Effects of acupuncture on the outcome of in vitro fertilisation and intracytoplasmic sperm injection in women with polycystic ovarian syndrome

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ABSTRACT

Background Different mechanisms have been described for the effects of acupuncture on fertility. Acupuncture may mediate neurotransmitter release, which results in the stimulation of gonadotrophin-releasing hormone secretion. The production of neurotransmitters such as endogenous opioids may also inhibit central nervous system outflow and biological stress response. Acupuncture may also stimulate blood flow to the uterus by inhibiting uterine central sympathetic nerve activity. Despite some evidence suggesting beneficial effects of acupuncture on in vitro fertilisation (IVF) success rates, recent clinical trials could not duplicate these effects, especially in patients who are infertile with polycystic ovarian syndrome (PCOS) who are undergoing IVF.

Methods A total of 62 women with PCOS undergoing IVF/intracytoplasmic sperm injection (ICSI) at Shayamehr IVF Clinic in Tehran (Iran) participated in a randomised, controlled trial. Participants were randomly allocated to one of two groups: there were 31 women each in the acupuncture (group I) and control groups (group II). Acupuncture based on traditional Chinese medicine was performed in group I versus no adjunctive treatment in group II. All acupuncture procedures were performed in five sessions: start of downregulation, start of stimulation, 2 days before ovum pick-up, and immediately before and after embryo transfer. We measured the rate of oocytes in metaphase II, the fertilisation rate and the quality of embryos.

Results Our results showed a statistically higher mean of good quality embryos in group I compared with group II (p=0.044). However, the mean number of metaphase II oocytes retrieved and fertilisation rate were similar between the two groups. We also could not find any significant differences among clinical, biochemical or ongoing pregnancy rates.

Conclusions Acupuncture at an early stage of oocyte recruitment may have a beneficial effect on embryo quality. However, it seems to have no significant effect on other IVF/ICSI outcomes of women with PCOS.

Trial registration number (IRCT ID: 201011275181N4)

INTRODUCTION

Many advances have been made in assisted reproductive technologies. Nevertheless, nearly 75% of in vitro fertilisation (IVF) cycles are unsuccessful.1 Thus, it seems sensible to consider whether complementary medicine can also play a role. One such option is acupuncture,23 which has been used in China for centuries to regulate the female reproductive system.4 The concept of medical acupuncture is based on the integration of traditional Chinese medicine (TCM) with modern evidence-based medicine, which is our approach in the design and performance of this study.

Although the scientific rationale for this approach during IVF or intracytoplasmic sperm injection (ICSI) has not been entirely accepted, there is some evidence showing that acupuncture stimulates uterine blood flow, leading to the enhancement of uterine receptivity5 and relaxation.6

Furthermore, acupuncture may increase blood flow to the ovaries and reduce ovarian volume and the number of ovarian cysts in polycystic ovarian syndrome.
There is some evidence that PCOS is associated with hyperactivity of the sympathetic nervous system, and the density of innervations by catecholaminergic nerve fibres in the ovaries of women with PCOS is greater than in normal ovaries. The ovary is a highly vascularised organ, and maintenance of high blood flow is important for the ovulatory process. The ovarian sympathetic nerves are important regulators of ovarian blood flow, so if we can modify the sympathetic drive in the ovaries we could theoretically improve the physiological function of the ovaries. Clinical and experimental evidence suggests that acupuncture can be a suitable alternative or complement to pharmacological induction of ovulation in women with PCOS, and may also relieve other symptoms without significant adverse side effects if the regimen is administered by a trained acupuncturist, particularly one who specialises in treating fertility disorders. Briefly, two potential mechanisms have been described for the effects of acupuncture on fertility. Firstly, acupuncture may mediate neurotransmitter release, which results in the stimulation of gonadotrophin-releasing hormone secretion, thereby influencing the menstrual cycle and ovulation. The production of neurotransmitters such as endogenous opioids may also inhibit central nervous system outflow and biological stress response. Secondly, acupuncture may stimulate blood flow to the uterus by inhibiting uterine central sympathetic nerve activity.

