

# Effect of acupuncture on the outcome of in vitro fertilization and intracytoplasmic sperm injection: a randomized, prospective, controlled clinical study

Stefan Dieterle, M.D.,<sup>a</sup> Gao Ying, M.D.,<sup>a,b</sup> Wolfgang Hatzmann, M.D.,<sup>a</sup> and Andreas Neuer, M.D.<sup>a</sup>

<sup>a</sup>Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Witten/Herdecke, Dortmund, Germany; and <sup>b</sup>Department of Obstetrics and Gynecology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

**Objective:** To determine the effect of luteal-phase acupuncture on the outcome of IVF/intracytoplasmic sperm injection (ICSI).

**Design:** Randomized, prospective, controlled clinical study.

**Setting:** University IVF center.

**Patient(s):** Two hundred twenty-five infertile patients undergoing IVF/ICSI.

**Intervention(s):** In group I, 116 patients received luteal-phase acupuncture according to the principles of traditional Chinese medicine. In group II, 109 patients received placebo acupuncture.

**Main Outcome Measure(s):** Clinical and ongoing pregnancy rates.

**Result(s):** In group I, the clinical pregnancy rate and ongoing pregnancy rate (33.6% and 28.4%, respectively) were significantly higher than in group II (15.6% and 13.8%).

**Conclusion(s):** Luteal-phase acupuncture has a positive effect on the outcome of IVF/ICSI. (Fertil Steril® 2006; xx:xxx. ©2006 by American Society for Reproductive Medicine.)

**Key Words:** Acupuncture, assisted reproduction, pregnancy rate, IVF, ICSI

The scientific clinical significance of acupuncture is the subject of controversy. Acupuncture is an ancient traditional Chinese treatment technique with an empirical basis. Its theory is based on the energy flow of *Qi*. Imbalances are believed to cause diseases, which can be treated by stimulating specific points on the body surface. However, the scientific rationale has yet to be established. Studies have suggested that the effects of acupuncture might be mediated through neuropeptides in the central nervous system (1, 2).

A National Institutes of Health Consensus Development Panel (3) found effects of acupuncture on nausea, vomiting, and pain. A randomized, placebo-controlled patient and observer blind trial demonstrated the effectiveness of acupuncture on nausea and vomiting (4).

The role of acupuncture in the treatment of female infertility is unclear (5). Options for patients who undergo several IVF/intracytoplasmic sperm injection (ICSI) cycles without success remain unsatisfactory. Various approaches have been suggested to increase the pregnancy rate. It has been

shown that the receptivity of the endometrium (6) and the uterine contraction frequency at the time of ET (7) are critical for embryo implantation. In a previous randomized, prospective, controlled study, it was demonstrated that acupuncture before and after ET resulted in a higher pregnancy rate compared with a group without acupuncture (8). Further studies were suggested with a placebo control group (9).

The aim of this study was to investigate the effect of luteal-phase acupuncture on IVF/ICSI outcome. To minimize psychological effects, a group of patients with acupuncture according to the principles of traditional Chinese medicine was compared with a group of patients receiving placebo acupuncture.

## MATERIALS AND METHODS

### Patients

The present investigation was designed as a randomized, prospective, controlled trial. The study was approved by the institutional review board. Written, informed consent was obtained from each participant. All patients underwent IVF or ICSI and participated only once.

Patients were randomized with sealed randomization envelopes. A total of 225 infertile patients were included: 116 women were randomized into group I (study group), and 109

Received May 8, 2005; revised and accepted September 13, 2005.

Reprint requests: Stefan Dieterle, M.D., University of Witten/Herdecke, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Olpe 19, Dortmund D-44135, Germany (FAX: 49-231-55754598; E-mail: Dieterle@IVF-Dortmund.de).

women were randomized into group II (control group). The random allocation was concealed from the physician performing the ET. All patients received acupuncture by the same physician.

