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Influence of acupuncture on the pregnancy rate in patients who undergo assisted reproduction therapy

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Objective: To evaluate the effect of acupuncture on the pregnancy rate in assisted reproduction therapy (ART) by comparing a group of patients receiving acupuncture treatment shortly before and after embryo transfer with a control group receiving no acupuncture.

Design: Prospective randomized study.

Setting: Fertility center.

Patient(s): After giving informed consent, 160 patients who were undergoing ART and who had good quality embryos were divided into the following two groups through random selection: embryo transfer with acupuncture (n = 80) and embryo transfer without acupuncture (n = 80).

Intervention(s): Acupuncture was performed in 80 patients 25 minutes before and after embryo transfer. In the control group, embryos were transferred without any supportive therapy.

Main Outcome Measure(s): Clinical pregnancy was defined as the presence of a fetal sac during an ultrasound examination 6 weeks after embryo transfer.

Result(s): Clinical pregnancies were documented in 34 of 80 patients (42.5%) in the acupuncture group, whereas pregnancy rate was only 26.3% (21 out of 80 patients) in the control group.

Conclusion(s): Acupuncture seems to be a useful tool for improving pregnancy rate after ART. (Fertil Steril®2002;77:721- 4. ©2002 by American Society for Reproductive Medicine.)

Key Words: Acupuncture, assisted reproduction, embryo transfer, pregnancy rate

Acupuncture is an important element of traditional Chinese medicine (TCM), which can be traced back for at least 4,000 years. Acupuncture has been shown to alleviate nausea and vomiting, dental pain, addiction, headache, menstrual cramps, tennis elbow, fibromyalgia, myofascial pain,

osteoarthritis, carpal tunnel syndrome, and asthma. Both physiologic and psychological benefits of acupuncture have been scientifically demonstrated in recent years.

However, so far there have been only a few serious trials concerning the use of acupuncture in reproductive medicine. Publications focus primarily on acupuncture therapy for male infertility (1, 2). Electroacupuncture may reduce blood flow impedance in the uterine arteries of infertile women (3). A positive impact of electroacupuncture on endocrinologic parameters and ovulation in women with polycystic ovary syndrome has been demonstrated (4). In addition, auricular acupuncture was successfully used in the treatment of female infertility (5). In the present study, we chose acupuncture points that relax the uterus according to the principles of TCM. Because acupuncture influences the autonomic nervous system, such treatment should optimize endometrial receptivity (6). Our main objective was to evaluate whether acupuncture accompanying embryo transfer increases clinical pregnancy rate.

Materials and Methods

This study was a prospective randomized trial at the Christian-Lauritzen-Institut in Ulm, Germany. It was approved by the ethics committee of the University of Ulm. A total of 160 healthy women undergoing treatment with in vitro fertilization (IVF; n = 101) or intracytoplasmic sperm injection (ICSI; n = 59) were recruited into the study. The age of the patients ranged from 21 to 43 (mean age: 32.5 = 4.0 years). The cause of infertility was the same for both groups (Table 1). Only patients with good embryo quality were included in the study. Using a computerized randomization method, patients were assigned into either the acupuncture group or the control group.

Table 1
Descriptive data on acupuncture and control group (mean ± SD or total number).

	Control group (n = 80)	Acupuncture group (n = 80)	Statistics Statistics
Age of patients (years)	32.1 ± 3.9	32.8 ± 4.1	NS
No. of previous cycles	2.0 ± 2.0	2.1 ± 2.1	NS
No. of transferred embryos	2.1 ± 0.5	2.2 ± 0.5	NS
IVF (n)	54	47	NS
ICSI (n)	26	33	NS
No. of cycles with male factor infertility	46	47	NS
No. of cycles with tubal disease	21	22	NS
No. of cycles with polycystic ovaries	2	2	NS
No. of cycles with unknown cause of infertility	11	9	NS
Endometrial thickness (mm)	9.9 ± 2.7	9.1 ± 2.4	NS
Plasma estradiol on day of embryo transfer (pg/mL)	1001 -± 635	971 ± 832	NS
Pulsatility index of uterine arteries (PI) before embryo transfer	2.00 ± 0.56	2.02 ± 0,45	NS
Pulsatility index of uterine arteries (PI) after embryo transfer	2.19 ± 0.52	2.22 ± 0,44	NS
Pregnant	21/80 (26.3%)	34/80 (42.5%)	*P*=.03

NS = not significant (P>.05).
Paulus. Acupuncture in ART. Fertil Steril 2002.

