Acupuncture for frozen-thawed embryo transfer cycles: a double-blind randomized controlled trial

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ABSTRACT

The role of acupuncture on the pregnancy rate has not been evaluated in frozen-thawed embryo transfer (FET) cycles. This randomized double blind study aimed to determine whether acupuncture performed on the day of FET improves clinical outcomes. On the day of FET, 226 patients were randomly allocated to either real or placebo acupuncture according to a computer-generated randomization list in sealed opaque envelopes. They received a session of real or placebo acupuncture for 25 minutes on site immediately after FET. The anxiety level and serum cortisol concentration were evaluated before and after real and placebo acupuncture. There were no significant differences in rates of overall pregnancy, clinical pregnancy, ongoing pregnancy, livebirth and implantation in the placebo acupuncture group, when compared with the real acupuncture group. The anxiety level and serum cortisol concentration were similar for both groups. Only the placebo acupuncture group had significantly higher ongoing pregnancy (P=0.022) and implantation rates (P=0.038) than those who declined to join the study and received no acupuncture. In conclusion, comparable pregnancy and live birth rates of FET treatment were found in patients who had one session of real or placebo acupuncture after FET.

Keywords: acupuncture / frozen-thawed embryo transfer / pregnancy rate

SUMMARY FOR LAY READERS

The role of acupuncture on the pregnancy rate has not been evaluated in frozen-thawed embryo transfer (FET) cycles. This randomized double blind study aimed to determine whether acupuncture performed on the day of FET improves clinical outcomes. On the day of FET, 226 patients were randomly allocated to either real or placebo acupuncture according to a computer-generated randomization list in sealed opaque envelopes. They received a session of real or placebo acupuncture for 25 minutes on site immediately after FET. The anxiety level and serum cortisol concentration were evaluated before and after real and placebo acupuncture. There were no significant differences in rates of overall pregnancy, clinical pregnancy, ongoing pregnancy, livebirth and implantation between the placebo acupuncture group and the real acupuncture group. The anxiety level and serum cortisol concentration were similar for both groups. Only the placebo acupuncture group had significantly higher ongoing pregnancy and implantation rates than those who declined to join the study and received no acupuncture. In conclusion, comparable pregnancy and live birth rates of FET treatment were found in patients who had one session of real or placebo acupuncture after FET.

INTRODUCTION

In vitro fertilization-embryo transfer (IVF-ET) is an effective treatment for various causes of subfertility. Despite improvement in ovarian stimulation regimens, culture media conditions and the technique of ET, the implantation rates of cleaving embryos have remained steady at 20-25% for a long time (European Society of Human Reproduction and Embryology [ESHRE], 2001 and 2008). Therefore, multiple embryos are usually replaced to compensate for their low implantation potential but this will be associated with a high risk of multiple pregnancies. In order to reduce the chance of multiple pregnancies, patients are usually advised to have two or three embryos replaced in the stimulated cycle while excess good quality embryos will be cryopreserved for transfer later. Pregnancy rates of frozen-thawed embryo transfer (FET) cycles are still inferior to that of IVF cycles and have remained steady at 15-20% (ESHRE, 2001 and 2008).

Acupuncture has been used on the day of ET with an aim to improve the pregnancy rate of IVF treatment (Paulus et al., 2002 and 2003; Dieterle et al., 2006; Smith et al., 2006; Westergaard et al., 2006; Craig et al., 2007; Domar et al., 2008; Fratterelli et al., 2008; Moy et al., 2008; So et al., 2009). Four meta-analyses (Cheong et al., 2008; Manheimer et al., 2008; Ng et al., 2008; El-Toukhy et al., 2008) have been published on the role of acupuncture in IVF. Three (Cheong et al., 2008; Manheimer et al., 2008; Ng et al., 2008) of these showed an improvement of pregnancy rate and live birth rate following acupuncture while El-Toukhy et al. (2008) could not find any differences in pregnancy rate and live birth rate between the acupuncture group and the control group. The positive effect of acupuncture during IVF treatment may be related to the change in uterine blood flow and uterine contractility, and relaxation of stress (Ng et al., 2008).