Although some evidence exists on the beneficial effects of acupuncture on IVF success rates, some recent clinical trials could not duplicate these findings. Given the fact that infertility treatment in women with PCOS is mostly associated with extremely low or high ovarian response, we hypothesised that acupuncture may help the ovarian response and influence the success rate positively. The aim of this study was therefore to investigate the effects of early acupuncture on the outcome of IVF/ICSI in women with PCOS in comparison to no acupuncture.

MATERIALS AND METHODS

A randomised clinical trial was conducted at Shayamehr Infertility Clinic in Tehran from June 2009 to September 2010. This study was approved by the institutional review board of Tehran University of Medical Sciences and informed consent was obtained from each participant (IRCT ID: 201011275181N4). The infertility specialist, embryologist and data analyst were not party to the computerised randomisation of participants.

A total of 92 patients with PCOS signed up to participate, of whom 62 were included according to the inclusion criteria.

Our coordinating staff in the acupuncture clinic generated a random allocation sequence. Inclusion criteria were as follows: participants were infertile women aged 18–40 years with PCOS who were candidates for IVF/ICSI. PCOS diagnosis was based on the Rotterdam criteria (European Society of Human Reproduction and Embryology and American Society for Reproductive Medicine, 2003). After the exclusion of related disorders, PCOS was diagnosed on the basis of two out of three of the following: oligo-ovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound.

Exclusion criteria were infertility for other reasons such as male factor, endometriosis, and/or the combination of male and female factors who were candidates for ovum or embryo donation. Patients with uncontrolled systemic disorders after consultation with a medical specialist were also excluded from the study.

The 62 subjects were randomly allocated to either the acupuncture group or control group (31 in each). Prior to IVF/ICSI, all patients were examined by an infertility specialist. Data on baseline characteristics, medical history, IVF/ICSI indications, number of previous IVF/ICSI attempts and laboratory and ultrasound examinations were collected. All interventions and evaluations were performed by the same infertility specialist, acupuncturist and embryologist.

The two groups received the controlled ovarian hyperstimulation, ovum pick-up (OPU), IVF/ICSI procedures and embryo transfer (ET) methods as in routine practice in our infertility centre. The two groups used the long protocol, including gonadotrophin releasing hormone agonist (Buserelin; Avintis, France, 500 μg daily), from day 21 of the previous cycle until the day of human chorionic gonadotrophin (HCG) administration. Ovarian stimulation was performed with recombinant follicle-stimulating hormone (FSH) (follitrophin α, Gonaf; Merck Serono, Switzerland). Initially, the dosage of Gonaf was 150 IU daily beginning on day 3 of the most recent cycle. The dosage was then adjusted depending on the ovarian response. When at least two follicles had a diameter of ≥17 mm, HCG (Choriomone, Ibsa, Switzerland) triggered ovulation. Ultrasound-guided oocyte retrieval was performed 36 h after HCG injection (10 000 IU). Patients in both groups received progesterone (Cyclogest, Actover, UK; 400 mg twice daily) vaginally early on the day of OPU. At 2 days after OPU, a maximum of four embryos were transferred into the uterus transvaginally. The control group had no other adjunctive treatment.

However, we also used acupuncture in the intervention group. Acupuncture treatment was based on the TCM style of acupuncture and information from previous trials. It was performed by an expert acupuncturist and was reported according to the revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) in this study. All acupuncture procedures were performed at five sessions: on the 21st day of the previous cycle (start...
of downregulation), the first day of stimulation, 2 days before OPU, and immediately before and after ET. The insertion of the acupuncture needle into an acupuncture point typically generates a range of sensations called de qi; this sensation was maintained throughout the session of acupuncture mentioned above. The points were needled bilaterally to a depth of 25 mm and stimulated for 30 min by an Electronic Acupunctoscope, (Model WQ-6F, Beijing Electronic Instrument Co., Ltd., Beijing, China). The needles were stainless steel (0.22 mm in diameter, Natural Manufactory, China).

