Acupuncture for uterine fibroids (Review)

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[Intervention Review]

Acupuncture for uterine fibroids

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Editorial group: Cochrane Menstrual Disorders and Subfertility Group.
Publication status and date: New, published in Issue 1, 2010.
Review content assessed as up-to-date: 20 May 2009.

Citation: Zhang Y, Peng W, Clarke J, Liu Z. Acupuncture for uterine fibroids. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No.: CD007221. DOI: 10.1002/14651858.CD007221.pub2.

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ABSTRACT

Background

Uterine fibroids (UFs) are benign growths within the uterine muscle and are present in 30% of women during their reproductive years. With the exception of hysterectomy, there are no effective medical and surgical treatments for women with uterine fibroids . Acupuncture is an ancient Chinese method which has been used for both the prevention and treatment of diseases for over three thousand years. There are many types of acupuncture used to manage UFs, with body acupuncture being the most commonly used. The literature reporting the benefits or harms of acupuncture for the management of UFs has not yet been systematically reviewed.

Objectives

To assess the benefits and harms of acupuncture in women with uterine fibroids

Search strategy

The following electronic databases were searched 21st May 2009: the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; AMED; the Menstrual Disorders and Subfertility Group's Specialised Register of Trials; Chinese Biomedical Literature Database (CBM); Traditional Chinese Medical Literature Analysis and Retrieval System (TCMLARS); Chinese Medical Current Contents (CMCC) and China National Knowledge Infrastructure(CNKI). Citation lists, experts in the field and grey literature were also referred to. No restrictions such as language were applied.

Selection criteria

All randomised controlled trials (RCTs) comparing acupuncture management with placebo acupuncture, no management, Chinese medication, Western medication or other managements of uterine fibroids were considered for inclusion. Acupuncture management included either traditional acupuncture or contemporary acupuncture, regardless of the source of stimulation (for example, body, electro, scalp, elongated, fire, hand, fine needle, moxibustion). Acupuncture management without needling was excluded.

Data collection and analysis

Two review authors assessed trial risk of bias according to our a priori criteria. No trials were included in this version of the review, therefore no data was collected.

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Main results

No randomized double-blind controlled trials met the inclusion criteria .

Authors' conclusions

The effectiveness of acupuncture for the management of uterine fibroids remains uncertain. More evidence is required to establish the efficacy and safety of acupuncture for uterine fibroids.There is a continued need for well designed RCTs with long term follow up.

PLAIN LANGUAGE SUMMARY

Acupuncture for uterine fibroids

There is no reliable proof of effectiveness of acupuncture for uterine fibroids due to lack of randomized controlled trials up to now.

BACKGROUND

Description of the condition

Uterine fibroids (UFs) are benign growths of the uterine muscle and are very common in women during the reproductive years (Kevin 2001). The terminology for fibroids depends on its location, for example intramural fibroids are located within the uterine muscle; subserosal fibroids project out from the outer uterine surface and submucosal fibroids project into the uterine cavity.

The primary cause and pathogenesis of uterine fibroids remains largely unknown (Andersen 1998; Chen 2001). Exposures to oestrogen and progesterone seem to be considered as one of etiologic factors (Rein 1995). Growth of uterine fibroids is regulated by the complex cross-talk between sex-steroid hormones and growth factors (Faerstein 2001; Maruo 2004). Published results from the few contemporary epidemiologic studies that have been conducted emphasise associations with reproductive history, markers of exposure to steroid hormones (Marshall 1998; Chiaffarino 1999) and ethnicity (Faerstein 2001).

Fibroids are typically discovered in the late reproductive period. They are present in 30% of women of reproductive age (Reiter 1992; ACOG 1994) and in up to 40% of women after the age of forty (Marshall 1997). The true clinical prevalence may be higher. Careful pathological examination of surgical specimens suggests that the prevalence is as high as 77% (Stewart 2001; Vollenhoven 1998). In China, the prevalence rate of uterine fibroids has been documented at 9%, with 22% of those in women aged 40 to 49 and nearly 1% in women below 29 (Zheng 2005).

Among women undergoing hysterectomy, black women were found to have a higher incidence of UFs when compared to white women. Prospective studies show that black women have over three times the incidence rates for myoma (embryonic connective tissue tumour) and a relative risk of two to three times that of white women (Meilahn 1989; Marshall 1997).

The vast majority of leiomyomas are asymptomatic (Lumsden 1998). Intervention is warranted in the minority of those who are symptomatic due to the debilitating nature of these symptoms. Symptoms attributable to uterine fibroids can generally be classified as: abnormal uterine bleeding, pelvic pressure and pain, and reproductive dysfunction (Vercellini 1993; Stewart 2001). The severity of the symptoms usually reflects the size, position and number of fibroids present (Benecke 2005).

