

Effects of Acupuncture on Anxiety in Infertile Women: A Systematic Review of the Literature

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ARTICLE INFO	ABSTRACT
<p><i>Article type:</i> Review article</p>	<p>Background & aim: Stress and anxiety due to waiting for treatment results and uncertainty of treatment success are common problems in infertile women. Acupuncture has been suggested as an effective strategy to relieve anxiety. This study aimed to review the available evidence on the effects of acupuncture on anxiety in infertile women.</p> <p>Methods: This systematic review was conducted via searching in databases such as MEDLINE, PubMed, Cochrane Library, and PsycINFO, as well as clinical trial registries and reference lists of the retrieved articles. Selected articles included the studies published since the initiation of each database until March 2015. All randomized controlled trials regarding the effects of acupuncture on the anxiety of infertile women were reviewed in this study. Moreover, methodological qualities of the selected studies were examined based on the checklist of Oxford Center for Evidence-Based Medicine by two independent investigators.</p> <p>Results: Literature search yielded 193 relevant titles and abstracts, which were narrowed down to four randomized controlled trials involving 595 women. The majority of the reviewed articles showed that use of acupuncture could decrease anxiety in infertile women.</p> <p>Conclusion: According to the results of this systematic review, acupuncture is an effective technique in controlling the anxiety of infertile women. However, it is recommended that future studies with more appropriate design and methodology be conducted in this regard.</p>
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Introduction

In the past three decades, an increasing number couples have been in need of the services of human reproduction clinics in order to diagnose and manage the problems associated with infertility. According to the World Health Organization, 8-10% of couples may experience fertility problems during the reproductive age (1).

Infertility intensifies psychological distress, and evidence suggests that stress could adversely affect the outcomes of infertility treatment (2). For many women, infertility is accompanied by substantial emotional and psychological challenges. Furthermore, it is considered a remarkably distressful experience

for women, which might lead to psychological morbidity in the form of anxiety, depression, and chronic stress (3).

On the other hand, assisted reproductive technology (ART) could be a predisposing factor for emotional and physical stress in infertile women (4). Today, it is well established that emotional and behavioral disorders lead to immune system damage (5).

Women show different reactions to ineffective pregnancy attempts; such examples are disappointment, annoyance, and significant psychological distress. Emotional responses to infertility have been associated with feelings of

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grief, depression, anxiety or chronic stress, which adversely affect the hypothalamic-pituitary axis and even the possibility of a successful pregnancy following in-vitro fertilization (6). In-vitro fertilization (IVF) has been shown to be a stress-causing procedure, giving rise to anxiety in most of the cases. Moreover, waiting for treatment results and uncertainty of success may appear as other sources of stress, anxiety, and even depressive symptoms in infertile women (1).

Considering the significant emotional and financial stress associated with IVF, many women are in search of alternative therapies to diminish stress and achieve higher IVF success rates (7). Currently, various psychological interventions are implemented for individuals who are under emotional pressure regarding their response to infertility or subfertility treatments. These interventions are mostly focused on particular therapeutic approaches, such as psychodynamic-analytic interventions, mind/body-oriented relaxation, cognitive-behavioral therapies, training and education, and online counseling (6).

Acupuncture and traditional Chinese medicine have been widely used as a key remedy for mental disorders since 1100 BC (1). The first reports on the application of acupuncture in infertility treatment were published during 1960s (8). According to statistics, anxiety and depression are prevalent disorders in female populations, with the incidence twice higher compared to male populations. Management of these psychological disorders is rather complex considering the high prevalence rates and medication side effects.

In this regard, evidence supports the effectiveness of acupuncture to overcome the limitations of current therapeutic approaches (9). Use of acupuncture in the treatment of psychological disorders has been on a rising trend, and several studies have denoted the reduction of anxiety level following acupuncture (1, 10, 11).

Previous studies have investigated the possibility of alleviating anxiety and stress through sympathoinhibitory exclusivity and impact on β -endorphin levels (12, 13). Furthermore, evidence suggests that acupuncture could remarkably improve debilitated immune functions in anxious women, while diminishing increased immune parameters (e.g., superoxide

anion levels and lymphoproliferation) (5).

According to the literature, acupuncture enhances IVF outcome through four feasible mechanisms, including the adjustment of neuro-endocrinological factors, increasing blood flow to the uterus and ovaries, modulation of cytokines, and alleviating stress, anxiety, and depression (14, 15).

In this regard, findings of So et al. were indicative of decreased anxiety levels in both study groups receiving real and placebo acupuncture (16). However, in another study by Isoyama et al., mean score of Hamilton Anxiety Rating Scale after a tentative period was significantly lower in the experimental group compared to the control group (1). In a research by Balk et al., women who received an acupuncture treatment regimen had lower stress scores before and after embryo transfer compared to other subjects (17).