### IVF Protocol

All patients were down-regulated according to the long protocol, with a GnRH agonist (nafarelin 0.4 mg daily), beginning on day 21 of the previous cycle until the day of hCG injection. Ovarian stimulation was performed with recombinant FSH or hMG. Ovulation was triggered with hCG (10,000 IU) when at least three follicles had a diameter of  $\geq 18$  mm with an adequate serum  $E_2$  concentration. Transvaginal oocyte retrieval was performed under ultrasound guidance 35 hours after hCG administration.

According to the German Embryo Protection Law, a maximum number of three embryos was transferred into the uterus 2 to 3 days after oocyte retrieval. Embryo selection is not allowed in Germany. In addition, the German Board of Physicians recommends a transfer of two embryos for women aged  $<35$  years. Patients in both groups were supplemented with P (200 mg three times daily) starting the day after oocyte retrieval. Biochemical pregnancies were diagnosed by serum hCG measurement 2 weeks after ET. Clinical pregnancies were confirmed by transvaginal ultrasound 4–6 weeks after ET demonstrating at least one gestational sac.

### Acupuncture Treatment

For acupuncture, 4-cm-long disposable stainless steel needles (Suzhou Acupuncture and Medical Instruments Co. Ltd., Suzhou, Jiangsu, P. R. China) were used. In both groups, acupuncture was applied for 30 minutes immediately after ET and again 3 days later. The needles were inserted to a depth of 15–30 mm, depending on the region of the body. They were rotated to evoke the needle reaction of *Deqi* sensation (numbness, soreness, and distention around the acupoint). Fifteen minutes later, the needles were rotated again to maintain *Deqi* sensation. After ET, the following acupoints were used in group I: *Guanyuan* (ren [RN]4), *Qihai* (RN6), *Guilai* (stomach [ST]29), *Neiguan* (pericardium [PC]6), *Xuehai* (spleen [SP]10), and *Diji* (SP8).

At the same time, a special Chinese medical drug (the seed of Caryophyllaceae) was placed on the patient's ear. The following points were used: ear point 55 (*Shenmen*), ear point 58 (*Zigong*), ear point 22 (*Neifenmi*), and ear point 33 (*Pizhixia*). The seeds remained in place for 2 days and were pressed twice daily for 10 minutes. Three days after ET, all patients received a second acupuncture treatment. The following locations were used: *Hegu* (large intestine [LI]4), *Sanyinjiao* (SP6), *Zusanli* (ST36), *Taixi* (kidney [KI]3), *Taichong* (liver [LR]3). In addition, the same ear points were pressed at the opposite ear twice daily. The seeds were removed after 2 days.

In group II, the following acupuncture points were used after ET and again 3 days later: San Jiao [SJ]9 (*Sidu*), SJ12 (*Xiaoluo*), gallbladder (GB)31 (*Fengshi*), GB32 (*Zhongdu*), and GB34 (*Yang ling qua*). As in group I, patients received acupuncture treatment for 30 minutes. At the same time, the following ear points were used: ear point 17 (*Shangzhi*), ear point 14 (*Feng si*), ear point 8 (*Sisheng*), and ear point 53 (*Jian*). Equal numbers of needles were applied to the study and control groups. The placebo acupuncture treatment was designed not to influence fertility.

### Statistical Analysis

The primary outcome measure was the clinical pregnancy rate, which was used for sample size calculation. We estimated a required sample size of 110 patients in both groups. This was based on the assumption of a clinical pregnancy rate of 20% in the control group, a minimal detectable difference of clinical pregnancies between study group and control group of 15% at a power of 80% (according to a  $\beta$  of 20%), and a type I error ( $\alpha$ ) of 5%. The sample size calculation assumed a one-sided test situation and was performed with an unconditional exact test (StatXact Version 6; CYTEL Software, Cambridge, MA). Secondary outcome measures were the biochemical and the ongoing pregnancy rates. Student's *t*-test was performed for comparison of continuous