For many women their symptoms are relieved at the time of menopause, when menstrual cycles and steroid-hormone concentrations wane (Stewart 2001). Fibroids will usually shrink to about half their original size after menopause (Ang 2001). Increasingly, there are reports of women who develop symptoms or have persistent symptoms while taking hormone-replacement therapy in their post-reproductive years (Stewart 2001).

There are many predisposing factors for uterine fibroids, such as obesity (Shikora 1991). Family history is associated with a risk three times higher in first-degree relatives, and evidence suggests that genetic alterations play an important role in uterine-fibroid development (Lumbiganon 1996; Luoto 2000; Alan 2005). Sterilisation, cigarette smoking and current alcohol consumption are associated with an increase in fibroid prevalence (WHO 1992; Lumbiganon 1996; Samadi 1996; Chen 2001). Use of oral contraceptives at young ages was reported to be associated with an elevated risk (Marshall 1998). Moreover, there is an association between nulliparity and uterine fibroids, and an inverse relationship between number of pregnancies and uterine fibroids (Farquhar 2000).

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Description of the intervention

There are many forms of medical and surgical management for uterine fibroids, but there is no defined gold standard on which to base practice (David 2005). When heavy menstrual bleeding occurs in association with uterine fibroids, hysterectomy has long been considered the definitive management (Clarke 1995). Recently, techniques such as laparoscopy and hysteroscopy have provided additional management options; myomectomy (surgical removal of uterine fibroids) is typically performed via a laparoscopy (David 2005).

Uterine artery embolization (UAE) has been reported to be an effective and safe alternative in the management of menorrhagia and other fibroid-related symptoms (Duncan 2001). The benefits of embolization (less pain, shorter hospitalisation and recovery time) must be weighed against the risks, such as late adverse events and greater chance of management failure (Edwards 2007). Gupta 2006 concluded that in women who had UAE (compared to those who did not have UAE) there was a higher minor complication rate after discharge as well as increased need for unscheduled visits, readmission and long-term follow up.

Medical managements, including Gonadotrophin-releasing hormone agonists (GnRHa) and GnRH analogue management for three months followed by combined 'add-back' therapy (oestrogen plus progestin), works towards reducing the size of uterine fibroids and relieving symptoms (Albano 2001; Huirne 2001). However, rapid recurrence frequently occurs after the therapy is stopped (Imai 2003). Unpleasant side effects and a reduction in bone-mineral density limit the use of GnRHas (Farquhar 2000). Gestrinone (Coutinho 1989) and Danazol are effective in reducing uterine and fibroid size (DeCherney 1983; Ueki 1995). Danazol has also been reported to prevent rebound growth after GnRH analogue management (De Leo 1997), but androgenic side effects may limit its use (Farquhar 2000). A Cochrane systematic review considered the role of pre-management with gonadotropin-releasing hormone (GnRH) analogues prior to a major surgical procedure, either hysterectomy or myomectomy, for uterine fibroids (Lethaby 2001).The authors of the review concluded that GnRH analogues for three to four months prior to fibroid surgery reduced both uterine volume and fibroid size.

Oral contraceptives may reduce menstrual blood loss with a resultant improvement in hematocrit, but they are not effective in shrinking fibroid size (Friedman 1995). Studies report that synthetic steroids in combination with anti progesterones, such as mifepristone may be used to slow or stop the growth of fibroids.

Progesterone and its derivatives can be used for short-term management of bleeding due to fibroids and for inhibiting the fibroids' growth (Grigorieva 2003; Maruo 2004). Hormone-replacement therapy (HRT) and non-steroidal anti-inflammatory drugs (NSAIDs) should not be used to treat fibroids, as they are not effective in reducing uterine fibroid size (Farquhar 2000).

Herbal managements for fibroids are traditionally used in several countries (Fugh-Berman 2004). Some studies showed that Chinese herbal preparations might be able to relieve symptoms and shrink the volume of fibroids without significant adverse effects (Huang 2003). A systematic review assessing the potential effectiveness and/or safety of herbal preparations for treating uterine fibroids was required.

Moxibustion is a therapy used to treat and prevent diseases by applying burning moxa to warm and open meridian, regulate and harmonize qi and blood (Zhang 2003). Accompanying with acupuncture, moxibustion may be used as warm needle to treat fibroids (Yu 2005), but no effectiveness and/or safety of moxibustion is assessed by systematic review.

