

## Clinical Experience

# Acupuncture Enhances Chances of Pregnancy in Unexplained Infertile Patients Who Undergo A Blastocyst Transfer in A Fresh-Cycle

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**ABSTRACT** **Objective:** To analyze the effects of acupuncture on *in vitro* fertilization patients with unexplained infertility. **Methods:** We retrospectively analyzed the charts of a total of 302 cycles performed in 273 patients attending Assisted Reproductive Technology (ART) Centre from August 2013 to August 2016. During the study period, embryo transfer with acupuncture (Acupuncture group, 46 cases) and without acupuncture (Control group, 42 cases) were applied. Prior to embryo transfer, the following points were used in the acupuncture group: Neiguan (CX 6), Diji (SP 8), Taichong (Liv 3), Baihui (Gv 20), and Guilai (S 29). These sessions were carried out two times before and after embryo transfer in a single day. In addition, auricular acupuncture was also performed at ear points, including ear point 55 (Shenmen), ear point 58 (Zhi Gong), ear point 22 (Neifenmi) and ear point 34 (Naodian). The biochemical pregnancy rate and clinical pregnancy rate after transplantation were compared between two groups. **Results:** The clinical pregnancy rate in the acupuncture group was higher than that in the control group [60.9% (28/46) vs. 33.3% (14/42), respectively,  $P < 0.05$ ]. Likewise, the live birth rate in the acupuncture group was also higher than that in the control group [71.7% (33/46) vs. 31.0% (12/42),  $P < 0.01$ ]. **Conclusion:** Administration of acupuncture on the day of embryo transfer dramatically improved fertility results in women who underwent *in vitro* fertilization/intra-cytoplasm sperm injection for reproduction.

**KEYWORDS** acupuncture, assisted reproduction, embryo transfer, pregnancy rate

Acupuncture is a significant component of conservative Chinese medicine that dates back to at least 3,000 years. It was reported that the mechanisms of acupuncture in infertility therapy were to increase ovarian and uterine blood flow, improve hormone regulation due to increases in endometrial thickness, and decrease stress.<sup>(1)</sup> There is enough evidence for the application of acupuncture for infertility in two surveys. First, findings from 9,408 patients who consulted acupuncturists revealed a 1.3% success for the participants that had used acupuncture for fertility assistance.<sup>(2)</sup> Second, a survey in the United Kingdom demonstrated a 15% success rate for those provided with fertility support. Therefore, for some practitioners, acupuncture therapy has constituted a big part of their workload.<sup>(3)</sup>

A well-done *in vitro* fertilization (IVF) and embryo transfer (ET) demand optimum endometrial receptivity during implantation. The endometrial circulation or blood flow impedance in the uterine arteries, evaluated according to the Pulsatil Index (PI), is regarded as a

useful tool for determining endometrial receptivity.<sup>(4)</sup> Acupuncture has been observed to improve endometrial receptivity in rats<sup>(5,6)</sup> by decreasing the impedance of uterine artery blood flow, thus improving blood flow to the uterus.<sup>(7)</sup> This increased blood flow could enhance implantation and increase the chances of successful pregnancy and live birth. Paulus, et al<sup>(8)</sup> reported an increase in clinical pregnancy rates when a standard acupuncture administration was carried out prior to and following fresh, non-donor IVF-ET. The aim of this

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study was to analyze the effects of acupuncture on *in vitro* fertilization patients.

## METHODS

### Inclusion Criteria

The following inclusion criteria were used: (1) women were between 20 and 35 years old who had regular menstrual cycles of 21–45 days; (2) no evidence of endocrine disorders [normal thyroid stimulating hormone (TSH), prolactin, testosterone, and androstenedione levels] was observed; (3) BMIs ranging from 18–28 kg/m<sup>2</sup>; (4) they have husbands whose sperm concentrations met the World Health Organization (WHO) standards (2010) of  $\geq 15 \times 10^6$ /mL and a total motility of  $\geq 40\%$  or a total motile sperm count of  $\geq 9$  million; (5) they were not on hormone therapy for the previous 3 months; (6) all of the patients had unexplained infertility at primary level; (7) patients underwent recombinant follicle stimulating hormone (rFSH), and an antagonist protocol was applied to all patients; (8) patients underwent a fresh IVF or intracytoplasmic sperm injection cycle; and (9) underwent a single embryo transfer and a blastocyst embryo transfer.