We have recently published a randomized double blind study comparing real and placebo acupuncture in patients undergoing IVF treatment (So et al., 2009). Our results indicated that placebo acupuncture was associated with a significantly higher overall pregnancy rate when compared with real acupuncture. There is still no study investigating the role of acupuncture on the pregnancy rate of FET treatment. The endometrial receptivity of fresh ET and FET cycles may be different as ovarian stimulation used in the great majority of IVF cycles may impair the endometrial receptivity in fresh ET. The aim of this randomized double blind study was to determine whether acupuncture performed on the day of FET improves pregnancy outcomes. The hypothesis was that real acupuncture performed on the day of FET significantly improved the pregnancy rate of FET.

MATERIALS AND METHODS

Subfertile patients undergoing FET treatment in the Centre of Assisted Reproduction and Embryology, The University of Hong Kong-Queen Mary Hospital, were recruited if they had a normal uterine cavity shown on ultrasound scanning on the day of oocyte retrieval. Exclusion criteria were: (a) frozen embryo(s) replaced in stimulated IVF cycles, (b) lysis of all frozen embryos on thawing, (c) recipients of donor oocytes and (d) those undergoing preimplantation genetic diagnosis. Every patient gave an informed written consent prior to participating in the study, which was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKClinicalTrials.com--HKCTR-686). Patients were recruited to join the study only once and did not receive any monetary compensation for participation in the study.

The details of the long protocol of ovarian stimulation regimen, gamete handling, assessment of embryo quality, ET and FET at our centre have been previously published (Ng et al., 2000).

IVF cycles

All women were pre-treated with Buserelin (Suprecur, Hoechst, Frankfurt, Germany) nasal spray 150 μg 4 times a day from the mid-luteal phase of the cycle preceding the treatment cycle. On the second day of the treatment cycle, transvaginal scanning was performed to count the number of antral follicles and blood was then taken for basal serum oestradiol (E2) concentration. Antral follicle count was the sum of antral follicles on the left and right ovaries. When the ultrasound scanning showed no ovarian cyst and serum E2 concentrations were below 200 pmol/l, human menopausal gonadotrophin (HMG, Menogon, Ferring GmbH, Kiel, Germany) was started for ovarian stimulation. Ovarian response was monitored by serial transvaginal scanning and hCG (Profasi, Serono, Geneva, Switzerland) was given intramuscularly when the leading follicle reached 18 mm in diameter and there were at least three follicles of ≥16 mm in diameter. Serum E2 concentration was measured on the day of hCG administration.

Transvaginal ultrasound-guided oocyte retrieval was scheduled 36 hours after the hCG injection. A maximum of two normally cleaved embryos were replaced into the uterine cavity 48 hours after the retrieval and excess good quality embryos were frozen. All fresh embryos were cryopreserved if patients had developed symptoms suggestive of ovarian hyperstimulation syndrome (OHSS) or serum E2 on the day of hCG injection was >20,000 pmol/L in order to reduce the risks of OHSS.

FET cycles

Patients who did not achieve a pregnancy in the stimulated IVF cycle and had frozen embryos would undergo FET at least two months after the stimulated cycle. A maximum of three frozen-thawed embryos after thawing were transferred in natural, clomiphene-induced

or hormonal replacement cycles. Those patients having regular ovulatory cycles would undergo FET in their natural cycles. Clomiphene citrate (CC, Clomid, Merrell, Staines, U.K.) 50-100 mg was given daily for five days from Days 3-7 to patients with irregular / long cycles or absence of E2 rise / LH surge in previous natural cycles. During natural or CC-induced cycles, patients were monitored daily for serum E2 and LH levels from 18 days before the expected date of next period. The transfer was performed on the third day after the LH surge and a maximum of two normally cleaving embryos were replaced. The luteal phase was supported by two doses of hCG injections as in fresh ET.