How the intervention might work

Acupuncture has been used for both the prevention and management of disease for over 3,000 years (Ulett 1998). Acupuncture is one of the main management modalities of Traditional Chinese Medicine (TCM) (Wu 1996). Acupuncture is also increasingly practiced in many Western countries (Johansson 1993; NIH 1998) in the management of a wide variety of disorders, some of which are chronic and resistant to conventional management (Helene 2001). TCM theory suggests that acupuncture can stimulate the body and activate its regulating functions to improve and rectify the disturbed and dysfunctional organs in the body. The treatment of diseases with acupuncture is accomplished by the transmitting activites of the meridians in regulating meridian qi to restore the normal functions of the viscera and meridians (Zhao 2002). The exact benefit of acupuncture remains uncertain (Lo 2003). Moffet suggests that acupuncture results in the release of neurochemicals (usually endogenous opioids (beta endorphins, enkephalins and dynorphins) or serotonin) (Moffet 2006). Acupuncture may stimulate gene expression of neuropeptides (Kaptchuk 2002). The puncturing of connective tissue with the needle may deliver a mechanical signal into the tissue, which may be the key to acupuncture's therapeutic mechanism (Langevin 2002).

Based on the Langevin 2002 theory that the growth of uterine fibroids is regulated by the complex feedback loops between sex-steroid hormones and growth factors, and the theory that acupuncture has a regulative effect on the pituitary gland, the thyroid gland system, and the central nervous system (Lu 2000), without presenting pharmacological interference or having a long-term effect, it may be legitimate to consider acupuncture as a potential therapy for uterine fibroids.

There are many types of acupuncture (body, electro, scalp, elongated needle and fire needling) used to treat uterine fibroids in hospitals in China, with body acupuncture being the most commonly used technique (Lan 1997).

- Body acupuncture is defined as treating disease through acupuncture of points along the channels of the human body and is separated from acupuncture on the head or other affected areas (Lan 1997).

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- Electroacupuncture is a therapeutic method combining acupuncture with electrical stimulation (Zhang 2003).

- Scalp acupuncture is a therapeutic method for treating disease associated with the nervous system by using acupuncture needles along the surface of the head, also known as Head Skin Acupuncture (Zhang 2003).

- Elongated needle is a special long needle that is often longer than 125mm and has a stronger function of dredging and activating the meridian than the filiform needle that is usually used (Zhang 2003).

- Fire needling is a special acupuncture technique. When used, the tip of a metal needle is burnt red before it is inserted into the skin. It is used for subcutaneous tissue needling and should be withdrawn swiftly (Zhang 2003).

Why it is important to do this review

A preliminary search revealed more than 20 studies of acupuncture for managing uterine fibroids. The literature reporting the benefits or harms of acupuncture for the management of uterine fibroids had not yet been systematically reviewed.
The aim of this review was to evaluate the possible benefits and/or harms of acupuncture for the management of uterine fibroids in women.

OBJECTIVES

To assess the benefits and harms of acupuncture in women with uterine fibroids

METHODS

Criteria for considering studies for this review

Types of studies

All truly randomised controlled trials (RCTs) comparing acupuncture management versus no management, placebo acupuncture for management of uterine fibroids , were sought. We excluded quasi-randomised studies.

Types of participants

Women of reproductive age diagnosed with uterine fibroids. This diagnosis was confirmed by any means such as: surgery, ultrasound or clinical signs and symptoms.

Types of interventions

Any type of traditional acupuncture with needling compared to the following:

- 'sham' acupuncture;
- no management;
- placebo acupuncture;
- Chinese medication;
- Western medication or;
- other management.

Traditional acupuncture, in which needles are inserted in classical meridian points, or contemporary acupuncture, in which the needles are inserted in non-meridian or trigger points, regardless of the source of stimulation (for example, body, electro, scalp, elongated, fire, hand, fine needle, moxibustion). We compared these forms of acupuncture with medical therapy and placebo acupuncture.
Placebo acupuncture is also called as sham acupuncture, where placebo acupuncture involves the needling of non-acupuncture points proximally and/or distally to the true acupuncture points excluding trigger points.
We excluded trials of acupuncture management without needling, such as point injection, acupressure, laser acupuncture, tap-pricking or cupping on pricked superficial blood vessels.
We excluded trials comparing different acupuncture managements alone.

Types of outcome measures

Primary outcomes

Resolution or reduction of uterine-fibroid-related symptoms

- such as heavy, irregular, or prolonged menstrual periods, or bleeding between periods, assessed subjectively by the woman and by change in haematologic indices (gm/dl);
- pelvic or low-back pain, assessed subjectively by the woman or with the Visual Analogue Scale (VAS);
- low-abdominal pressure symptoms such as frequent or urgent urination, or constipation;
- reduction in uterine volume and/or fibroid volume (ml/cm), measured by ultrasonography, CT or magnetic resonance imaging (MRI);
- reduction in number of fibroids.