With this background in mind, a systematic review is required in order to reconcile these contradictory findings. This study aimed to investigate the effects of acupuncture on anxiety in infertile women receiving ART.

Materials and Methods

Literature search strategy

This systematic review was conducted via searching in databases such as MEDLINE, PubMed, Cochrane Library, and PsycINFO, as well as clinical trial registries (clinicaltrials.gov) and reference lists. Related articles that were published since the initiation of each database until March 2015 were included in this study. Keywords and medical subject headings used in the literature search were as follows: acupuncture AND infertility AND (depression OR anxiety OR stress).

Titles and abstracts of all the retrieved articles were reviewed, and relevant studies were obtained in full text. Inclusion criteria were randomized controlled trials and studies published in English. Reference lists of the eligible articles were reviewed for replication.

We also carried out a forward citation searching in the selected articles via Google Scholar, and studies using acupuncture in cases with IVF or intracytoplasmic sperm insemination were included in this review. Process of article selection is illustrated in Figure 1 (18).

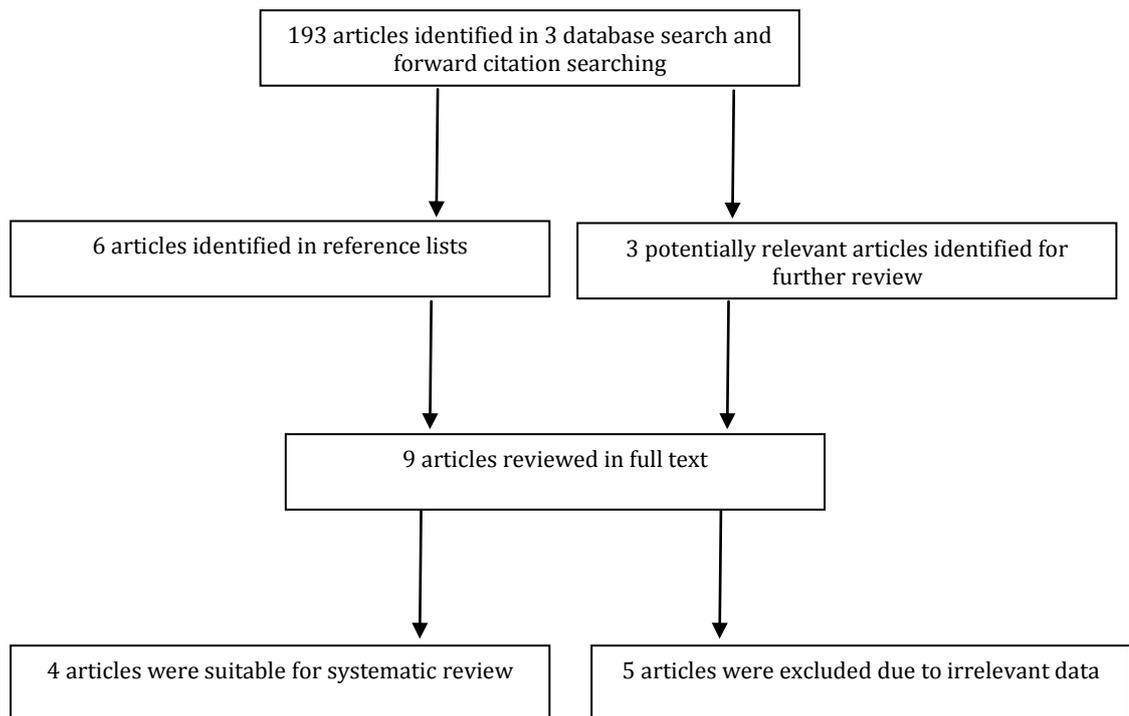


Figure 1. PRISMA flow diagram of systematic literature review

Article selection

Two reviewers independently assessed each article in order to determine their eligibility. All randomized controlled trials performed to investigate the effects of acupuncture on the anxiety of infertile women were included in this study. For the trials to be qualified, data on the final outcome of anxiety level were extracted, as obtained based on Spielberger's State-Trait Anxiety Inventory (STAI) (8), shortened version of the 20-item STAI (10 items) (6), Hamilton Anxiety Scale (HAS) (1), and the Chinese version of STAI questionnaire (16).