### Exclusion Criteria

The following exclusion criteria were used: (1) the patients who smoke; (2) endometriosis; (3) polycystic ovary syndrome; (4) body mass index  $> 28$  kg/m<sup>2</sup>; (5) hyperprolactinemia [defined as 2 prolactin (PRL) levels of  $\geq 25$  ng/mL at least 1 week apart or as determined by local normative values]; (6) irregular menstruation (interval: less than 21 days or more than 45 days); (7) endocrine diseases (thyroid disease, diabetes mellitus, or Cushing's syndrome), hormonal contraceptive use, follicle-stimulating hormone (FSH) levels  $> 15$  mIU/mL; (8) other major medical illnesses, such as positive human immunodeficiency virus status, severe bleeding dyscrasia, heart disease, severe hypertension, uncontrolled diabetes mellitus which possibly hamper IVF or pregnancy; (9) those who have obtained donor eggs, have cutaneous lesions within the acupoint area and had previously taken part in this research or undergone acupuncture (in whatever mode) as infertility therapy were also excluded from this study.

### Ethical Statement

An ethics committee report was taken from Department of Medicine, University of Harran. This research was carried out once the regional ethics committee consent had been received and each

participant had signed an informed approval form.

### Subjects

We retrospectively analyzed the charts of a total of 302 cycles performed in 273 patients attending Diyar Life Assisted Reproductive Technology Centre from August 2013 to August 2016. This research assessed the results of 88 women who received medical help in the form of a standardized treatment package for unexplained infertility. During the study period, embryo transfer with acupuncture (acupuncture group, 46 cases) and embryo transfer without acupuncture (control group, 42 cases) were applied.

### Application of Acupuncture

Following the study by Paulus, et al,<sup>(7)</sup> the acupuncture points employed in this study were chosen pursuant to the principles of Chinese medicine. In this approach, an acupuncture application of 25 min prior to and after blastocyst embryo transfer was performed in each patient in the acupuncture group. These sessions were carried out two times only in a single day by using disposable needles (0.25 mm  $\times$  0.25 mm). As a needle reaction, there was numbness and soreness surrounding the acupoint which means Deqi sensation. Ten minutes later, the needles were revolved so as to resume Deqi sensation. The needles stayed in the position for 25 min. The depth of needle application was ranging from 10 to 20 mm, according to the area of the body that receives therapy. Prior to embryo transfer, the following points were used: Neiguan (CX 6), Diji (SP 8), Taichong (Liv 3), Baihui (GV20), and Guilai (S29). Following the embryo transfer, the needles were placed at these locations: Zusanli (ST 36), Sanyinjiao (SP 6), Xuehai (SP10) and Hegu (LI4).

Furthermore, we utilized tiny rust-free needles (0.2 mm  $\times$  13 mm) for auricular acupuncture at these locations: ear point 55 (Shenmen), ear point 58 (Zhigong), ear point 22 (Neifenmi) and ear point 34 (Naodian). Two needles were placed in the right ear, and the other two in the left. The four needles stayed in the ears for 25 min. In the control group, embryos were transferred without any supplementary treatment.

Acupuncture was performed with Seirin brand (Japan, 0.16 mm  $\times$  15 mm, J-type ear) needles for auricular points and Vinco brand (China, 0.22  $\times$  30–40 mm needles) for body points, except

Yintang, which was needed with a 0.16 mm × 15 mm, J-type Seirin brand ear needle.