Secondary outcomes

- health-related quality of life, assessed by one or more of the EQ-5D, the SF-36 and The Uterine Fibroid Symptom and Quality of Life (UFS-QOL) indicators;
- safety as measured by incidence and severity of adverse effects, such as bleeding, hematoma and fainting on acupuncture;
- acceptability of management to women.

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Search methods for identification of studies

Electronic searches

We searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; AMED; the Menstrual Disorders and Subfertility Group's Specialised Register of Trials (see Appendix 1, Appendix 2, Appendix 3, and Appendix 4), Chinese Biomedical Literature Database (CBM), Traditional Chinese Medical Literature Analysis and Retrieval System (TCMLARS), Chinese Medical Current Contents (CMCC) and China National Knowledge Infrastructure(CNKI), using the following terms: uterine fibroid, acupuncture, traditional medicine, traditional Chinese Medicine, Chinese medicine, and complementary medicine, Pin Yin (including "Zhen ci, or Zhen jiu, or Hao zhen, or Ti zhen, or Dian zhen, or Tou zhen, or Mang zhen, or Shou zhen, or Huo zhen, or Jiu" "and" "Zi gong ji liu, or Ji liu" in the title and keywords sections). We searched the Menstrual Disorders and Subfertility Group's Specialised Register of Trials for any trials that have the terms: "Leiomyoma, or myoma, or fibroid, or fibromyoma, or fibroma" "and" "acupuncture or electroacupuncture or acupoint or meridian or needling" in the title and keywords sections.

Searching other resources

We screened reference lists of retrieved trials and reviews, and we sought unpublished data from the authors of published trials and abstracts. No language restrictions were applied.

Data collection and analysis

Two reviewers (Yan Zhang and Weina Peng) considered titles and abstracts identified from the search for inclusion. No disagreement required resolution by discussion between the reviewers or through arbitration by a third reviewer (Zhishun Liu).
We used the checklist of items to consider for data collection and extraction, Appendix 5, as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008).

Selection of studies

No studies were included.

Data extraction and management

Had we had trials for inclusion two reviewer authors (YZ and WP) would have performed data extraction; and entered the data onto a data-extraction form and then into Revman. Discrepancies would have been resolved by a third reviewer (ZL). We contacted the author of one RCT (Yu 2005) regarding missing study data.

Assessment of risk of bias in included studies

Had we had trials for inclusion then the Review authors would have used the criteria for making judgements about risk of bias as provided in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008) Appendix 6. There are three potential responses, 'yes', 'no' and 'unclear'. In all cases, an answer 'yes' indicates a low risk of bias, and an answer 'no' indicates high risk of bias. If insufficient detail was reported in the study, the judgement will usually be 'unclear' risk of bias. An 'unclear' judgement was also be made if what happened in the study was known, but the risk of bias is unknown; or if an entry was not relevant to the study at hand (particularly for assessing blinding and incomplete outcome data, when the outcome being assessed by the entry has not been measured in the study).
The following six domains of bias would have been considered:

- Sequence generation
- Allocation concealment
- Blinding (or masks)
- Incomplete data assessment
- Selective outcome reporting
- Other sources of bias

Measures of treatment effect

Had we had trials for inclusion we would have undertaken a statistical summary of the data. We would have expressed dichotomous data as a Peto odds ratio (OR) with corresponding 95% confidence intervals (95% CIs) and combined for meta-analysis with RevMan software using the Peto-modified Mantel-Haenszel method.
We would have expressed continuous data as mean differences (MD) with 95% CIs, or as standardised weighted mean difference if outcomes are conceptually the same but measured in different ways. We would have used both fixed and random-effect models to estimate the pooled-effect size, depending on the I^2 statistic.

Unit of analysis issues

Had we had trials for inclusion the primary analysis would have been per woman randomised. For any included trials which used cross over methodology we would have used data from the first phase of the trial, which was pre-crossover.

Dealing with missing data

We contacted one trial author during the screening process (Yu 2005) regarding missing data.

Assessment of heterogeneity

If we had included trials we would have heterogeneity that was seen by visually inspecting the overlaps of the confidence intervals

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for the results of individual studies. If there was poor overlap, this would have been suggestive of statistical heterogeneity and we would have included a more formal chi-squared (Chi^2) test. A low P value (or a large chi-squared statistic relative to its degree of freedom) would have provided evidence of heterogeneity of intervention effects (variation in effect estimates beyond chance). We would have measured inconsistency across trials in the meta-analysis using I^2. This describes the percentage of total variation across studies that are due to heterogeneity rather than chance (Higgins 2008).
If there was significant heterogeneity seen we we would reconsider whether it was appropriate or not to pool the data.