Hormonal replacement cycles were offered to those patients who showed no ovulatory responses after taking CC 150 mg daily for five days. After down-regulation by Buserelin nasal spray (150 μg four times a day), Estrofem (Novo Nordisk, U.K.) 6 mg daily were started from the third day of the next menstrual cycle onwards. Cyclogest vaginal pessaries (Cox Pharmaceuticals, Barnstaple, UK) 400 mg twice daily were given if endometrial thickness measured on day 16 of the cycle by ultrasound scanning was ≥8 mm. The transfer was carried out on the fourth day of starting progesterone.

A urine pregnancy test was performed 16 days after FET. If it was positive, ultrasound examination was performed 10-14 days later to confirm intrauterine pregnancy and to determine the number of gestational sacs present.

Serum E2 and LH concentrations were measured using commercially available kits (Access Immunoassay System, Beckman Coulter, CA, USA). The sensitivity of the E2 assay was 73 pmol/L and the intra- and inter-assay coefficients of variation were 4.4% and 7.6% respectively. The sensitivity of the LH assay was 0.2 IU/L and the intra- and inter-assay coefficients of variation were 3.8% and 6.4% respectively.

Traditional Chinese Medicine (TCM) diagnosis

Eligible patients were informed of the study on the commencement of FET cycle and those who agreed to join the study were further counselled on the day of FET. A registered TCM practitioner (EWSS) diagnosed these patients' conditions by the four diagnostic methods: observation, auscultation, interrogation and palpation according to the TCM principles (Maciocia, 1998). They were classified into the related syndromes which included Kidney Yang/Yin deficiency, Liver Qi stagnation with Blood stasis, Spleen Qi deficiency with Phlegm and combination of those syndromes.

Assignment and masking

Patients were then randomized according to a computer-generated randomization list in sealed, opaque envelopes into two groups: real acupuncture and placebo acupuncture groups. The randomization sequence was in a block of 10 with 1:1 ratio. The randomization list was generated and kept by a project nurse not involved in the clinical care of these patients. 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 the completion of the whole study and statistical analysis.

All acupuncture treatments were performed on site in the same way by the same certified acupuncturist (EWSS) who had completed the degree of Chinese Medicine and had 3 years of experience in acupuncture, as described in the previous study (So et al., 2009). The acupuncturist followed a standard way of communicating with patients whether they were in the real or placebo acupuncture groups.

Real acupuncture group

Patients in the real acupuncture group received a single session of real acupuncture for 25 minutes immediately after FET. Sterile disposable stainless steel needles (Mayfair

Medical Supplies Ltd., Hwato, Suzhou, China; 0.30 × 40 mm) were inserted into the acupoints. The acupoints used were ST36 (Zusanli), SP6 (Sanyinjiao), SP10 (Xuehai), and LI4 (Hegu). The designation of acupoints adhered to the second edition of the Standard Acupuncture Nomenclature (World Health Organization Regional Office for the Western Pacific, 1993).

The depth of the needle insertion into the skin depended on the location of the acupoints, ranging from 10 to 20 mm. Needle reaction (soreness, numbness, or distension around the puncture sites or sometimes propagation along the corresponding meridians, termed the DeQi sensation) was elicited during the initial insertion. After 10 minutes, the needles were stimulated manually by rotating, lifting and thrusting the handle of the needle in order to maintain DeQi sensation. The needles were retained in position for 25 minutes and then removed.

Placebo acupuncture group

Patients in the placebo acupuncture group received a single session of placebo acupuncture for 25 minutes immediately after FET. The Streitberger's placebo needles (Streitberger and Kleinhenz, 1998; Asiamed, Pullach, Germany; 0.30 × 30 mm) were used. The placebo needle was not fixed into the copper handle and the tip of the needle was blunt. When it was pushed forward against the skin, the needle slid into the handle and the whole needle appeared shortened. This also gave patients a pricking penetration sensation. To place the placebo needle in position, the Park's placebo device (Park et al., 1999; Dong Bang AcuPrime, Exeter, UK) was used. The same acupoints and procedures were applied as in the real acupuncture group.