SP and ST channels are considered sources of Qi (vital force and energy) and blood. It was believed that they are important channels for sexual function, the menstrual cycle and for their general effects on pelvic organs. In particular, SP6 is considered as a crossing point of the three Yin meridian of the foot and for its general homeostatic effect. SP6 is deemed an area of influence point of the pelvis.

The LR channel is supposed to regulate Qi and the endocrine glands. LR3 is considered as the source point of the LR channel and believed to have great harmonising effects when used in combination with LI4 to ‘open relevant meridians and calm the mind’.14 GV20 is believed to have a significant sedating and relaxing effect and also is effective in reproductive function.14 CV is considered to control all the Yin channels, and to be effective for disorders of reproductive function and also for disorders of the pelvic and nervous system.

In the first three sessions we used: LI4, SP6, LR3, CV4, GV20, ST36 and the Ovary and Uterus auricular points, bilaterally.14 25 In the pre-ET and post-ET acupuncture treatment we used: LR3, SP10, PC6, ST29 and the Shenmen auricular point, bilaterally.14 25

Results were recorded from the day of OPU until ET, 2, 4 and 18 weeks after ET, and also postpartum. The main outcomes of the study were the number of oocytes in metaphase II, fertilisation rates and embryo quality. In this study, biochemical pregnancy (defined as elevated βHCG 2 weeks after ET), clinical pregnancy (defined as the presence of at least one normal gestational sac 2 weeks after positive βHCG) and ongoing pregnancy rate 18 weeks after ET were assessed. Take-home baby rate was defined as at least one live birth after 36 weeks. Miscarriage was diagnosed if spontaneous abortion had occurred at >12 weeks. If fetal heart rate was not demonstrated within the sac, another ultrasound examination was carried out 1–2 weeks later. Sonography was performed using a Honda Ultrasound HS-4000 (7.5 MH vaginal probes).

Embryological characteristics were calculated by the following correlations: rate of oocytes in metaphase II=(no. of metaphase II/no. of oocytes retrieved)×100 and fertilisation rate=(no. of 2PN/no. of metaphase II)×100.

Embryo quality=grading based on the shape of cells and fragmentation (score: 0–4). The embryologist who scored the embryo quality was blinded to the patient group.

Assuming that acupuncture results in a 10% improvement in the number of metaphase II (mature) oocytes, a sample of 30 in each arm was calculated to yield a significance of 0.05 with a power of 0.8 (Sigmastat/Jandel Scientific; San Rafael, California, USA). Results were reported as means±SD for the quantitative variables and percentages for the categorical variables. Between-group differences of normally distributed continuous variables were assessed by Student t test, whereas the Mann–Whitney U test was used as the data were not normally distributed. The groups were compared using the χ² test (or Fisher’s exact test, if required) for the categorical variables. p Values of 0.05 or less were considered statistically significant. All statistical analyses were performed using SPSS V16.0 (SPSS Inc., Chicago, Illinois, USA) and SAS V9.1 for Windows (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS
In total, 62 patients were included in the study. Group I comprised 31 patients who received acupuncture according to the principles of TCM. All participants completed our study; none were lost to follow-up. Only two patients had ovarian hyperstimulation syndrome. One of these achieved two live births in the acupuncture group, but the other had no ET in the control group. Consequently, this patient was excluded from the analysis. In addition, cleavage did not occur in one patient in the control group. Baseline characteristics and clinical data of patients in both groups are presented in table 1.

No differences regarding days of stimulation, number of oocytes retrieved, or number of embryos transferred were observed between the acupuncture and control groups. Clinical, biochemical and ongoing pregnancy rates were similar between the groups.

