

Effect of Acupuncture on Symptoms of Anxiety in Women Undergoing In Vitro Fertilisation



A Prospective Randomised Controlled Study

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Abstract and Introduction

Abstract

Purpose To determine if acupuncture improves symptoms of anxiety in infertile women undergoing in vitro fertilisation (IVF) treatment.

Methods A randomised clinical trial was performed in 43 patients undergoing IVF. The patients were randomised into two groups: test group (n=22) and control group (n=21). The anxiety level of each patient was analysed before and after treatment using the Hamilton Anxiety Rating Scale (HAS). Treatment sessions consisted of four weekly sessions. In the test group, needles were inserted at points HT7, PC6, CV17, GV20 and *Yintang*. In the control group, needles were inserted in areas near but not corresponding to acupuncture points.

Results The mean HAS score after the 4-week experimental period was significantly lower in the test group than in the control group (19.4±3.2 vs 24.4±4.2; p=0.0008).

Conclusions The results indicate that acupuncture can reduce anxiety symptoms observed by the reduction of psychological parameters of women undergoing IVF. Further evidence should be sought as to whether acupuncture might be a complementary option for patients undergoing IVF.

Introduction

The number of couples seeking the services of human reproduction clinics for the evaluation of problems related to infertility has increased dramatically in the last 30 years.^[1] According to the World Health Organization, 8–10% of couples have some infertility problem during their reproductive lives.^[2 3]

Infertility brings a series of significant losses in the life of a couple, associated with increased levels of depression and anxiety, anger and frustration.^[4 5] In vitro fertilisation (IVF) in itself is a stressful factor on several levels; the treatment itself is stressful and, in most cases, causes anxiety. The wait for the outcome of treatment and uncertainty of success also cause stress and anxiety, sometimes accompanied by depressive symptoms.^[5 6] The different phases of the treatment process cause an emotional response,^[5] and anxiety can negatively affect the results of IVF.^[6 7]

Acupuncture and Chinese medicine have been used to treat mental illness since 1100BC.^[8] The use of acupuncture in the treatment of psychological disorders has increased considerably and many clinical studies (using different models and methods) report reductions in anxiety levels.^[8] By observing how IVF and acupuncture affect infertility and the anxiety it causes, it will be possible to establish what each technique has to offer and how the two methods can complement or improve the outcome for each other.

This study aims to elucidate whether acupuncture improves symptoms of anxiety in infertile women undergoing IVF treatment.

Methods

Trial Design and Participants

We conducted a prospective randomised controlled clinical study in women undergoing treatment at the Clinic for Human Reproduction, Faculty of Medicine of ABC, Santo André SP, Brazil given IVF treatment from February to October 2009. During that period, all women admitted to the clinic for IVF treatment of infertility were invited to participate. The following exclusion criteria were applied: women aged >45 years; previous psychiatric illness; use of antidepressants and/or anxiolytics; previous use of acupuncture.

The selected patients were informed about the purpose and procedures of the study and written informed consent was obtained from each participant. The research project was approved by the ethics committee in research of the Faculty of Medicine of ABC (number 073/2009).

The patients were randomised according to a computer-generated randomisation list placed in sealed opaque envelopes cards indicating one of two groups: control and sham acupuncture groups. The randomisation sequence was in a block of 10 with a ratio of 1:1 and was stratified according to the cycle number (ie, whether first cycle or repeated cycle). The randomisation list was generated and kept by the acupuncturist. The sequence of randomisation was concealed until the first interview. Patients, clinical staff involved in the care of patients and embryologists were blinded to the treatment group assigned. The codes for the treatment groups were revealed only after completion of the study and statistical analysis.

Acupuncture Treatment

Each patient was given a total of four sessions of acupuncture at weekly intervals (period which comprised the whole IVF process from induction of ovulation to the result of β -human chorionic gonadotrophin). The last treatment was given after embryo transfer. All sessions—both traditional acupuncture and sham acupuncture—were performed by the same professional acupuncturist.

Acupuncture was normally performed once a week (although occasionally twice a week when the patients came to the clinic for an ultrasound control) over a 4-week period, giving a minimum of four sessions and a maximum of six. Traditional acupuncture was used, respecting the classical acupuncture points including the depth of insertion. Single-use sterile copper-handle prepacked needles were used with guide tubes 40×0.25 mm (Dongbang Acupuncture; Boryeong City, South Korea). The location and depth of insertions were as described in traditional texts. In all acupuncture sessions a total of seven needles were used, always attempting to achieve the de Qi sensation (sensation of soreness, numbness or distension around the point). The points used were as follows: HT7 and PC6 points on forearm (bilaterally), CV17 on chest, *Yintang* on the face and GV20 at the apex of head. The choice of acupuncture points was based on their specific traditional properties. Needles were left in place for about 25 min. Neither electrostimulation nor ear acupuncture was used.

