⁶ Shortly after birth, Field and colleagues enrolled a group of 32 depressed adolescent mothers in a randomized trial comparing massage therapy to a relaxation therapy group. The women in this study were taking no other medication for depression but did have elevated scores on the Beck Depression Inventory. The patients in the massage therapy (MT) group received two half-hour sessions per week for five weeks of a standardized massage routine (total of 10 massages). The subjects receiving relaxation training (RT) spent an equal amount of time in a relaxation group as the massage group, although they practiced a combination of yoga and progressive muscle relaxation.

A number of scales for depression, anxiety, behavior, and mood were recorded on the first and last days of the

interventions. Physiological measures, such as pulse and salivary cortisol, also were collected. Although the groups were equivalent at the beginning of the trial, the MT group had significantly lower scores in the measures of anxiety, mood, pulse, and cortisol levels. They also demonstrated greater improvements in stress-related behavior such as restlessness. This study demonstrated both a subject and objective response to the massage intervention, which was greater than the effects observed for the RT groups. Interestingly, the subjects in the RT group complained that they felt less relaxed with their therapy, because they felt that had to work too hard in the group to truly feel relaxed. The age and special circumstances of this group may make generalization difficult, but this is a moderately strong effect for a non-invasive therapy in a generally difficult-to-treat group.

A second study examined the effects of infant massage, performed by depressed mothers, on the mother-infant interaction.⁷ Post-partum women were screened using the Edinburgh Postnatal Depression Scale (EPDS). Women who scored greater than 13, compatible with a diagnosis of major depression, were offered enrollment in a study comparing the results of a weekly infant-massage class plus a support group to a support group alone. Thirty-four women (an average of nine weeks post-partum) were entered into the trial and randomly assigned to one of the two interventions for five weeks.

The mother's level of depression and the characteristics of her interaction with her baby were evaluated at the beginning and end of the trial. The EPDS scores of the massage group decreased by 66% and were significantly better ($P = 0.03$) than the scores for the control group. A great deal of the change occurred even before the intervention began, demonstrating an anticipatory effect of this type of intervention. However, improvement continued, showing a specific effect of this therapy as well. Further, the interactions of the massage group mothers and infants also markedly and consistently improved throughout the trial. One major limitation of this study was the dropout rate in the massage group, reportedly due to the inconvenient scheduling of classes. Despite this, the massage intervention not only seemed to help the mothers' depression, but also addressed the potential adverse effects depression can have on mother-infant bonding.

For those patients who are unfortunate enough to suffer from depression in what should otherwise be a joyful time, these two studies suggest that massage may be an important adjunctive treatment for PPD. The interventions are non-invasive and non-pharmacological, which is important to many breastfeeding mothers. This therapy should be affordable for many patients, and family

members may be taught simple massage techniques. Post-partum programs should include classes in infant massage. If practitioners encourage this low-tech, but compassionate intervention, family members and practitioners may be able to offer tangible support to affected mothers through massage and help ease mothers and babies through a difficult time. ❖

References

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CE Objectives

After reading *Alternative Therapies in Women's Health*, the health care professional will be able to:

1. evaluate alternative medicine and complementary therapies for women's health concerns;
2. identify risks and interactions associated with alternative therapies;
3. discuss alternative medicine options with patients; and
4. offer guidance to patients based on the latest science and clinical studies regarding alternative and complementary therapies.

CE/CME Instructions

Physicians and nurses participate in this continuing medical education/continuing education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, you must complete the evaluation form provided and return it in the reply envelope provided at the end of the semester to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

CE/CME Questions

35. There is limited evidence that CAM therapy is successful in the treatment or prevention of uterine leiomyomas.

- a. True
- b. False

36. CAM modalities that affect smooth muscle cell and collagen proliferation, angiogenesis, and steroid

metabolism could be effective therapies for uterine leiomyomas but have not been investigated.

- a. True
- b. False

37. What CAM therapy may diminish symptoms of dysmenorrhea associated with uterine leiomyoma?

- a. Acupuncture
- b. Acupressure
- c. Both a and b

Answers: 35. a, 36. a, 37. c.

News Briefs

Get Antioxidants from Food, Not Supplements

A panel of experts at the American Heart Association (AHA) in Dallas, TX, is recommending that the public get its antioxidants from food sources, such as fruits, vegetables, whole grains, and nuts, rather than from supplements.

“We know that diets high in fruits and vegetables are associated with decreased risk of cardiovascular disease,” says Penny M. Kris-Etherton, PhD, RD, lead author of the association panel, and Distinguished Professor of Nutrition in the Department of Nutritional Sciences at the Pennsylvania State University in University Park. “Thus, following a diet consistent with the American Heart Association’s dietary guidelines is recommended.” The group advises eating five or more servings of fruits and vegetables each day and at least six servings of grain products, including whole grain foods.

Antioxidants, including vitamins C and E and beta-carotene, target a process called oxidation in which cell-damaging substances called free radicals accumulate. In 1999, the AHA began advising the public to consume foods that are rich in antioxidants, but concluded that there was not enough evidence to recommend the use of antioxidant supplements.

During the past five years, several clinical trials have investigated the effect of antioxidant supplements on heart disease, and a panel of AHA experts reviewed the results to see whether it was time to start recommending antioxidant supplements. Most studies have not demonstrated that antioxidant supplements have cardiovascular benefits, the panel reports in the Aug. 3 issue of *Circulation*. In fact, a few studies found that antioxidant supple-

ments may have a detrimental effect on cardiovascular risk.

But the apparent lack of an effect of antioxidant supplements in recent clinical trials does not mean that oxidation does not play a role in the development of artery disease, the panel says.

“While the research shows that antioxidant supplements have no benefit, the role oxidative stress plays in the development and progression of heart disease has yet to be clarified,” Kris-Etherton explains.

FDA Requires Pancreatic Extract Makers to Submit Marketing Applications

FDA has notified manufacturers of pancreatic insufficiency products that these drugs must get approval by FDA within the next four years to remain on the market.

FDA decided to require approval of new drug applications for all pancreatic extract products after reviewing data that showed substantial variations among currently marketed products. Specifically, the FDA review found that variations in the formulation, dosage, and manufacturing processes affected the potency—in terms of both the products’ activity and release rate—of the enzymes after patients take them. The resulting variations in drug potency could significantly affect the safety and effectiveness of the drugs.

FDA does not expect prices to change as a result of this notice. FDA’s economic analysis of this action found that although some firms may choose to discontinue marketing, enough manufacturers would continue producing pancreatic enzyme products to keep the market competitive. ❖

In Future Issues:

St. John’s Wort for Depression
Garlic for Cardiovascular Disease
Feverfew for Migraine