

Influence of acupuncture stimulation on pregnancy rates for women undergoing embryo transfer

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Objective: To evaluate the effects of acupuncture on clinical pregnancy rates for women undergoing ET.

Design: Single-blind, randomized controlled trial using a noninvasive sham acupuncture control.

Setting: Repromed, The Reproductive Medicine Unit of The University of Adelaide.

Patient(s): Women undergoing IVF.

Intervention(s): Women were randomly allocated to acupuncture or noninvasive sham acupuncture with the placebo needle. All women received three sessions, the first undertaken on day 9 of stimulating injections, the second before ET, and the third immediately after ET.

Main Outcome Measure(s): The primary outcome was pregnancy. Secondary outcomes were implantation, ongoing pregnancy rate at 18 weeks, adverse events, and health status.

Result(s): Two hundred twenty-eight subjects were randomized. The pregnancy rate was 31% in the acupuncture group and 23% in the control group. For those subjects receiving acupuncture, the odds of achieving a pregnancy were 1.5 higher than for the control group, but the difference did not reach statistical significance. The ongoing pregnancy rate at 18 weeks was higher in the treatment group (28% vs. 18%), but the difference was not statistically significant.

Conclusion(s): There was no significant difference in the pregnancy rate between groups; however, a smaller treatment effect can not be excluded. Our results suggest that acupuncture was safe for women undergoing ET. (Fertil Steril® 2006;85:1352–8. ©2006 by American Society for Reproductive Medicine.)

Key Words: Acupuncture, clinical trial, embryo transfer, pregnancy rate

Some couples might choose to try complementary and alternative medicines before they commence infertility treatment or might choose to use it as an adjunct while undergoing infertility treatment. Acupuncture has long been used for gynecological and obstetric problems, such as amenorrhea, menorrhagia, morning sickness, and problems during labour and delivery (1), and is one complementary and alternative medicine considered by some women to assist with infertility treatment. Classic acupuncture refers to the insertion of fine needles into specific points of the body. This treatment has a history dating back 2,500 years and treats illness by restoring a balance in the flow of *Qi* (energy) in the human body. Acupuncture today involves modes of stimulation, such as acupressure, transcutaneous electrical nerve stimulation, moxibustion, ear acupuncture, and the use of lasers.

There have been few randomized controlled trials of acupuncture in the area of reproductive medicine. Two studies of acupuncture for male infertility (2, 3) concluded that acupuncture might be a useful treatment for men with poor sperm density; however, these studies were small and un-

controlled. Successful IVF and ET require optimal endometrial receptivity at the time of implantation. Blood flow impedance in the uterine arteries as measured by transvaginal ultrasonography expressed as a resistance index, the pulsatility index, is considered to be a useful method for assessing uterine receptivity. In one small, uncontrolled study of electro-acupuncture, lower pulsatility index values were found after acupuncture treatment (4).

There have been two randomized controlled trials of acupuncture administered to women undergoing IVF (5, 6). In the trial undertaken by Paulus et al. (5), 160 healthy women undergoing IVF or intracytoplasmic sperm injection (ICSI) in Germany were randomized to receive acupuncture or no acupuncture. Acupuncture was administered 25 minutes before and after ET. Needles were inserted, and the *Deqi* needling sensation was obtained. Needles were retained for 25 minutes before and after the transfer, and acupuncture points were used to move *Chi* and *Blood* and *calm Chi*. Treatment used a fixed combination of body and auricular acupuncture points. A higher pregnancy rate was found in the acupuncture group compared with the control group (42.5% vs. 26.3%, $P < .03$). However, bias might have arisen from inadequate blinding, and insufficient details were reported on the sample and effect size.

Quintero (6) evaluated the effectiveness of acupuncture as an adjunct to IVF. Seventeen women were randomized to

Received September 15, 2005; revised and accepted December 10, 2005.

Supported by research funds from Repromed and the University of South Australia.

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receive acupuncture or sham acupuncture in a double-blind, crossover trial; however, only seven women completed the study. Two women in each group achieved an ongoing pregnancy. Of the seven who crossed over to the other treatment arm, two women in the acupuncture group achieved an ongoing pregnancy, compared with one in the sham acupuncture group. Although the investigators found that acupuncture significantly reduced the amount of gonadotropin used ($P < .05$), no effect on the pregnancy rate was found.