Ovarian stimulation, oocyte retrieval, and in vitro culture were performed as previously described (7). Transvaginal ultrasound-guided needle aspiration of follicular fluid was performed 36 to 38 hours after hCG administration. Immediately after follicle puncture, the oocytes were retrieved, assessed, and fertilized in vitro. Sperm preparation and culture conditions did not differ for either group.

In cases of severe male subfertility, ICSI was preferred, as described in the literature (8). Forty-eight hours after the IVF or ICSI procedure, embryos were evaluated according to their appearance as type 1 or 2 (good), type 3 or 4 (poor), as described in literature (9).

Just before and after embryo transfer, all patients underwent ultrasound scans of the uterus using a 7-MHz transvaginal probe (LOGIQ 400 Pro, GE Medical Systems Ultra-sound Europe, Solingen, Germany). Pulsed Doppler curves of both uterine arteries were measured by one observer. The pulsatility index (PI) for each artery was calculated electronically from a smooth curve fitted to the average waveform over three cardiac cycles.

A maximum of three embryos, in accordance with German law, were transferred into the uterine cavity on day 2 or 3 after oocyte retrieval. For embryo replacement, the patient was placed in a dorsal lithotomy position, with an empty bladder. The cervix was exposed with a bivalved speculum, then washed with culture media prior to embryo transfer. Labotect Embryo Transfer Catheter Set (Labotect GmbH, Go¨ ttingen, Germany) was used for atraumatic replacement owing to the curved guiding cannula with a ball end, allowing the set to be used reliably even with difficult anatomic conditions. The metallic reinforced inner catheter shaft al lowed safe passage through the cervical canal. When the catheter tip lay close to the fundus, the medium containing the embryos was expelled and the catheter withdrawn gently. After this procedure, the patient was placed at bed rest for 25 minutes. All oocyte retrievals and embryo transfers were performed by one examiner using the same method. The examiner was not aware of the patient's treatment group (control or acupuncture).

At the time of the embryo transfer, blood samples (10 mL) were obtained from the cubital vein. Plasma estrogen was determined by an immunometric method using the IMMULITE 2000 Immunoassay System (DPC Diagnostic Product Corporation, Los Angeles, CA).

Luteal phase support was given by transvaginal progesterone administration (Utrogest®, 200 mg, three times per day; Kade, Berlin, Germany). Progesterone administration was initiated on the day after oocyte retrieval and was continued until the serum ß-hCG measurement 14 to 16 days after transfer and, in cases of pregnancy, until gestation week 8.

Each patient in the experimental group received an acupuncture treatment 25 minutes before and after embryo transfer. Sterile disposable stainless steel needles (0.25 X 25 mm) were inserted in acupuncture point locations. Needle reaction (soreness, numbness, or distention around the point = Deqi sensation) occurred during the initial insertion. After 10 minutes, the needles were rotated in order to maintain Deqi sensation. The needles were left in position for 25 minutes and then removed. The depth of needle insertion was about 10 to 20 mm, depending on the region of the body undergoing treatment. Before embryo transfer, we used the following locations: Cx6 *(Neiguan)*, Sp8 *(Diji)*, Liv3 *(Taichong)*, Gv20 *(Baihui)*, and S29 *(Guilai)*.

After embryo transfer, the needles were inserted at the following points: S36 *(Zusanli)*, Sp6 *(Sanyinjiao)*, Sp10 *(Xuehai)*, and Li4 *(Hegu)*.