Assessment of reporting biases

Our search was extensive and designed to expose and minimise the potential impact of publication and reporting bias.

Data synthesis

Had we had trials for inclusion and if their clinical characterstics were sufficiently similar for pooling we would have combined the data using a fixed effect model using the following comparisons:

- any type of traditional acupuncture with needling versus no management or placebo stratified by classical or contemporary acupuncture regardless of the source of stimulation;
- any type of traditional acupuncture with needling versus medical therapy Chinese,Western medication or other management.

A graphical display of any effect (either beneficial or detrimental) would have been evident from the meta-analysis.

Subgroup analysis and investigation of heterogeneity

We had no planned subgroup analyses.
Had we had trials for inclusion we would have investigated heterogeneity based on the results of the I^2 as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Sensitivity analysis

Had we had trials for inclusion we would have conducted a sensitivity analysis in order to confirm the reliability of our conclusions. The analysis would consider
1. inclusion of studies without :

- high risk of bias;
- outlying results.

2. adoption of alternative imputation and random effects strategies

RESULTS

Description of studies

See: Characteristics of excluded studies.

Results of the search

Having excluded all the duplications, 106 citations were then retrieved from the electronic searches. All of the studies except five were published in Chinese. Ninety- five trials did not have any control group. Five trials had the control groups but did not mention randomization. Six trials were randomized control trials (RCTs). Of these six references, one reference (Yu 2005) was considered as potentially eligible after screening but then was also later excluded , this trial compared acupuncture with Chinese herbal medicine.

Participants

Sixty-two participants with uterine fibroids were randomized. The diagnosis was confirmed through routine gynaecological examination and by type B ultrasound. Ages ranged from 25 to 45 years. Baseline data suggested comparability between groups.

Interventions

Warm needle was used on EX-CA1, which involves heating and handle of the acupuncture needle with moxa at the end to produce a combined effect of heat and acupuncture stimulation. Other acupoints were treated by fine needle. Needles retention for 30 minutes; 5 treatment sessions per week were carried out; 30 sessions of treatment in 6 weeks were given. The controls were Chinese herb medicine Gongliuqing capsule, given 3.33g daily, three times a day, with a treatment period of 6 weeks.

Outcomes

Outcomes were reported as disappearance of uterine fibroids and volume of fibroids, measured by type B ultrasound. Follow up was reported only after the end of treatment. The trial didn't report change in hematologic indices, the Visual Analogue Scale (VAS), quality of life, incidence and severity of adverse effect. This trial didn't assess acceptability and satisfaction of using acupuncture.

Included studies

There were no studies eligible for inclusion in this edition of the review.

Excluded studies

The reasons for exclusion of six RCTs(Deng 2008; Engman 2008; Hamza 1999; Wang 2005 Yu 2005; Zhao 1999)were as follows:
1) One trial could not evaluate the effect of acupuncture, because it compared acupuncture plus herb medicines with mifepristone (Deng 2008). The procedure of randomization and allocation concealment weren't described and authors can't be contacted.

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2) The object of 4 trials weren't uterine fibroids. Three of them didn't refer to uterine fibroids (Hamza 1999, Wang 2005, Engman 2008) and one of them observed acupuncture for the exsufflation of patients after gynaecological operation (Zhao 1999). Therefore, there is no need to further analyse the methodology of these four excluded trials.
3) One trial (Yu 2005) conducted in China and published in Chinese could not be included because of its high risk of bias. The bias was confirmed after contact with the trial author. The trial author was not able to provide details regarding methods for sequence generation and allocation concealment. Both the participants and investigators were not blinded; this was assessed as high risk of bias. Any information in the publication about dropouts could not be provided and intention to treat analysis was thus presumed; this was assessed as uncertain risk of bias. See Characteristics of excluded studies

Risk of bias in included studies

No RCTs were identified.

Effects of interventions

No RCTs were identified.

DISCUSSION

There were no good quality randomized double-blind controlled trials of acupuncture for treatment of women with uterine fibroids available for inclusion.

One trial (Yu 2005) of 62 women compared acupuncture with Gongliuqing capsule evaluated the effect of acupuncture on the disappearance of uterine fibroids, volume of fibroids measured by type B ultrasound after treatment. The dose of Gongliuqing capsule was 3.33gm daily with a treatment period of six weeks. There was no significant difference between acupuncture and Gongliuqing capsule in the number of women with disappearance of uterine fibroids (OR 2.54, 95% CI 0.69 to 9.38, P=0.16) ,50% reduction in fibroid volume (OR 2.86, 95% CI 1.02 to 8.04, P= 0.05) or a 30% reduction in fibroid volume (OR 3.75, 95% CI 0.69 to 20.28, P=0.12). No data on adverse effects at the end of treatment were reported. Adverse events should be critically assessed by standardized monitoring and more attention should be paid to the long-term efficacy and possible long-term adverse effects of acupuncture.