Measurement of serum cortisol concentration and the anxiety level

Blood samples were drawn before and after the real or placebo acupuncture treatment. Serum was stored at -20^{o}C until assayed. Serum cortisol concentration was then determined by using a chemiluminescent immunoassay (ADVIA Centaur® Immunoassay System, Siemens Medical Solutions Diagnostics Ltd., HK, China). The sensitivity of the cortisol assay was 0.2 μg/dL with intra- and inter-assay coefficients of variation 3.69 and 5.45%, respectively.

The anxiety level was assessed before and after the real or placebo acupuncture treatment by State-Trait Anxiety Questionnaire (Shek, 1993).

Evaluation of side effects and blindness of the study

At the end of the real or placebo acupuncture treatment, the occurrence of side effects was reported by a self-completed questionnaire and the validity of blindness to the group assignment was assessed by asking patients to guess whether they were placed in the real or placebo acupuncture groups.

Statistical analysis

The pregnancy rates in the acupuncture group and the control group were 42.5% and 26.3% respectively (Paulus et al., 2002), representing 16.2% increase in pregnancy rate after acupuncture. Assuming that the pregnancy rate of FET would be increased from 29.5% per transfer (our result from January to June 2006) to 47.6% per transfer after acupuncture, 113 patients in each arm was required at a power of 80% and a significance level of 5% (Sigmastat, Jandel Scientific, San Rafael, CA, USA). Therefore, 226 patients were recruited in this study.

The primary outcome measure was the overall pregnancy rate which was defined by a positive urinary pregnancy test. Secondary outcome measures included the implantation rate,

the clinical pregnancy rate, the ongoing pregnancy rate, the livebirth rate, the cortisol concentration and the anxiety level. The implantation rate was the proportion of embryos transferred resulting in an intrauterine gestational sac. Patients with one or more intrauterine gestational sacs on scanning or the histological confirmation of gestational product in miscarriages were considered as having clinical pregnancies. Ongoing pregnancies were those pregnancies beyond 10 weeks of gestation and the patients were at the stage of referral to antenatal care. A baby born after 24 weeks gestation was classified as a live birth.

One sample of the Kolmogorov-Smirnov test was used to test the normal distribution of continuous variables. Continuous variables were given as mean ± standard deviation if normally distributed, and as median (interquartile range) if not normally distributed. Statistical comparison was carried out according to the intention to treat by Student's T test, Mann-Whitney *U*-test, Wilcoxon signed ranks test for continuous variables and chi-squared test for categorical variables, where appropriate. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Version 15.0, Chicago, USA). Pregnancy outcomes were presented as relative risks (RR) with 95% confidence interval (CI). The two-tailed value of $P < 0.05$ was considered statistically significant.

RESULTS

Participant flow

During the study period between October 2006 to November 2007, 457 women underwent FET treatment. After screening, 125 women were not eligible: 10 had FET canceled because of lysis of all embryos; 105 had joined the study before; 2 were recipients of donor oocytes, 3 underwent preimplantation genetic diagnosis and 5 had an abnormal uterine cavity. Another 106 women declined the invitation because of personal reasons and therefore 226 eligible women participated in the study. All recruited patients completed the study and their pregnancy outcomes were available for analysis. The flow chart of subjects is shown in *Figure 1*.

Analysis

The age of women at freezing, duration of subfertility, proportion of primary subfertility, smoking habit, previous experience in acupuncture, the cause of subfertility, the cycle number, the insemination method, body mass index, basal FSH concentration, antral follicle count, the dosage and duration of HMG, serum E2 on the day of hCG, the number of oocytes obtained and the number of embryos frozen were comparable for the real and placebo acupuncture groups *(Table I*).

The age of women at thawing, the type of FET cycles, the number of emnbryos thawed / transferred were similar for the real and placebo acupuncture groups (*Table II*). The distribution of TCM syndromes and embryo quality in terms of blastomere number and grading of embryos at the time of freezing and thawing were comparable for the real and placebo acupuncture groups (data not shown). There were no significant differences in rates of overall pregnancy, clinical pregnancy, ongoing pregnancy, livebirth, implantation and

miscarriage in the placebo acupuncture group when compared to the real acupuncture group *(Table III)*.