Table 1 Baseline characteristics and clinical data of study patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Acupuncture group (n=31)</th>
<th>Control group (n=31)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>31.03±4.82</td>
<td>32.10±4.68</td>
<td>0.71</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.83±4.61</td>
<td>26.10±4.15</td>
<td>0.32</td>
</tr>
<tr>
<td>Duration of infertility, years</td>
<td>9.09±4.65</td>
<td>9.41±4.93</td>
<td>0.89</td>
</tr>
<tr>
<td>Infertility type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>25 (80.6)</td>
<td>22 (71.0)</td>
<td>0.22†</td>
</tr>
<tr>
<td>Secondary</td>
<td>6 (19.4)</td>
<td>9 (29.0)</td>
<td></td>
</tr>
<tr>
<td>No. of IVF cycles</td>
<td>1.48±1.73</td>
<td>1.06±1.28</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Values are mean±SD or number (%). *Student t test unless stated. †Fisher’s exact test. IVF, in vitro fertilisation.
pregnancy rates were similar between the two groups. The miscarriage rate was two cases versus one case in the acupuncture and control groups, respectively (table 2).

According to table 3, the rate of oocytes in metaphase II was 78.37±22.01 vs 73.84±19.96 in the acupuncture and control groups, respectively (p=0.400). The fertilisation rate was similar between groups; however, there was a significant difference in embryo quality score between the acupuncture and control groups (p=0.044).

DISCUSSION
Our findings showed a beneficial effect of acupuncture at an early stage of oocyte recruitment on embryo quality. However, acupuncture had no significant effect on other IVF/ICSI outcomes of women with PCOS such as number of MII oocytes retrieved, fertilisation or pregnancy rates.

This research will add new knowledge to help define the role of certain acupuncture protocols applied at different stages of IVF treatment in patients with PCOS, including: on the 21st day of the previous cycle (start of downregulation), the first day of stimulation, 2 days before OPU, and immediately before and after ET from a clinical perspective. The very small patient groups restrict the ability of our results to demonstrate clear-cut differences in terms of clinical pregnancy and abortion rates. However, our results can inform future studies involving similar populations.

In recent decades, investigators have focused on the use of acupuncture in patients undergoing IVF/ICSI to improve success rates. These studies have varied in design and had inconclusive or conflicting results, so could not recommend the use or omission of acupuncture during IVF as a clinical treatment. Depending on the time and session when the acupuncture was applied, previous studies showed different results regarding the therapeutic effects of acupuncture in comparison to common protocols. For instance, Humaidan and Stener-Victorin performed acupuncture based on the day of oocyte retrieval. Clinical pregnancy rates were not significantly different in the two groups. In our study, clinical pregnancy rates were 25.8% in the acupuncture group compared with the control group rate of 16.1%. However, this numerical difference was not statistically significant.

Most studies performed acupuncture around the time of ET. In one study by Smith et al., the pregnancy rates were 31% in the acupuncture group and 23% in the control group. For subjects receiving acupuncture, the odds of achieving a pregnancy were 1.5 times higher than for the control group, but the difference did not reach statistical significance. Domar et al. indicated that the use of acupuncture in patients undergoing IVF was not associated with an increase in pregnancy rates. However, Paulus et al. found clinical pregnancy rates of 42.5% in the acupuncture group, but only 26.3% in the control group. For subjects receiving acupuncture, the odds of achieving a pregnancy were 2.3 times higher than for the control group, confirming that acupuncture may be useful in improving pregnancy rates after treatment with assisted reproductive technology. Another study performed by Dieterel et al. demonstrated the benefit of acupuncture on clinical pregnancy and ongoing pregnancy rates. The results of some studies within the last decade are in accordance with our study. A systematic review and meta-analysis by EI Toukhy and colleagues showed no difference in clinical pregnancy rates depending on time of acupuncture application (OPU or ET).