Data extraction and quality assessment

One investigator abstracted the details regarding the author(s), year of study, randomization, interventions, follow-ups and results, while the second investigator reviewed the obtained data in terms of accuracy. Any disagreement in this process was evaluated based on the expert opinion of the third researcher. In addition, possible duplicate publications were conferred. Quality of the selected articles was assessed based on the checklist of Oxford Center for Evidence-Based

Medicine (19), which consists of four main sections, as follows: 1) randomized assignment of patients to treatment groups and similarity of groups at the beginning of the trial, 2) additional treatments and intention-to-treat analysis, 3) placebo or sham treatment, and 4) statement of the results. Results of the quality assessment of the selected studies are presented in Table 1.

Outcome measures

In one of the selected articles, anxiety level was considered as the outcome measure (1). In two other studies, in addition to anxiety level, other outcome measures were evaluated, including overall pregnancy rate, implantation rate, clinical pregnancy rate, ongoing pregnancy rate, live birth rate, endometrial and subendometrial vascularity, cortisol concentration (16), perceived stress using the fertility problem inventory, and infertility self-efficacy based on the infertility self-efficacy scale (6). Moreover, outcome measures were not clarified in one study, while the authors noted factors such as pregnancy rate, anxiety level, and personal differences in optimism and pessimism using the Life Orientation Test Revised (LOT-R) (8).

Study	Impact of acupuncture on in-vitro fertilization outcomes	Effect of acupuncture on psychosocial outcomes of women with infertility: A pilot randomized controlled trial	Effect of acupuncture on symptoms of anxiety in women undergoing in-vitro fertilization: A prospective randomized controlled study	A randomized double-blind comparison of real and placebo acupuncture in IVF treatment
Authors (year)	Domar AD et al. (2008)	Smith CA et al. (2011)	Isoyama D et al. (2012)	So EW et al. (2009)
1a. Was the assignment of patients to treatments randomized?(Yes/No/Unclear)	Yes	Yes	Yes	Yes
2a. Were the groups similar at the start of the trial? (Yes/No/Unclear)	Yes	Yes	Yes	Yes
1b. Aside from the allocated treatment, were the groups treated equally? (Yes/No/Unclear)	Yes, this study assessed positive β hCG or pregnancy rates, determined anxiety level, and presented relaxation techniques for two groups (acupuncture and placebo).	No	No	Yes, this study assessed pregnancy rates and determined general anxiety in two groups.
2b. Were all the patients entering the trial accounted for? Were they analyzed in the groups to which they were randomized?(Yes/No/Unclear)	Intention-to-treat: Not reported Lost to follow-up: 2.6%	Intention-to-treat: Yes Lost to follow-up: 6.25%	Intention-to-treat: No Lost to follow-up: No	Intention-to-treat: Yes Lost to follow-up: No
3. Were measures objective or were the patients and clinicians blinded to treatments? (Yes/No/Unclear)	Yes	Yes	Yes	Yes
4. What were the results?	Acupuncture group reported significantly lower anxiety levels after embryo transfer compared to the control group	Lower anxiety levels (MD: 2.54; 95% CI: 5.95-0.86; P=0.008) in the acupuncture group compared to the wait-list control	Mean HAS score after a four-week experimental period was significantly lower in the test group compared to the control group (19.4 \pm 3.2 vs. 24.4 \pm 4.2; P=0.0008).	Reduction of the anxiety level was observed following real and placebo acupuncture although there was no significant difference in the changes between the two groups.

Results

Diagram of the retrieved articles in this systematic review is depicted in Figure 1. In total, 193 studies were found in the first literature search, which seemed to be potentially relevant to the study subject. However, 190 articles with irrelevant subjects were eliminated after the screening of the titles and/or abstracts. The remaining articles (n=9) were obtained in full text and assessed in depth. Among the selected studies, four randomized controlled trials conducted on a total of 595 participants met the inclusion criteria of this review (1, 6, 8, 16).

In the reviewed studies, acupuncture points were selected in accordance with the guidelines of traditional Chinese medicine or based on specific traditional characteristics and previously published protocols (1, 6, 16, 20).

In two articles, anxiety level was assessed as an

item on the side (8, 16), and evaluation of anxiety was performed based on Spielberger's STAI in two studies (6, 8). Moreover, one study used HAS (1), and another research by Shek was performed based on the state-trait anxiety questionnaire (16). In two studies, 95% confidence interval (CI) was considered for reporting the results regarding the anxiety level (1, 6).

In one study, the difference in the anxiety level before and after intervention in the real acupuncture group was reported to be 1.18 \pm 4.9, while it was 1.28 \pm 5.67 in the sham acupuncture group (P=0.468). However, no statistically significant differences were observed in the changes of anxiety level between these groups (16). In another article, relative risk of anxiety in the control and acupuncture group was determined at 4.77 (95% CI: 1.61-14.14) (P=0.0004). In other words, risk of anxiety was

4.77 times higher in subjects of the control group (1).