For women in the control group, sham acupuncture points were used. These were located close to but not on the real acupuncture points. The same number of needles (and the same type of needles) were placed in the same regions but at a distance of approximately 1.5 cm, in regions that do not correspond to known acupuncture points, to a depth of 2 mm without needle stimulation. Needles were left in place for about 25 min (the same time as in the acupuncture group).

Outcome Measures

After agreeing to participate in the study, patients were interviewed by the researcher who applied a standard questionnaire in order to assess the degree of anxiety before starting the ovulation induction for IVF. This researcher was blinded to the patient group. The questionnaire used was the Hamilton Anxiety Scale (HAS) which was developed in 1959 as a tool to be used by doctors and therapists to determine the severity of the anxiety of a patient. HAS is a rating scale developed to quantify the severity of anxiety symptomatology, often used in psychotropic drug evaluation. It consists of 14 items, each defined by a series of symptoms. Each item is rated on a 5-point scale ranging from 0 (not present) to 4 (severe).^[9] A reduction of 30% in the HAS score is considered to be clinically significant.^[9]

After the four weekly treatment sessions, all patients returned to the same researcher for reapplication of the HAS and final evaluation. The change in HAS score was the primary outcome measure. The choice of this scale for this study was based on its specific reference to comprehensive neurovegetative complaints typical of anxiety, and its acceptability for determining the relative effectiveness of treatments in clinical trials.^[9]

Statistical Analysis

The primary outcome was the change in HAS score, which was used for sample size calculation. We estimated a sample size of 20 patients in both groups was required based on the assumption of a differential reduction of 30% in HAS score and a power of 80% (according to a β of 20%) and a type I error (α) of 5%. The sample size calculation assumed a one-sided test situation and was performed with an unconditional exact test. The initial analysis examined the demographic and baseline characteristics of women randomised to the trial. Data were expressed as mean \pm SD. The Student t test was used to test for possible imbalances between the groups regarding the following variables: age (years), duration of infertility (years), HAS score before and after treatment. For analysis of the HAS score the results were tested by non-parametric Wilcoxon statistics and illustrated by a box plot graph. The Fisher exact test was applied to compare frequencies between groups such as the therapeutic effect on the levels of anxiety (HAS) and pregnancy rates. A threshold of 30% reduction in HAS score is considered a response to treatment.^[9] A p value of <0.05 was considered significant. All data were analysed using Stata Statistical Software.

Results

A total of 43 patients were included in the study: 22 patients received acupuncture according to the principles of traditional Chinese medicine (test group) and 21 patients received sham acupuncture (control group). There were no dropouts and/or withdrawals and all 43 patients completed the study. No patient was lost to follow-up.

The test and control groups were comparable in terms of age, duration of infertility and HAS score before treatment (Table 1). The mean HAS score after the 4-week experimental period was significantly lower in the test group than in the control group (19.4 \pm 3.2 vs 24.4 \pm 4.2, $p=0.0008$; Table 1). Reduction in anxiety was 19.4% in the control group and 34.9% in the test group (Table 1).

Table 1. Control variables, demographic data

| Variables | Control group (n=21) | Test group (n=22) | p Value† |
|----------------------------------|----------------------|-------------------|----------|
| Age (years)* | 34.3 \pm 4.6 | 34.1 \pm 4.6 | 1.0000 |
| Duration of infertility (years)* | 4.7 \pm 2.8 | 3.4 \pm 1.5 | 0.1351 |
| HAS score before treatment | 28.4 \pm 3.8 | 29.8 \pm 3.3 | 0.2535 |
| HAS score after treatment | 24.4 \pm 4.2 | 19.4 \pm 3.2 | 0.0008 |

* Mean \pm SD.

† Mann–Whitney test.

HAS, Hamilton Anxiety Rating Scale.

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The number of patients scoring a reduction of >30% (considered a response for treatment) was significantly lower in the control group than in the test group (14.3% vs 68.2%; RR 4.77, 95% CI 1.61 to 14.14, p=0.004; Table 2). No significant differences in rates of clinical pregnancy were demonstrated between the control and test groups (19.0% vs 41.0%; RR 1.72, 95% CI 0.69 to 4.29, p=0.1924; Table 2).