Although the trial (Yu 2005) mentioned randomization, authors could not describe the method of randomization or allocation concealment. Neither blinding nor long term follow-up were mentioned.The trialist's reported on both the control and the intervention which was a Chinese herbal medicine with uncertain efficacy. The trial was also underpowered to reach any reliable conclusion.Therefore this trial was considered to be of low quality.

Only the number of patients with either disappearance of uterine fibroids or reduction in fibroid volume were reported as an outcome measures. No data about volume and number of fibroids were described. More outcome measures such as pelvic pain or low-back pain, uterine fibroid related symptoms and quality of life should be evaluated.

Evidence from a second trial excluded because of its methodological inadequacies were also inconclusive (Deng 2008) .This trial used acupuncture with another therapy in the treatment group, including external and oral herb medicines. Therefore, it could not evaluate the efficacy of acupuncture alone.

Summary of main results

Currently no high quality adequate evidence available to allow assessment of the efficacy of acupuncture in the treatment of uterine fibroids.

Quality of the evidence

It is important that transparent, pragmatic high quality research methodologies are incorporated so that they are able to consider the complex, unique nature of acupuncture. Future research should also incorporate quality of life outcome measures and qualitative research methods to provide a more detailed account of the effect of acupuncture on the lives of women suffering from uterine fibroids.

Agreements and disagreements with other studies or reviews

The findings of this review are consistent with those made by the authors of another Cochrane review of Chinese herbal medicine for endometriosis where there were no methodologically sound RCTs for inclusion (Flower 2009).

AUTHORS' CONCLUSIONS

Implications for practice

There is currently no evidence available from sufficiently high quality randomized controlled trials to allow assessment of the efficacy of acupuncture in the treatment of uterine fibroids.

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Implications for research

Although acupuncture is widely used in the treatment of uterine fibroid in China, high quality RCT is non-existent. It's importance to design placebo and no intervention as control intervention in acupuncture for uterine fibroids clinical trials. There is a continued need for randomized controlled trials of acupuncture for managing uterine fibroids to be conducted.

ACKNOWLEDGEMENTS

The authors acknowledge the helpful comments of those who refereed previous versions of the protocol and thank the Cochrane Menstrual Disorders and Subfertility Group for their expertise and supports.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Deng 2008	The trial compared acupuncture plus herb medicines with mifepristone. It could not evaluate the effect of acupuncture.
Engman 2008	The trial did not refer to uterine fibroids.
Hamza 1999	The trial did not refer to uterine fibroids.
Wang 2005	The trial did not refer to uterine fibroids.
Yu 2005	Sixty-two women comparing acupuncture with Gongliuqing capsule evaluated the effect of acupuncture on the disappearance of uterine fibroids, volume of fibroids measured by type B ultrasound after treatment.
Zhao 1999	The trial observed acupuncture for the exsufflation of patients after gynaecological operation. The research did not consider uterine fibroids.

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DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. MEDLINE search strategy

Ovid MEDLINE(R)
1 Leiomyoma/
2 (fibroid$ or fibromyoma).tw.
3 uterine fibroma.tw.
4 Leiomyom$.ti,ab,sh.
5 myoma/ or myoma.tw.
6 or/1-5
7 acupuncture therapy/ or acupressure/ or acupuncture analgesia/ or acupuncture, ear/ or electroacupuncture/ or meridians/ or moxibustion/ (9410)
8 Acupuncture/
9 acupuncture.tw.
10 (electroacupuncture or electro-acupuncture).tw.
11 acupoint$.tw.
12 ((meridian or non-meridian or trigger) adj5 point$).tw.
13 needl$.tw.
14 or/7-13
15 6 and 14
16 randomized controlled trial.pt.
17 controlled clinical trial.pt.
18 Randomized Controlled Trials/
19 Random allocation/
20 Double-blind method/
21 Single-blind method/
22 or/16-21
23 clinical trial.pt.
24 exp clinical trials/
25 (clin$ adj25 trial$).ti,ab,sh.
26 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab,sh.
27 Placebos/
28 placebo$.ti,ab,sh.
29 random$.ti,ab,sh.
30 Research design/
31 or/23-30
32 animal/ not (human/ and animal/)
33 22 or 31
34 33 not 32
35 15 and 34
36 from 35 keep 1-7

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Appendix 2. EMBASE search strategy