**TABLE 1**

#### Patient characteristics.

Characteristic	Group I (n = 116)	Group II (n = 109)	P
Age (y)	35.1 $\pm$ 3.8	34.7 $\pm$ 4.0	NS
BMI (kg/m <sup>2</sup> )	24.5 $\pm$ 5.1	24.1 $\pm$ 4.7	NS
Duration of infertility (ys)	5.4 $\pm$ 3.4	5.3 $\pm$ 3.1	NS
Primary infertility	93	86	NS
Secondary infertility	23	23	NS
Tubal infertility	38	35	NS
Endometriosis	18	11	NS
Male infertility	58	60	NS
Other causes	13	8	NS
Previous IVF/ICSI cycles			
0 cycles	19	18	NS
1 cycle	29	30	NS
2 cycles	35	35	NS
3 cycles	22	17	NS
4 cycles	8	4	NS
5 cycles	2	4	NS
6 cycles	1	1	NS

Note: Data are presented as mean  $\pm$  SD or n. NS = nonsignificant; BMI = body mass index.

Dieterle. Acupuncture in IVF/ICSI. Fertil Steril 2006.

parameters between the study and control groups. Comparison of discrete parameters was made by  $\chi^2$  analysis. A level of significance of 5% was chosen for both tests.

## RESULTS

A total of 225 patients with a transfer of at least one embryo was included in the study. All patients were randomized: 116 patients received acupuncture according to the principle of traditional Chinese medicine (group I), and 109 patients received placebo acupuncture (group II). All 225 patients completed the study. No patient was lost to follow-up.

Fifty-six clinical pregnancies were confirmed by ultrasound. The clinical characteristics of the patients in both groups are presented in Table 1. There were no significant differences in terms of age, body mass index, duration of infertility, cause of infertility, and number of previous IVF/ICSI cycles between groups I and II.

Table 2 shows the outcome of IVF/ICSI in both groups. No differences regarding the days of stimulation, the number

of FSH units required, and serum E<sub>2</sub> concentrations on the day of hCG injection were observed. The number of oocytes, the fertilization rate, and the number of embryos transferred were similar in both groups. The data demonstrate that the implantation rate was significantly higher in group I than in group II (14.2% vs. 5.9%,  $P < .01$ ). Clinical pregnancy and ongoing pregnancy rates per transfer were significantly higher in group I (33.6% and 28.4%, respectively) than in group II (15.6% and 13.8%,  $P < .01$ ).

The experimental event rates and the control event rates, including 90% confidence intervals, are listed in Table 3. The numbers needed to treat are 5.5 for the clinical and 6.8 for the ongoing pregnancy rate.

Thirty-seven patients (group I = 19, group II = 18) underwent their first IVF/ICSI cycle, 59 patients (group I = 29, group II = 30) had their second cycle after failing to achieve a pregnancy in their first attempt, and 129 women (group I = 68, group II = 61) received more than two previous IVF/ICSI cycles (Table 4).

**TABLE 2**

**IVF/ICSI data.**

Variable	Group I (n = 116)	Group II (n = 109)	P
IVF cycles	34	36	NS
ICSI cycles	67	59	NS
ET after cryopreservation	15	14	NS
Previous IVF/ICSI cycles	1.8 ± 1.3	1.8 ± 1.3	NS
No. of ampoules	42.2 ± 23.5	42.7 ± 23.7	NS
Days of stimulation	10.2 ± 1.9	9.9 ± 1.7	NS
E <sub>2</sub> at ovulation induction (pg/mL)	1,818 ± 1,317	1,887 ± 1,299	NS
Endometrial thickness (mm)	10.5 ± 1.8	10.2 ± 1.7	NS
No. of oocytes retrieved	11.2 ± 7.2	12.7 ± 9.4	NS
Fertilization rate (%)	50.2 ± 22.3	50.6 ± 21.6	NS
IVF (%)	46.7 ± 21.3	52.8 ± 15.5	NS
ICSI (%)	50.9 ± 24.4	46.3 ± 27.8	NS
ET (n)	116	109	NS
No. of embryos transferred	2.6 ± 0.7	2.6 ± 0.7	NS
3 embryos transferred	83	79	NS
2 embryos transferred	22	20	NS
1 embryo transferred	11	10	NS
Implantation rate (%)	14.2	5.9	<.01
No. of biochemical pregnancies	41	18	<.01
Biochemical pregnancy rate (%)	35.3	16.5	<.01
No. of clinical pregnancies	39	17	<.01
Clinical pregnancy rate (%)	33.6	15.6	<.01
No. of ongoing pregnancies	33	15	<.01
Ongoing pregnancy rate (%)	28.4	13.8	<.01
Miscarriages (%)	15.4	11.8	NS

Note: Data are presented as mean ± SD or n. NS = nonsignificant.