The median general anxiety state scales were similar for the real and placebo acupuncture groups (46.2±4.7 vs 46.1±4.3). There were no significant differences in the anxiety level and serum cortisol concentration between the placebo and real acupuncture groups, before and after the acupuncture treatment (data not shown). However, the anxiety level ~~in the real placebo acupuncture~~[CF1] and serum cortisol concentration in both real and placebo acupuncture groups were significantly (P<0.001) lower after the acupuncture treatment, when compared with that before the acupuncture treatment.

No significant differences were found in the occurrence of side effects between the real and placebo acupuncture groups *(Table IV)*. The severity of these side effects was mild to moderate and no serious adverse effects were reported. Significantly more patients in the placebo acupuncture guessed that they had received the placebo acupuncture, when compared to that of the real acupuncture group *(Table IV)*.

Comparison with the decline group

Patients who declined to join the study received the usual care without real or placebo acupuncture on the day of FET. There were no differences in the demographic characteristics, ovarian responses of the indexed IVF cycle, the type of FET cycles, the number of frozen-thawed embryos transferred and the embryo quality among the decline group, the real acupuncture group and the placebo acupuncture group (data not shown).

The placebo acupuncture had significantly higher ongoing pregnancy rate (38.9% vs 23.6%, P=0.022, RR: 1.651 95%CI 1.102-2.502) and implantation rate (28.4% vs 19.2%, P=0.038, RR: 1.484 95% CI 1.042-2.217) than that of the decline group. There was a non-

significant trend of higher overall pregnancy rate, clinical pregnancy rate, ongoing pregnancy rate, livebirth rate and implantation rate in the real acupuncture group when compared with those of the decline group.

DISCUSSION

All previous studies (Paulus et al., 2002 and 2003; Dieterle et al., 2006; Smith et al., 2006; Westergaard et al., 2006; Craig et al., 2007; Domar et al., 2008; Fratterelli et al., 2008; Moy et al., 2008; So et al., 2009) evaluated the role of acupuncture in the pregnancy rate of IVF treatment during stimulated cycles. To the best of our knowledge, this is the first study comparing real and placebo acupuncture in relation to the pregnancy rates of patients undergoing FET treatment. There were no significant differences in rates of overall pregnancy, clinical pregnancy, ongoing pregnancy, live birth and implantation in the placebo acupuncture group, when compared with the real acupuncture group. The anxiety level and serum cortisol concentration before and after the real and placebo acupuncture were similar for the real and placebo acupuncture groups.

Results of the present study corresponded with that of our recent study (So et al., 2009), which found a significantly higher overall pregnancy rate of IVF cycles and comparable rates of clinical pregnancy, ongoing pregnancy, live birth and implantation in the placebo acupuncture group than those of the real acupuncture group. Significant changes in endometrial and subendometrial vascularity determined by transvaginal power Doppler ultrasound examination, the anxiety level and serum cortisol concentration were demonstrated following both real and placebo acupuncture. Therefore, we postulated that the placebo acupuncture is not inert and may be associated with a higher pregnancy rate.

When we planned these two acupuncture studies (So et al., 2009 and the present study), we believed that the best way to study the effect of acupuncture was a double blind setting and did not include a third arm of patients receiving usual care only. Only 12 patients declined to join the study conducted during IVF cycles (So et al., 2009) and 106 patients did not join this study during FET cycles. Patients who declined to join this study did not receive real or placebo acupuncture and were compared to those in the real and placebo acupuncture

groups as retrospective comparison. No differences in the pregnancy and livebirth rates were shown between the real acupuncture group and the decline group while significantly higher ongoing pregnancy and implantation rates were found in the placebo acupuncture group than the decline group. These findings reinforce our belief that the placebo acupuncture is not inert. We are fully aware that patients in the decline group were not randomized and the comparison results have to be interpreted with caution.