**Ovulation Induction Protocol**

All participants had ovarian stimulation on the 3rd day of the menstrual cycle. Young women (< 35 years) began with 150 IU of rFSH (GonalF; Serono, Zug, Switzerland) every day. At 12 mm of follicle size, a gonadotropin-releasing hormone antagonist was also used. Follicle size and number were followed by ultrasound (Aloka, Japan), and serum levels of estradiol, progesterone and luteinizing hormone were evaluated as well. Should the day-8 estradiol (E<sub>2</sub>) level be < 100 pg/mL, then the daily gonadotropin dosage was enhanced to 225 IU of rFSH for younger participants. If a low E<sub>2</sub> level on menstrual day 8 (< 50 pg/mL) and ill follicle growth were observed during controlled ovarian hyper-stimulation, cancellation procedures were applied. Gonadotropin and cetorelix (Cetrotide- Merck-Serono) application pursued till two or more follicles were assessed to be >17 mm, then 250 mg of recombinant human chorionic gonadotropin (hCG, Ovitrelle®) was applied. Oocytes were withdrawn trans-vaginally after 36 h. Oocyte culture, ET, and cryopreservation were carried out in normal conditions.

Five days later, an embryo was transferred into every patient. The luteal stage was assisted with hCG 0.5 h before and after embryo transfer, and 400 mg of progesterone was used from 1st day after ET. Clinical pregnancy was identified when an elevated serum β-hCG was observed 12 days after ET and a gestational sac was seen through ultrasound.

**Outcome Measures**

The outcome measures were clinical pregnancies, spontaneous abortions, ectopic pregnancies, gestational age, singleton, twin and triplet pregnancy, live birth after 24 weeks' gestation. Biochemical pregnancy was defined as a positive serum β-HCG but failed to develop to the clinically identifiable stage on ultrasound evaluation. Spontaneous abortion is described to be the natural loss of a pregnancy with an ultrasound-confirmed gestational sac before 20 gestational weeks.

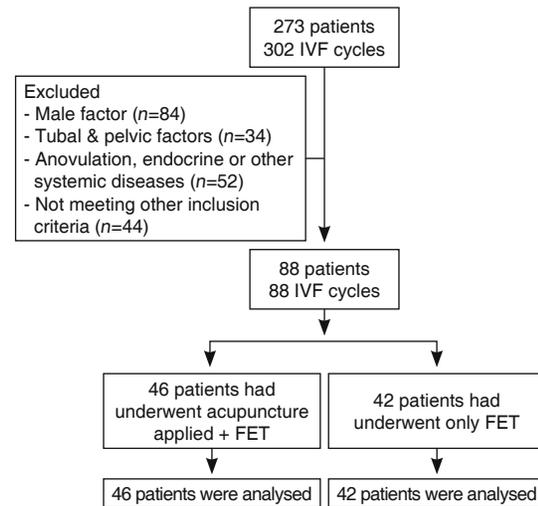
**Statistical Analysis**

All statistical analyses were performed by SPSS 20.0s (ORs SPSS Inc., Chicago, IL, USA) and the 95% confidence intervals (CIs). *P*<0.05 was thought to be statistically important. Mean ± standard deviation ( $\bar{x} \pm s$ ) was used for normally distributed measurement data. Student's *t*-test and Mann-Whitney U test were used for statistical analysis.

**RESULTS**

**Comparison of Baseline between Two Groups**

A flow chart is shown in Figure 1. The demographic and baseline characteristics of the patients were shown in Table 1, and no statistical difference was observed between the two groups in age, BMI and infertility time (*P*>0.05).



**Figure 1. Flow Chart for Infertile Patients Who Undergo A Blastocyst Transfer**

**Comparison of Outcomes between Two Groups**

No side effects and complications during treatment. The clinical pregnancy rate in the acupuncture group was higher than that in the control group [60.9% (28/46) vs. 33.3% (14/42), respectively, *P*<0.05]. Likewise, the live birth rate in the acupuncture group was also higher than that in the control group [71.7% (33/46) vs. 31.0% (12/42), *P*<0.01, Table 2). No side effects and complications were found during the treatment.