Based on previous findings on the beneficial endocrine and reproductive effects of acupuncture in PCOS, we hypothesised that certain effects of acupuncture might be obtained if it is applied at the early stage of follicular recruitment and development. Therefore, acupuncture was performed in all patients at two early points: the luteal phase of the previous cycle and the first day of stimulation, as well as on the days of OPU and ET. Our findings in terms of oocyte quality and higher embryo quality were similar to those of Cui et al. Regarding the duration of follicular growth, which lasts about 3–4 months, we hypothesise that certain effects of acupuncture especially on pregnancy rate may be obtained if it is begun up to 3–4 months before starting an assisted reproductive technology (ART) cycle. This kind of

Table 2  In vitro fertilisation/intracytoplasmic sperm injection data of study groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Acupuncture group (n=31)</th>
<th>Control group (n=31)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of stimulation</td>
<td>9.42±1.89</td>
<td>10.03</td>
<td>0.613*</td>
</tr>
<tr>
<td>No. of oocytes retrieved</td>
<td>8.68±5.68</td>
<td>9.23</td>
<td>0.371*</td>
</tr>
<tr>
<td>No. of embryos transferred</td>
<td>2.68±1.01</td>
<td>2.42</td>
<td>0.702*</td>
</tr>
<tr>
<td>Biochemical pregnancy rate, n (%)</td>
<td>8 (25.8)</td>
<td>5 (16.1)</td>
<td>0.152†</td>
</tr>
<tr>
<td>Clinical pregnancy rate, n (%)</td>
<td>8 (25.8)</td>
<td>5 (16.1)</td>
<td>0.152†</td>
</tr>
<tr>
<td>Ongoing pregnancy rate, n (%)</td>
<td>6 (19.4)</td>
<td>4 (12.9)</td>
<td>0.490†</td>
</tr>
<tr>
<td>Miscarriage rate, n (%)</td>
<td>2 (6.6)</td>
<td>1 (3.3)</td>
<td>0.573†</td>
</tr>
</tbody>
</table>

Values are means±SD or number (%).
*Student t test unless stated.
†Fisher’s exact test.
‡Mann–Whitney U test.

Table 3  Embryological characteristics in the study groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Acupuncture group (n=31)</th>
<th>Control group (n=31)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metaphase II oocytes rate</td>
<td>78.37±22.01</td>
<td>73.84±19.96</td>
<td>0.400</td>
</tr>
<tr>
<td>Fertilisation rate</td>
<td>77.32±22.30</td>
<td>66.61±29.71</td>
<td>0.114</td>
</tr>
<tr>
<td>Embryo quality†</td>
<td>3.75; 0.45</td>
<td>3.5; 0.82</td>
<td>0.044**</td>
</tr>
</tbody>
</table>

Values are means±SD or number (%).
*Student t test unless stated.
†Median; IQR.
‡Mann–Whitney U test.

treatment seems to lead to better therapeutic effects but the extent to which this holds true needs to be examined. Differences in published results may be due to inappropriate study design and small sample size.

In conclusion, we have demonstrated that acupuncture during IVF/ICSI treatment may have beneficial effects on embryo quality in patients with PCOS if applied at the early stages of follicular development. However more trials are needed for confirmation of our results. Further investigation is also needed to show how we could convert the improved embryo quality into an improved pregnancy rate when administered 3–4 months before starting an IVF cycle. However, to evaluate the effect of acupuncture on abortion rate it should be used throughout the first trimester since incidences of abortion are most frequent within the first 3 months of pregnancy.

Acknowledgements This research project is a specialty thesis supported by Tehran University of Medical Sciences. The authors thank our colleagues Dr Salehpour and Dr Movahhedin. We especially thank Mrs Malakooti for helping to collect the data.

Funding This study was backed by funds provided through research deputy of Tehran University of Medical Sciences.

Contributors BHR designed the study, participated in acquisition and interpretation of data, helped to draft the questionnaire and participated in writing the draft and its final revised format. EST participated in the design of the study, NA conceived the study, and participated in its design and performed the acupuncture. LP as her thesis discussed and evaluated the results and helped to draft the manuscript.

Competing interests None.

Ethics approval Ethical committee of Tehran University of Medical Sciences.

Provenance and peer review Not commissioned; externally peer reviewed.

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*Acupunct Med* 2013 31: 151-156 originally published online February 1, 2013
doi: 10.1136/acupmed-2012-010198

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