Dieterle. Acupuncture in IVF/ICSI. Fertil Steril 2006.

TABLE 3

Pregnancy rates.			
Parameter	Group I (n = 116)	Group II (n = 109)	P
Biochemical pregnancy rate (%)	35.3 (28.0–43.3)	16.5 (11.0–23.5)	<.01
Clinical pregnancy rate (%)	33.6 (26.4–41.5)	15.6 (10.2–22.5)	<.01
Ongoing pregnancy rate (%)	28.4 (21.6–36.1)	13.8 (8.7–20.4)	<.01

Data are presented as experimental event rate (group I) or control event rate (group II), with 95% confidence interval in parentheses.

Dieterle. *Acupuncture in IVF/ICSI. Fertil Steril* 2006.

Clinical pregnancy rates and implantation rates declined with an increasing number of treatment cycles. After the first cycle, the clinical pregnancy and implantation rates were 47.4% and 28.9%, respectively, in group I, and 33.3% and 11.1% in group II; after the second cycle, 34.5% and 15.2% in group I and 23.3% and 8.6% in group II. After three or more cycles, the clinical pregnancy rate was 29.4% in group I and 8.2% in group II ( $P<.01$ ), and the implantation rate was 12.6% in group I and 3.2% in group II ( $P<.01$ ).

## DISCUSSION

The physiologic mechanisms and clinical significance of acupuncture have not been completely revealed and have been the subject of controversy (10). Recent studies support the concept that acupuncture activates endogenous opioids in the central nervous system, which inhibit central sympathetic neural outflow (11). Functional magnetic resonance imaging, a technique sensitive to changes in regional blood oxygenation as an index of neuronal activity to map human brain functions, has been used for quantitative studies of the correlation between various acupoints and specific functional areas of the brain (12). Wu et al. (13) characterized a pathway in the hypothalamus and limbic system that might mediate acupuncture. Cho et al. (11) demonstrated a correlation between brain activation and corresponding acupoint stimulation. Acupuncture might change the charge and po-

tential of neurons and the concentrations of electrolytes and neuropeptides, such as  $\beta$ -endorphin (1, 2, 14). In addition, psychological effects of acupuncture have been demonstrated (15). Acupuncture can activate inhibitory systems in the spinal cord, which results in segmental inhibition of sympathetic outflow (16).

Acupuncture has been used in the treatment of female infertility. Although the mechanism of acupuncture in the treatment of female infertility is unknown, studies have demonstrated its potential impact on the hypothalamic–pituitary–ovarian axis and on the uterus (17, 18).

Successful IVF/ICSI demands optimal endometrial receptivity at the time of embryo implantation. Uterine receptivity is regulated by a number of factors, including uterine perfusion (19). Stener-Victorin et al. (20) demonstrated that acupuncture can reduce the uterine artery blood flow impedance. Ayoubi et al. (7) found that a high uterine contraction frequency in IVF at the time of ET comes from a delayed establishment of uteroquiescence after ovulation in IVF in contrast to the menstrual cycle. Fanchin et al. (21) showed that pregnancy rates are affected by uterine contractions at the time of ET. Kim et al. (18) demonstrated that acupuncture of acupoint LI14 can inhibit uterus motility.

Stener-Victorin et al. (22) compared electro-acupuncture analgesia with standard analgesia during oocyte aspiration.