Table 2. Therapeutic response on levels of anxiety (Hamilton Anxiety Rating Scale) and pregnancy rates

| Variables | Control (n=21) | Test (n=22) | RR | 95% CI | p Value* |
|------------------------|----------------|-------------|------|---------------|----------|
| Anxiety reduction ≥30% | 3 (14.3%) | 15 (68.2%) | 4.77 | 1.61 to 14.14 | 0.0004 |
| Pregnancy rates | 4 (19%) | 9 (41%) | 1.72 | 0.69 to 4.29 | 0.1924 |

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The box plot graph (figure 1) compares the HAS scores of the control and test groups before and after treatment. As can be seen from the graph, simple effects analyses showed that the HAS score declined significantly from baseline to end of

treatment in the acupuncture-treated group.

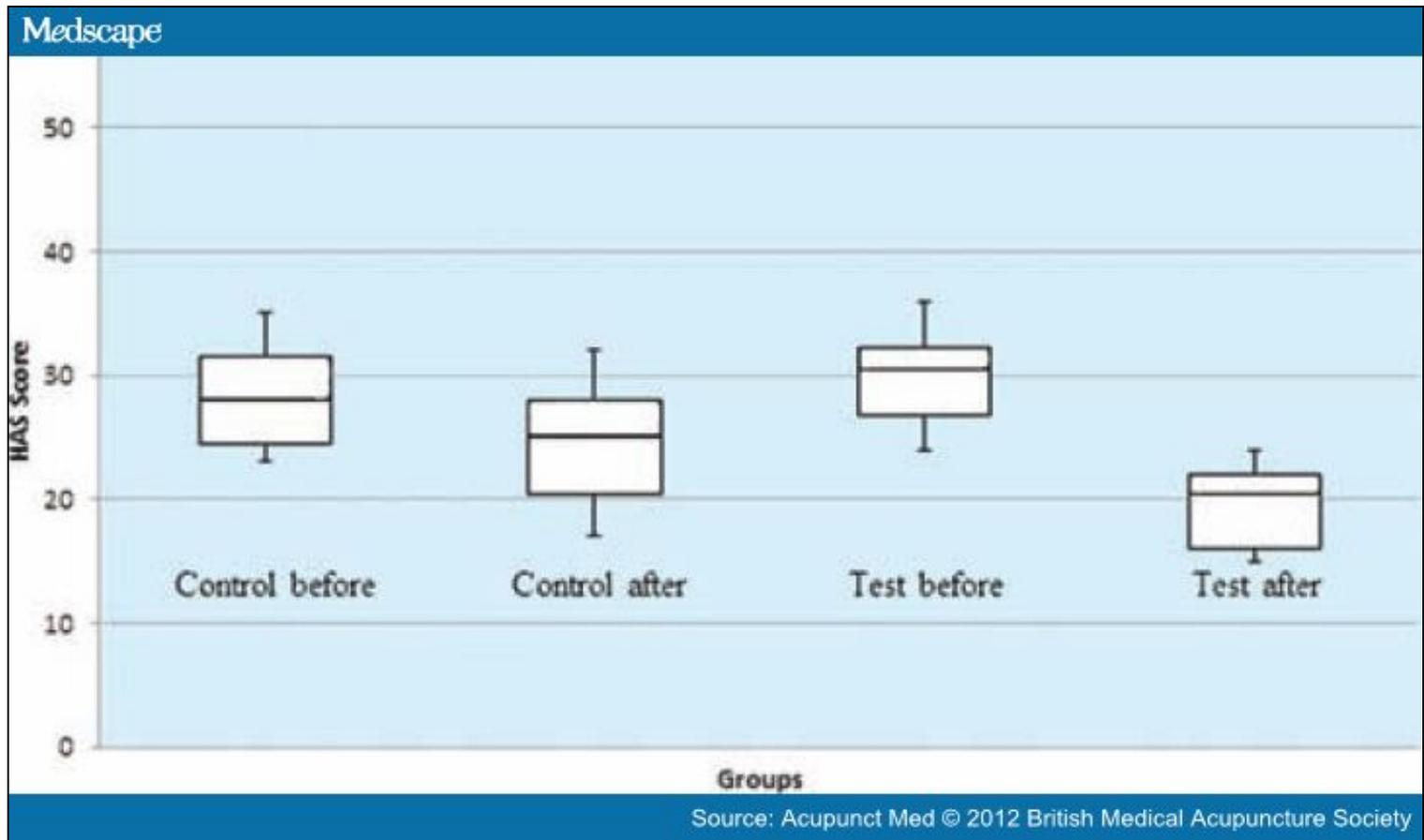


Figure 1. Box plot of Hamilton Anxiety Rating Scale (HAS) scores before and after acupuncture. Boxes show median and 25th percentiles, lines show outliers.