In addition, we used small stainless needles (0.2 X 13 mm) for auricular acupuncture at the following points, without rotation: ear point 55 *(Shenmen)*, ear point 58 *(Zhigong)*, ear point 22

(Neifenmi), and ear point 34 *(Naodian)*. Two needles were inserted in the right ear, the other two needles in the left ear. The four needles remained in the ears for 25 minutes. The side of the auricular acupuncture was changed after embryo transfer. The patients in the control group also remained lying still for 25 minutes after embryo transfer. All treatments were performed by the same well-trained examiner, in the same way.

The primary point of the study was to determine whether acupuncture improves the clinical pregnancy rate after IVF or ICSI treatment. Student's t-test was used as a corrective against any possible imbalance between the two groups regarding the following variables: age of patient, number of previous cycles, number of transferred embryos, endometrial thickness, plasma estradiol on day of transfer, method of treatment (IVF or ICSI), and blood flow impedance in the uterine arteries (pulsatility index). Chi-square test was used to compare the two groups. All statistical analyses were carried out using the software package Statgraphics (Manugistics, Inc., Rockville, MD).

Results

A total of 160 patients was recruited for the study. Patients who failed to conceive during the first treatment cycle were not reentered into the study. According to the randomization, 80 patients were treated with acupuncture, and 80 patients underwent the usual therapy without acupuncture.

As Table 1 shows, there were no statistically significant differences between the two groups with respect to the following covariants: age of patient, number of previous cycles, number of transferred embryos, endometrial thickness, plasma estradiol on day of transfer, or method of treatment (IVF or ICSI). Clinical indications for ART were the same for patients of both groups. The blood flow impedance in the uterine arteries (pulsatility index) did not differ between the groups before and after embryo transfer.

The analysis shows that the pregnancy rate for the acupuncture group is considerably higher than for the control group (42.5% vs 26.3%; *P*=.03).

Discussion

The acupuncture points used in this study were chosen according to the principles of TCM (10): Stimulation of *Taiying* meridians (spleen) and *Yangming* meridians (stomach, colon) would result in better blood perfusion and more energy in the uterus. Stimulation of the body points Cx6, Liv3, and Gv20, as well as stimulation of the ear points 34 and 55, would sedate the patient. Ear point 58 would influence the uterus, whereas ear point 22 would stabilize the endocrine system.

The anesthesia-like effects of acupuncture have been studied extensively. Acupuncture needles stimulate muscle afferents innervating ergoreceptors, which leads to increased ß-endorphin concentration in the cerebrospinal fluid (11). The hypothalamic ß-endorphinergic system has inhibitory effects on the vasomotor center, thereby reducing sympathetic activity. This central mechanism, which involves the hypothalamic and brainstem systems, controls many major organ systems in the body (12). In addition to central sympathetic inhibition by the endorphin system, acupuncture stimulation of the sensory nerve fibers may inhibit the sympathetic outflow at the spinal level. By changing the concentration of central opioids, acupuncture may also regulate the function of the hypothalamic-pituitary-ovarian axis via the central sympathetic system (13).

Kim et al. (14) suggested that Li4 acupuncture treatment could be useful in inhibiting the uterus motility. In their rat experiments, treatment on the Li4 acupoint suppressed the expression of COX-2 enzyme in the endometrium and myometrium of pregnant and nonpregnant uteri.

Stener-Victorin et al. (3) reduced high uterine artery blood flow impedance by a series of eight electroacupuncture treatments, twice a week for 4 weeks. They suggest that a decreased tonic activity in the sympathetic vasoconstrictor fibers to the uterus and an involvement of central mechanisms with general inhibition of the sympathetic outflow may be responsible for this effect. In our study, we could not see any differences in the pulsatility index between the acupuncture and control group before or after embryo transfer. This may be due to a different acupuncture protocol and the selected sample of patients with high blood flow impedance of the uterine arteries (PI ≥ 3.0) in the Stener-Victorin et al. study.

As we could not observe any significant differences in covariants between the acupuncture and control groups, the results demonstrate that acupuncture therapy improves pregnancy rate.

Further research is needed to demonstrate precisely how acupuncture causes physiologic changes in the uterus and the reproductive system. To rule out the possibility that acupuncture produces only psychological or psychosomatic effects, we plan to use a placebo needle set as a control in a future study.

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