**DISCUSSION**

Stress and anxiety are quite prevalent in the

**Table 1. Baseline Characteristics of Two Groups ( $\bar{x} \pm s$ )**

Group	Case	No. of oocyte retrieved per patient ( $\bar{x} \pm s$ )	Age (Year)	BMI (kg/m <sup>2</sup> )	Infertility time (Year)
Acupuncture	46	11.26 ± 4.18	28.24 ± 3.81	26.02 ± 4.07	8.13 ± 3.01
Control	42	10.40 ± 2.58	29.07 ± 3.76	26.29 ± 3.68	8.17 ± 2.56

**Table 2. Comparison of Outcomes between Two Groups [Case (%)]**

Group	Case	Ectopic pregnancy rate	Clinical pregnancy	Abortion rate	Live birth rate
Acupuncture	46	1 (2.2)	28 (60.9)*	5 (10.9)	33 (71.7%)**
Control	42	1 (2.4)	14 (33.3)	8 (19.0)	13 (31.0%)

Notes: \* $P < 0.05$ , \*\* $P < 0.01$  vs. control group

patients that have infertile problems. Particularly those undergoing IVF have stress-related infertile problems.<sup>(9)</sup> Anxiety and depression also lead to early drop-out following the primary IVF cycle and are associated with low pregnancy ratios.<sup>(10,11)</sup> Stress impairs pregnancy, live birth delivery, birth weight and multiple gestations as well.<sup>(12)</sup> A good psychology could also influence the implantation ratio. So, IVF patients commonly seek for supplementary and alternative treatments in order to eliminate anxiety.<sup>(13)</sup> A common action of acupuncture is reported to be decreasing stress. It was suggested that acupuncture has a big potency to be influential in patients have good quality embryos.<sup>(14)</sup> Acupuncture on or around day of embryo transfer does significantly reduce stress in IVF patients as shown in a randomized controlled trial (RCTs).<sup>(15)</sup> There is a broad literature about acupuncture's affirmative effects on pregnancy success. However, studies about the stress impacts on IVF success ratios have incoherent results, and the effect of psychological stress on IVF success seems restricted.<sup>(16)</sup>

On the other hand, acupuncture on or around day of embryo transfer does significantly increase in serum cortisol and prolactin and improved IVF outcomes in a prospective clinical trial.<sup>(17)</sup> In a randomized control study, Westergaard, et al<sup>(18)</sup> found that acupuncture improved IVF pregnancy rates, a dramatically higher clinical and ongoing pregnancy ratio were observed in the acupuncture group compared to the control group. Another study by Raymond, et al<sup>(19)</sup> established the underlying physiologic systems of acupuncture, such as the release of opioids and other peptides in the central and peripheral nervous system, and its inhibition of the sympathetic nervous system.

Similarly, a pilot study carried out by Judith, et al<sup>(20)</sup> showed that women who had acupuncture treatment achieved a 64.7% pregnancy ratio, while those receiving no acupuncture acquired a 42.5% pregnancy ratio. Moreover, in a prospective, randomised and controlled clinical trial by Daniela, et al<sup>(21)</sup> it is claimed

that acupuncture had an obvious effect on the outcomes of *in vitro* fertilisation. Another systematic review and meta-analysis also studied the efficacy of acupuncture in women having *in vitro* fertilisation or intracytoplasmic sperm injection.<sup>(22)</sup> It was shown that acupuncture may increase the clinical pregnancy rate and ongoing pregnancy rate and decrease the risk of ovarian hyper stimulation syndrome in women having IVF or ICSI. Qian, et al<sup>(23)</sup> found that acupuncture improved the clinical pregnancy rate among women having IVF.

In the present study, similar results to those revealed in the afore-mentioned studies were obtained. The study results shows that the selected acupuncture treatment increases the pregnancy rate in IVF receivers.

However, this study has some restrictions. First, the number of patients in the present research is small. Second, this study is based on a single-centre. Therefore, multi-centred studies with a large size of subjects can be more beneficial to elucidate this research area.

In conclusion, it is demonstrated that acupuncture supply on the day of embryo transfer significantly improves the fertility outcomes in women with *in vitro* fertilization.

### Conflict of Interest

All the authors declare that there is no conflict of interests regarding the publication of this paper.

### Author Contributions

Coksuer H. designed the project, performed the acupuncture application, and collected the data. Barut MU and Bozkurt M analyzed the data, wrote and revised the manuscript. Agacayak E, Sak S, Demir M. and Caliskan E helped write and revise the manuscript, as well. All authors took part in the final review of the manuscript.

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