Sham and placebo acupunctures have been used in acupuncture studies as controls. Sham acupuncture can be performed by inserting needles into non-acupoints or acupoints with superficial penetration (so-called minimal acupuncture). In placebo acupuncture, the tip of the placebo needle is blunt and would produce light pricking sensation during the manipulation without penetrating the skin (so-called non-invasive acupuncture). The most popular placebo needles are the Streitberger's placebo needles and the Park's placebo devices. Both the Streitberger's placebo needle (White et al., 2003) and the Park's device (Park et al., 2002 and 2005) have been confirmed to be reliable controls in randomized studies.

The sham acupuncture can still elicit a physiological effect and might not be an inactive control (Birch, 2006; Lund et al, 2009). A study (MacPherson et al., 2008) using functional magnetic resonance imaging found that superficial and deep needling of an acupuncture point elicited similar blood oxygen level–dependent responses. A large randomized controlled trial (Haake et al, 2007) showed both real and sham acupuncture were equally effective and was significantly superior to conventional care in chronic low back pain. The non-invasive placebo acupuncture was previously considered to be the best control in acupuncture studies. However, both standard and placebo acupuncture treatments were found to significantly reduce pain and improved function in patients with chronic low back pain, when compared with usual care (Cherkin et al., 2009). A recent meta-analysis (Madsen et al., 2009) of studies on the analgesic effect of acupuncture also showed a moderate difference

between placebo acupuncture and no acupuncture, favouring placebo acupuncture. There seems to be differential patterns of brain activation between real and sham acupuncture as shown by functional magnetic resonance imaging (Chae et al., 2009). Taking these studies together, sham and placebo acupunctures are active treatment.

Patients participating in the present study followed a standard protocol of ovarian stimulation, embryo freezing and the day of FET, similar to our previous study (So et al., 2009). As acupuncture treatment may work as behavioural conditioning (Lund et al., 2009), all real and placebo acupuncture procedures were performed by the same certified acupuncturist with the same care throughout the acupuncture treatment in order to minimize the difference of psychological effect between groups. In the present study, only one session of real or placebo acupuncture was performed after the transfer procedure while two sessions i.e. one prior to the ET and another after ET were performed in the previous study (So et al., 2009) and in the majority of relevant studies. Dieterle et al. (2006) compared one session of real acupuncture with one session of placebo acupuncture which was performed immediately after ET and again 3 days later. Their results showed the clinical and ongoing pregnancy rates of the real acupuncture group were significantly higher than that of the placebo acupuncture group. As ~~T~~there is no improvement in the pregnancy rate when acupuncture was administered 2-3 days after ET (Cheong et al., 2008), we hypothesize that it is the first session in the Dieterle study (2006) that influenced pregnancy rates and the second session may be unnecessary. Acupuncture may have sustained effects. Research into endorphin release indicates that physiological effects of acupuncture can continue for many hours (Han, 2004) and improvement of low back pain might be sustained over long periods following a short course of acupuncture (Thomas et al., 2007). It remains uncertain whether two sessions of acupuncture are better than one session. Randomized studies are warranted to find out any difference in the pregnancy rate between one and two sessions of acupuncture.

This is a double blind study as the patients and the clinicians / laboratory staff were blinded to the treatment groups. Despite the use of the placebo needles and the Park device, more patients in the placebo acupuncture group guessed that they received placebo acupuncture. In the placebo acupuncture group, nearly 50% of patients still thought that they received real acupuncture and another quarter was not sure about the treatment group. We do not think this would affect the pregnancy results shown here.

In conclusion, comparable pregnancy and livebirth rates of FET treatment were found in patients who had one session of real or placebo acupuncture after FET.

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Table I: Demographic characteristics and ovarian response of the indexed IVF cycle in the real and placebo acupuncture groups