EMBASE
1 Leiomyoma/
2 leiomyoma/ or uterus myoma/
3 Leiomyom$.ti,ab,sh.
4 (fibroid$ or fibromyoma).tw.
5 (uterine fibroma or uter$ myoma).tw.
6 Myofibrom$.tw.
7 or/1-6
8 acupuncture/ or acupuncture analgesia/ or electroacupuncture/
9 acupunctur$.tw.
10 (electroacupuncture or electro-acupuncture).tw.
11 acupoint$.tw.
12 ((meridian or non-meridian or trigger) adj5 point$).tw.
13 needl$.tw.
14 or/8-13
15 7 and 14
16 Controlled study/ or randomized controlled trial/
17 double blind procedure/
18 single blind procedure/
19 crossover procedure/
20 drug comparison/
21 placebo/
22 random$.ti,ab,hw,tn,mf.
23 latin square.ti,ab,hw,tn,mf.
24 crossover.ti,ab,hw,tn,mf.
25 cross-over.ti,ab,hw,tn,mf.
26 placebo$.ti,ab,hw,tn,mf.
27 ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).ti,ab,hw,tn,mf.
28 (comparative adj5 trial$).ti,ab,hw,tn,mf.
29 (clinical adj5 trial$).ti,ab,hw,tn,mf.
30 or/16-29
31 nonhuman/
32 animal/ not (human/ and animal/)
33 or/31-32
34 30 not 33
35 15 and 34
36 from 35 keep 1-22

Appendix 3. AMED search strategy

AMED (Allied and Complementary Medicine)
1 Leiomyoma/
2 (fibroid$ or fibromyoma).tw.
3 uterine fibroma.tw.
4 Leiomyom$.ti,ab,sh.
5 myoma/ or myoma.tw.
6 or/1-5
7 acupuncture therapy/ or acupressure/ or acupuncture analgesia/ or acupuncture, ear/ or electroacupuncture/ or meridians/ or moxibustion/
8 Acupuncture/
9 acupuncture.tw.

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10 (electroacupuncture or electro-acupuncture).tw.
11 acupoint$.tw.
12 ((meridian or non-meridian or trigger) adj5 point$).tw.
13 needl$.tw.
14 or/7-13
15 6 and 14
16 from 15 keep

Appendix 4. CENTRAL search strategy

EBM Reviews - Cochrane Central Register of Controlled Trials
1 Leiomyoma/
2 (fibroid$ or fibromyoma).tw.
3 uterine fibroma.tw.
4 Leiomyom$.ti,ab,sh.
5 myoma/ or myoma.tw.
6 or/1-5
7 acupuncture therapy/ or acupressure/ or acupuncture analgesia/ or acupuncture, ear/ or electroacupuncture/ or meridians/ or moxibustion/ (882)
8 Acupuncture/
9 acupuncture.tw.
10 (electroacupuncture or electro-acupuncture).tw.
11 acupoint$.tw.
12 ((meridian or non-meridian or trigger) adj5 point$).tw.
13 needl$.tw.
14 or/7-13
15 6 and 14
16 from 15 keep 1-2

Appendix 5. Checklist of items to consider in data collection or data extraction

Source

Study ID (created by review author);
Report ID (created by review author);
Review author ID (created by review author);
Citation and contact details.

Eligibility

Confirm eligibility for review;
Reason for exclusion.

Methods

Study design;
Total study duration;
Sequence generation;
Allocation sequence concealment;
Blinding;
Other concerns about bias.

Participants

Total number;
Setting;
Diagnostic criteria;
Age;
Sex;

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Country;
Co-morbidity;
Socio-demographics;
Ethnicity;
Date of study.

Interventions

Total number of intervention groups;

For each intervention and comparison group of interest:

Specific intervention;
Intervention details (sufficient for replication, if feasible);
Integrity of intervention;

Outcomes

Outcomes and time points (i) collected; (ii) reported;
For each outcome of interest:
Outcome definition (with diagnostic criteria if relevant);
Unit of measurement (if relevant);
For scales: upper and lower limits, and whether high or low score is good

Results

Number of participants allocated to each intervention group;

For each outcome of interest:

Sample size;
Missing participants;
Summary data for each intervention group (e.g. 2X2 table for dichotomous data; means and SDs for continuous data);
Estimate of effect with confidence interval; P value;
Subgroup analyses.

Miscellaneous

Funding source;
Key conclusions of the study authors;
Miscellaneous comments from the study authors;
References to other relevant studies;
Correspondence required;
Miscellaneous comments by the review authors.

Appendix 6. Criteria for judging risk of bias in the Risk of bias assessment tool

SEQUENCE GENERATION

Was the allocation sequence adequately generated?