TABLE 4

Number of IVF/ICSI cycles and IVF/ICSI outcome.							
No. of ART cycles	Group I (n = 116)			Group II (n = 109)			P
	No. of patients	Pregnancy rate (%)	Implantation rate (%)	No. of patients	Pregnancy rate (%)	Implantation rate (%)	
1	19	47.4	22.4	18	33.3	11.3	NS
2	29	34.5	15.2	30	23.3	8.6	NS
≥3	68	29.4	12.6	61	8.2	3.2	<.01

Dieterle. *Acupuncture in IVF/ICSI. Fertil Steril* 2006.

Implantation and “take-home baby” rates were significantly higher with electro-acupuncture than without. Paulus et al. (8) compared a group of 80 patients with acupuncture before and after ET with a control group of 80 patients without acupuncture. They found a significantly higher pregnancy rate in the acupuncture group than in the control group.

Infertility can cause stress, leading to a release of stress hormones. It has been suggested that stress reduction might improve fertility (23). Verhaak et al. (24) reported that differences in the emotional status between pregnant and nonpregnant women were present before treatment and became more apparent after the first IVF and ICSI cycle. Women who became pregnant showed lower levels of depression than those who did not. The use of acupuncture to reduce anxiety and stress, possibly through its sympathoinhibitory property and impact on  $\beta$ -endorphin levels, has been reviewed (25). Middlekauff (26) found that sympathetic activation during acute mental stress was eliminated after acupuncture.

When evaluating this study, it has to be considered that the pregnancy rates are affected by the German Embryo Protection Law. This law prohibits embryo selection. A maximum number of three oocytes in the pronuclear stage is allowed to develop and to be transferred. In addition, the mean age of 35.1 years in group I and 34.7 years in group II had an influence on the pregnancy rates. According to the German IVF/ICSI register (2003), the average clinical pregnancy rates for this age are 24.6% for IVF and 22.6% for ICSI. To minimize psychological effects, placebo acupuncture was used in the control group, which was designed not to influence fertility. However, it cannot be completely excluded that placebo acupuncture had an adverse effect on the pregnancy rate.

The results of this study support the significance of acupuncture for the outcome of IVF/ICSI. Even if further evidence has to be accumulated, acupuncture might be a complementary option for patients undergoing IVF/ICSI.