In the study by Smith et al. (2011), a non-significant difference of -2.54 (95% CI: -5.95-0.86) ($P=0.083$) was reported between the two groups in terms of anxiety level. However, anxiety was found to be less prominent in the acupuncture group compared to the control group (6). In the fourth article, the results were indicative of the lower anxiety level after embryo transfer in the experimental group compared to the control group ($P=0.015$) (8). In general, findings of the reviewed studies suggested that acupuncture could effectively reduce anxiety in infertile women. Timing of acupuncture intervention was variable in the reviewed trials. In the study by Domar et al. (2009), duration of acupuncture was 25 min after embryo transfer (8), while in the research by Isoyama et al. (2012), needles remained in the acupuncture points for about 25 min (1). In the studies conducted by Smith et al. (2011) (6) and So et al. (2009), duration of acupuncture was reported to be 45 and 25 min, respectively before and after embryo transfer (16).

It is also noteworthy that in two studies, the researchers used traditional Chinese medicine diagnosis and intention-to-treat analysis (6,16).

Discussion

To the extent of our knowledge, this is the first systematic review on the effects of acupuncture on infertility-related anxiety. According to our findings, acupuncture could be an effective strategy to alleviate stress and anxiety in infertile women.

The relationship between stress and infertility forms a vicious cycle. Social stigmatization, low self-esteem, unmet reproductive potential of sexual relationship, physical and mental burden of treatment, and lack of control over treatment outcomes are among the major contributing factors to psychological distress in couples receiving infertility treatment. Effectiveness of acupuncture in decreasing anxiety and stress could be attributed to its sympathoinhibitory properties, as well as its influence on endorphin levels (21).

In the trials assessed by Grant et al. (2014), which evaluated mental and emotional health during IVF treatment, acupuncture resulted in various positive outcomes, including the

alleviation of anxiety and stress, reducing social and relationship concerns, and enhanced psychological coping (22), which is in line with the results of the present review.

In the guidelines of traditional Chinese medicine, numerous syndromes have been noted to cause infertility. For instance, infertility could be induced by organ shortage, which is known as "Yin deficiency" (liver and kidney) or "Yang deficiency" (spleen and kidney). The liver supplies the blood and "reproductive essence", and kidneys supply the "Qi". Therefore, any dysfunction or inconsistency in each of these organs may lead to the imbalance of other body systems. Such failure in organ function causes endocrine discontinuity in the body, thereby leading to overall hormonal disproportion.

Some other syndromes associated with infertility are referred to as "stagnant Qi" (Qi stagnation) and "blood stasis". In these syndromes, despite normal hormonal balance, absence of circulation leads to inconceivable conception.

Blood stasis is found in the form of endometriosis in female body, and the end-syndrome is known as "damp heat" or "dampness in the lower burner." This syndrome mainly interferes with the functioning of internal organs and is similar to inflammation. Therefore, proper management of the damp-heat syndrome is essential to the correction of reproductive functions and sexual performance (23).

According to traditional Chinese medicine, crossing acupoints of the kidney, spleen, liver channels, and SP6 play a pivotal role in female infertility. As such, strengthening of the kidney and liver is possible through needling SP6, SP8, SP10, ST29, and ST36, which ultimately attune the Qi and blood perfusion to the uterus. However, the exact direction of blood perfusion to the uterus remains unclear. Other significant acupoints are LR3 and L1, also known as the "four gates", which prevent liver Qi stagnation and relax the mind. Furthermore, PC6 and GV20 are the acupoints considered to be involved in the alleviation of stress and anxiety (24).

In the study by So et al. (2009), the most common diagnoses based on the traditional Chinese medicine were spleen and kidney deficiency, liver Qi stagnation, and blood stasis. Therefore, the selected acupoints were suitable to the diagnoses of the majority of patients

(16). On the other hand, common acupoints used in the study by Smith et al. (2011) were in the kidney and chest, which is similar to the studies conducted by Neiguan (PC6), Jiansi (PC5), Tongli (HT5), and Shenmen (HT7) (6).

In the present review, we only investigated randomized controlled trials, and other low-quality evidence was excluded. One of the limitations of this systematic review was the use of different statistical instruments to measure the anxiety level in various studies; therefore, we could not perform a meta-analysis. Another shortcoming was the number of acupuncture sessions and differences of acupoints in the reviewed studies, which might have affected the outcomes of acupuncture with regard to anxiety level.

Conclusion

According to the results of this review, acupuncture could be effective in the management of anxiety in infertile women. However, it is recommended that future studies with more appropriate designs be conducted in this regard. Moreover, timing of acupuncture in terms of embryo transfer must be considered in future trials.

Conflicts of interest

None declared.

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