	Real acupuncture (n=113)	Placebo acupuncture (n=113)
Age of women at freezing (years)[a]	35.0 (33-38)	35.0 (33.5-37.5)
Duration of subfertility (years)[a]	5.0 (3.0-7.0)	5.0 (3.0-7.0)
Primary subfertility[b]	42 (37.2)	44 (38.9)
Smoker[b]	10 (8.8)	8 (7.1)
Previous acupuncture experience[b]	55 (48.7)	45 (39.8)
Cause of subfertility[b]		
Tuboperitoneal	19 (16.8)	22 (19.5)
Endometriosis	13(11.5)	12 (10.6)
Male	53 (46.9)	58 (51.3)
Unexplained	11 (9.7)	12 (10.6)
Mixed	17 (15.0)	9 (8.0)
Cycle number[b]		
First IVF cycle	75(66.4)	73(64.6)
Repeated IVF cycle	38(33.6)	40(35.4)
Insemination method[b]		
Conventional	76 (67.3)	78 (69.0)
ICSI	37 (32.7)	35 (31.0)
Body mass index (kg/m^2)[c]	21.6 ± 2.3	21.9 ± 2.6
Basal FSH concentration (IU/L)[c]	7.4 ± 2.2	7.3 ± 2.9
Antral follicle count[a]	12.0 (8-16)	11.0 (8-14)
HMG dosage (IU)[a]	1800 (1650-2175)	1932 (1650-2400)
HMG duration (days)[a]	10.0 (9-12)	10.0 (9-12)
E2 on day of hCG (pmol/L)[a]	11,199 (7464-15,869)	10,747 (7411-16,365)
No. of oocytes obtained[c]	12.9 ± 5.7	11.8 ± 5.8
No. of embryos frozen[c]	5.8 ± 3.7	5.0 ± 3.2

[a]Data are given in median (interquartile range)
[b]Data are given in number (%)
[c]Data are given in mean ± SD

Table II: Characteristics of frozen embryo transfer (FET) cycles in the real and placebo acupuncture groups

	Real acupuncture (n=113)	Placebo acupuncture (n=113)
Age of women at thawing (years)[a]	36.0 (34-38)	36.0 (34-39)
Type of FET cycle[b]		
Natural	88 (77.9)	89 (78.8)
Clomiphene citrate	16 (14.2)	13 (11.5)
Hormone replacement	9 (7.9)	11 (9.7)
No. of embryos thawed[b]		
One	6 (5.3)	8 (7.1)
Two	99 (87.6)	97 (85.8)
Three	8 (7.1)	8 (7.1)
No. of embryos transferred[b]		
One	15 (13.3)	13 (11.5)
Two	91 (80.5)	95 (84.1)
Three	7 (6.2)	5 (4.4)

[a]Data are given in median (interquartile range)
[b]Data are given in number (%)

Table III: Comparison of frozen embryo transfer pregnancy outcomes

	Real acupuncture (n=113)	Placebo acupuncture (n=113)	RR (95% CI)
Overall pregnancy rate	39.8 (45/113)	47.8 (54/113)	1.178 (0.899-1.543)
Clinical pregnancy rate	36.3 (41/113)	44.2 (50/113)	1.184 (0.898-1.561)
Ongoing pregnancy rate	30.1 (34/113)	38.9 (44/113)	1.294 (0.900-1.862)
Livebirth rate	29.2 (33/113)	35.4 (40/113)	1.212 (0.829-1.773)
Implantation rate	21.6 (47/218)	28.4 (62/218)	1.319 (0.949-1.834)
Miscarriage rate	15.6 (7/45)	11.1 (6/54)	0.714 (0.259-1.973)

Data are given in %. Therewere no statistically significant differences between the two groups.

Table IV: Comparison of side effects and guess of treatment groups

	Real acupuncture (n=113)	Placebo acupuncture (n=113)
Side effects		
Nausea	1 (0.9)	1 (0.9)
Dizziness	5 (4.4)	0 (0)
Fainting	6 (5.3)	2 (1.8)
Tiredness	17 (15.0)	15 (13.3)
Drowsiness	26 (23.0)	24 (21.2)
Headache	7 (6.2)	1 (0.9)
Chest pain	0 (0)	1 (0.9)
Puncture site itching	31 (27.4)	19 (16.8)
Guess of treatment groups		
Real	79 (69.9)	55 (48.7)
Placebo[a]	6 (5.3)	26 (23.0)
Uncertain	28 (24.8)	32 (28.3)

Data are given in %

[a]Statistically significant difference P<0.001.

Figure 1: Flow chart of the study