## REFERENCES

- Petti F, Bangrazi A, Liguori A, Reale G, Ippoliti F. Effects of acupuncture on immune response related to opioid-like peptides. *J Tradit Chin Med* 1998;18:55–63.
- Ku Y, Chang Y. Beta-endorphin- and GABA-mediated depressor effect of specific electroacupuncture surpasses pressor response of emotional circuit. *Peptides* 2001;22:1465–70.
- NIH Consensus Development Panel of Acupuncture. Acupuncture. *JAMA* 1998;280:1518–24.
- Streitberger K, Diefenbacher M, Bauer A, Conradi R, Bardenheuer H, Martin E, et al. Acupuncture compared to placebo-acupuncture for postoperative nausea and vomiting prophylaxis: a randomized placebo-controlled patient and observer blind trial. *Anaesthesia* 2004;59:142–9.
- Chang R, Chung PH, Rosenwaks Z. Role of acupuncture in the treatment of female infertility. *Fertil Steril* 2002;78:1149–53.
- Chien LW, Au HK, Chen PL, Xiao J, Tzen CR. Assessment of uterine receptivity by the endometrial-subendometrial blood flow distribution pattern in women undergoing in vitro fertilization-embryo transfer. *Fertil Steril* 2002;78:245–51.
- Ayoubi JM, Epiney M, Brioschi PA, Fanchin R, Chardonnens D, Ziegler D. Comparison of changes in uterine contraction frequency after ovulation in the menstrual cycle and in in vitro fertilization cycles. *Fertil Steril* 2003;79:1101–5.
- Paulus WE, Zhang M, Strehler E, El-Danasouri I, Sterzik K. Influence of acupuncture on the pregnancy rate in patients who undergo assisted reproduction therapy. *Fertil Steril* 2002;77:721–4.
- White AR. A review of controlled trials of acupuncture for women's reproductive health care. *J Fam Plan Reprod Health Care* 2003;29:233–6.
- Stener-Victorin E, Wikland M, Waldenstrom U, Lundeberg T. Alternative treatments in reproductive medicine: much ado about nothing. *Hum Reprod* 2002;17:1942–6.
- Cho ZH, Chung SC, Jones JP, Park JB, Park HJ, Lee HJ, et al. New findings of the correlation between acupoints and corresponding brain cortices using functional MRI. *Proc Natl Acad Sci U S A* 1998;3:2670–3.
- Zhang WT, Jin Z, Cui GH, Zhang KL, Zhang L, Zeng YW, et al. Relations between brain network activation and analgesic effect induced by low vs. high frequency electrical acupoint stimulation in different subjects: a functional magnetic resonance imaging study. *Brain Res* 2003;29:168–78.
- Wu MT, Hsieh JC, Xiong J, Yang CF, Pan HB, Iris Chen YC, et al. Central nervous pathway for acupuncture stimulation: localization of processing with functional MR imaging of the brain—preliminary experience. *Radiology* 1999;212:133–41.
- Andersson S, Lunderberg T. Acupuncture from empiricism to science: functional background to acupuncture effects in pain and disease. *Med Hypotheses* 1995;45:271–81.
- Luo H, Meng F, Jia Y, Zhao X. Clinical research on the therapeutic effect of the electroacupuncture treatment in patients with depression. *Psychiatry Clin Neurosci* 1998;52:338–40.
- Sato A, Sato Y, Schmidt RF. The impact of somatosensory input on autonomic functions. Heidelberg: Springer-Verlag, 1997:325.
- Chen BY, Yu J. Relationship between blood radioimmunoreactive beta-endorphin and hard skin temperature during the electro-acupuncture of ovulation. *Acupunct Electrother Res* 1991;16:1–5.
- Kim J, Shin KH, Na CS. Effect of acupuncture treatment on uterine motility and cyclooxygenase-2 expression in pregnant rats. *Gynecol Obstet Invest* 2000;50:225–30.
- Jinno M, Ozaki T, Iwashita M, Nakamura Y, Kudo A, Hirano H. Measurement of endometrial tissue blood flow: a novel way to assess uterine receptivity for implantation. *Fertil Steril* 2001;76:1168–74.
- Stener-Victorin E, Waldenstrom U, Andersson SA, Wikland M. Reduction of blood flow impedance in the uterine arteries of infertile women with electro-acupuncture. *Hum Reprod* 1996;11:1314–7.
- Fanchin R, Righini C, Olivennes F, Taylor S, de Ziegler D, Frydman R. Uterine contractions at the time of embryo transfer alter pregnancy rates after in-vitro fertilization. *Hum Reprod* 1998;13:1968–74.
- Stener-Victorin E, Waldenstrom U, Nilsson L, Wikland M, Janson PO. A prospective randomized study of electro-acupuncture versus alfentanil as anaesthesia during oocyte aspiration in in-vitro fertilization. *Hum Reprod* 1999;14:2480–4.
- Domar AS, Siebel MM, Benson H. The mind/body program for infertility: a new behavioral treatment approach for women with infertility. *Fertil Steril* 1990;53:246–9.
- Verhaak AM, Smeenk MJ, Eugster A, Minnen A, Kremer JA, Kraaiaart FW. Stress and marital satisfaction among women before and after their first cycle of in vitro fertilization and intracytoplasmic sperm injection. *Fertil Steril* 2001;76:525–31.
- Dong JT. Research on the reduction of anxiety and depression with acupuncture. *Am J Acupunct* 1993;21:327–30.
- Middlekauff HR. Acupuncture in the treatment of heart failure. *Cardiol Rev* 2004;12:171–3.

**000 Effect of acupuncture on the outcome of in vitro fertilization and intracytoplasmic sperm injection: a randomized, prospective, controlled clinical study**

S. Dieterle, G. Ying, W. Hatzmann, and A. Neuer  
*Dortmund, Germany, and Wuhan, China*

In a randomized, prospective, controlled clinical study, the clinical and ongoing pregnancy rates in patients undergoing IVF and intracytoplasmic sperm injection were significantly higher with luteal-phase acupuncture than with placebo acupuncture.