Criteria for a judgement of 'YES' (i.e. low risk of bias).

The investigators describe a random component in the sequence generation process such as:

- Referring to a random number table;
- Using a computer random number generator;
- Coin tossing;
- Shuffling cards or envelopes;
- Throwing dice;
- Drawing of lots;

Minimization*.

*Minimization may be implemented without a random element, and this is considered to be equivalent to being random.

Criteria for the judgement of 'NO' (i.e. high risk of bias).

The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example:

- Sequence generated by odd or even date of birth;
- Sequence generated by some rule based on date (or day) of admission;

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- Sequence generated by some rule based on hospital or clinic record number.

Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example:

- Allocation by judgement of the clinician;
- Allocation by preference of the participant;
- Allocation based on the results of a laboratory test or a series of tests;
- Allocation by availability of the intervention.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).
Insufficient information about the sequence generation process to permit judgement of 'Yes' or 'No'.

ALLOCATION CONCEALMENT
Was allocation adequately concealed?
Criteria for a judgement of 'YES' (i.e. low risk of bias).
Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:

- Central allocation (including telephone, web-based, and pharmacy-controlled, randomization);
- Sequentially numbered drug containers of identical appearance;
- Sequentially numbered, opaque, sealed envelopes.

Criteria for the judgement of 'NO' (i.e. high risk of bias).
Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:

- Using an open random allocation schedule (e.g. a list of random numbers);
- Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered);
- Alternation or rotation;
- Date of birth;
- Case record number;
- Any other explicitly unconcealed procedure.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).
Insufficient information to permit judgement of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

BLINDING OF PARTICIPANTS, PERSONNEL AND OUTCOME ASSESSORS
Was knowledge of the allocated interventions adequately prevented during the study?
Criteria for a judgement of 'YES' (i.e. low risk of bias).
Any one of the following:

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding;
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

Criteria for the judgement of 'NO' (i.e. high risk of bias).
Any one of the following:

- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding;
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).
Any one of the following:

- Insufficient information to permit judgement of 'Yes' or 'No';
- The study did not address this outcome.

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INCOMPLETE OUTCOME DATA

Were incomplete outcome data adequately addressed?

Criteria for a judgement of 'YES' (i.e. low risk of bias).

Any one of the following:

- No missing outcome data;
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;
- Missing data have been imputed using appropriate methods.

Criteria for the judgement of 'NO' (i.e. high risk of bias).

Any one of the following:

- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization;
- Potentially inappropriate application of simple imputation.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).

- Any one of the following:
- Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No' (e.g. number randomized not stated, no reasons for missing data provided);
- The study did not address this outcome.

SELECTIVE OUTCOME REPORTING

Are reports of the study free of suggestion of selective outcome reporting? [Short form: Free of selective reporting?]

Criteria for a judgement of 'YES' (i.e. low risk of bias).

Any of the following:

- The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

Criteria for the judgement of 'NO' (i.e. high risk of bias).

Any one of the following:

- Not all of the study's pre-specified primary outcomes have been reported;
- One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified;
- One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);
- One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
- Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).
- Insufficient information to permit judgement of 'Yes' or 'No'. It is likely that the majority of studies will fall into this category.

OTHER POTENTIAL THREATS TO VALIDITY

Was the study apparently free of other problems that could put it at a risk of bias?

Criteria for a judgement of 'YES' (i.e. low risk of bias).

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- The study appears to be free of other sources of bias.

Criteria for the judgement of 'NO' (i.e. high risk of bias).

- There is at least one important risk of bias. For example, the study:
- Had a potential source of bias related to the specific study design used; or
- Stopped early due to some data-dependent process (including a formal-stopping rule); or
- Had extreme baseline imbalance; or
- Has been claimed to have been fraudulent; or
- Had some other problem.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias).

There may be a risk of bias, but there is either:

- Insufficient information to assess whether an important risk of bias exists; or
- Insufficient rationale or evidence that an identified problem will introduce bias.

HISTORY

Protocol first published: Issue 3, 2008

Review first published: Issue 1, 2010

2 December 2007	New citation required and major changes	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Yan Zhang initiated, designed and drafted the Systematic Review. She searched trials, conducted quality assessment, and statistical analyses.

Weina Peng provided methodological perspectives, worked for quality assessment, revised the review.

Jane Clarke revised the review.

Zhishun Liu unified differences of opinion, revised and commented on the review.

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DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- New Source of support, Not specified.

INDEX TERMS

Medical Subject Headings (MeSH)

Acupuncture Therapy [adverse effects; *methods]; Leiomyoma [*therapy]

MeSH check words

Female; Humans

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