Discussion

This randomised controlled pilot trial indicates that acupuncture may be efficacious for reducing symptoms of anxiety in women undergoing IVF. Acupuncture provided treatment effects superior to a sham acupuncture control condition for anxiety reduction. All patients in this study followed our standard IVF protocol and all acupuncture procedures were performed by the same certified acupuncturist. The real and sham acupuncture groups were comparable for demographic characteristics. We found a significantly higher overall HAS score after treatment following sham acupuncture compared with real acupuncture. There was a trend towards higher rates of clinical pregnancy, although the differences did not reach statistical significance.

When we model the relationship of this acupuncture regimen to reduction on HAS score after treatment, women with acupuncture were 4.77 times more likely to have a reduction of 30% in anxiety symptoms. However, the CI is large (1.61 to 14.14).

Based on the results of this study, it would be interesting to offer acupuncture treatment for reducing anxiety levels at the time of IVF.

Scientific acupuncture emphasises the neuroanatomical and neurophysiological mechanisms of organs involved, explained mainly by the stimulation of acupuncture points linking with the somatovisceral reflex arc and brain structures such as the limbic system, reticular formation, hypothalamus and cortex.^[10 11]

Infertility can cause stress and anxiety leading to release of stress hormones.^[12] Verhaak *et al*^[6] reported that differences in the emotional status between pregnant and non-pregnant women were present before treatment and became more apparent after the first IVF cycle. Women who became pregnant had lower levels of depression than those who did not.^[12] The use of acupuncture to reduce anxiety—possibly involving a sympathoinhibitory property and impact on β -endorphin levels—has been reviewed. Fanti *et al*^[10] found that treatment with acupuncture decreased patients' demand for sedative drugs, reducing both discomfort and anxiety during the procedure.^[10] Eich *et al*^[12] showed that needle acupuncture leads to a significant clinical improvement and to a remarkable reduction in anxiety symptoms in patients with minor depression or with generalised anxiety disorders.^[12] Hong *et al*^[13] found that sympathetic activation during anxiety was eliminated after acupuncture. Studies on the neurohumoral mechanism of acupuncture have demonstrated its effect on the hypothalamic-pituitary-adrenal axis.^[11] This axis is directly related to the functions of the vegetative system (sympathetic and parasympathetic).^[12 13] The modulating effect of acupuncture in the autonomic system may explain the decrease in symptoms and signs of anxiety in this study.^[12 13]

It has previously been reported in the literature that acupuncture reduces the sympathoadrenal activity associated with stress, evidenced clinically as relaxation, calmness and a subjective decrease in excessive stress.^[11]

Recent research on emotional disorders has shown the involvement of neurotransmitters such as serotonin, dopamine, norepinephrine, GABA, CCK, Y neuropeptide, acetylcholine, CRF, among others;^[14] these same neurotransmitters are also involved in the mechanism of action of acupuncture.^[15 16] However, in generalised anxiety disorder or anxiety neurosis, it is difficult to interpret the findings of the studies of acupuncture because of the range of interventions against which acupuncture was compared.^[8] All trials reported positive findings but the reports lacked many basic methodological details.^[8]

Balk *et al*^[15] showed that acupuncture was associated with less stress both before and after embryo transfer, and it possibly improved pregnancy rates. Lower perceived stress at the time of embryo transfer may play a role in an improved pregnancy rate.^[15] In our study we did not find a statistical difference in pregnancy rates.

One limitation of this study is that it is small, with only 43 subjects. Previous studies have indicated that acupuncture improves pregnancy rates. This study is too small to determine a dose-response relationship, but future studies should explore this possibility.

One of the strengths of this study is that it is innovative. It is the first study to investigate the effects of acupuncture on anxiety symptoms at the time of IVF.

In spite of the limitations of this study, the data provide initial evidence that an acupuncture treatment approach may be effective and acceptable for treating anxiety symptoms. Future studies should investigate the dose-response relationship, mechanisms of action and the types of biases and directions of the biases that may confound the relationship between acupuncture and anxiety symptoms and pregnancy success.

In conclusion, the results indicate that acupuncture can reduce anxiety symptoms observed by the reduction of physiological parameters in women undergoing IVF. Further evidence should be sought as to whether acupuncture might be a complementary option for patients undergoing IVF.

Sidebar

Summary Points

- IVF procedures generate anxiety
- This RCT compared acupuncture and sham acupuncture
- Acupuncture led to significant reduction of anxiety

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Contributors

DI, CPB, STM: substantial contributions to conception and design, acquisition of data and analysis and interpretation of data. EBC, AMBSvanN, WPAdeC: drafting the article or revising it critically for important intellectual content. DI, CPB, AMBSvanN: final approval of the version to be published.

Patient consent

Obtained.

Ethics approval

Ethics approval was obtained from the Committee in Research of the Faculty of Medicine, ABC, number 073/2009.

Provenance and peer review

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