In two retrospective clinical studies (7, 8), Magarelli et al. explored the effects of acupuncture on IVF outcomes, using the protocols reported by Sterner-Victorin et al. (4) and Paulus et al. (5). Magarelli et al. (7) reported higher pregnancy rates (51% vs. 36%, $P < .05$) and lower miscarriage rates (8% vs. 20%, $P < .05$) among those subjects receiving acupuncture compared with subjects in the comparison group. The second study explored the influence of acupuncture stimulation among subjects described as “poor responders to IVF.” Fifty-seven subjects received acupuncture, and 94 received no acupuncture. A significant increase in the pregnancy rate was found for subjects receiving acupuncture (53% vs. 38%, $P < .01$) (8). Methodological limitations, such as selection bias, might have influenced the study findings.

The research to date suggests that acupuncture might have a role in increasing pregnancy rates among women undergoing IVF. There is clearly a need for a larger, pragmatic, well-designed, randomized controlled trial to determine the effectiveness of acupuncture on pregnancy rates among women undergoing IVF. In this article we report the findings from a randomized controlled trial evaluating the effect of acupuncture on pregnancy rates for women undergoing ET.

MATERIALS AND METHODS

Women undergoing IVF or ICSI were recruited from Repromed, The Reproductive Medicine Unit of The University of Adelaide. Women with a planned ET were eligible for inclusion; women previously randomized to the trial were excluded. Eligible women were identified by a research nurse and were provided with information about the study. The trial also received media coverage, resulting in some women self-referring to the study. Recruitment took place between May 2003 and January 2005 and was approved by the Women’s and Children’s Hospital’s research and ethics committee.

Information on demographics, fertility history, and health status was collected from subjects. Subjects were randomly allocated to a study group by selection of the next sealed envelope in the sequence for each stratification by number of IVF cycles (first, second, third, fourth, fifth or more) and maternal age (<35 years, 35–37 years, 38 to 39 years, and ≥ 40 years). Randomization was in balanced, variable blocks of random size (2, 4, 6) prepared by a researcher not involved in the trial. Women were allocated to receive treatment with acupuncture or with noninvasive sham acupuncture.

All women received three treatment sessions. The first took place on day 9 of stimulating injections, and the second and third were immediately before and after ET. The time from randomization to ET varied (depending on women’s response to stimulation); however, the mean length of time was 7 days.

A structured interview was used to determine the infertility diagnosis from a traditional Chinese medicine (TCM) perspective. This included a tongue examination, palpation of the radial pulse, and a history of symptoms. Diagnosis was made with the approach described in Maciocia (1). The patterns identified included kidney yang, kidney yin, blood deficiency, blood stagnation, damp, and *Qi* stagnation (9). The acupuncture treatment protocol was based on the protocol reported by Paulus et al. (5). Two modifications were made: an initial acupuncture treatment was administered before ET, and two acupuncture points were excluded (liver 4 and governing vessel 20). Acupuncture was administered with point selection based on the TCM diagnosis. Points were needled bilaterally, and Acuglide (Helio Medical Supplies, San Jose, CA) 0.18 mm \times 30 mm needles were inserted with a guide tube to tissue level and stimulated manually to elicit the *Deqi* response (needling sensation). The number of needles inserted ranged from 6 to 14 for the first treatment and were 13 and 10 in the second and third treatments, respectively. Needles were retained for 25 minutes per treatment. Two acupuncturists administered acupuncture treatments, with the majority being administered by the primary acupuncture researcher (M.C.).

For women in the control group, sham acupuncture points were used. These were located close to but not on the real acupuncture points. These included points located on the foot anterior to the junction of the third and fourth metatarsals, 4 cun (anatomical units) below and two fingerbreadths lateral to the knee, 2 cun above kidney 3 between the spleen and kidney meridians, 3 cun lateral to the midline level with conception vessel 5 and 7, and 2 cun above the wrist crease between the lung and pericardium meridians.

The Streitberger (Asiamed, Pullach, Germany) placebo needle (0.30 mm \times 30 mm) was used (10). Because the tip of the needle is blunted, skin penetration did not occur. Needles were manually “stimulated” by lifting and thrusting the handle of the needle and by running a fingernail along the handle. The acupuncturist held the placebo needle in place with one hand while “stimulating” the needle with the other hand. Each point was stimulated bilaterally for approximately 3 minutes. Treatment duration was approximately 25 minutes. This noninvasive sham procedure was selected because it closely resembles a style of TCM acupuncture without penetrating the skin.

The primary outcome was pregnancy, defined as the number of couples achieving a clinical pregnancy (demonstration of fetal heart activity on ultrasound scan). Secondary outcomes were implantation (defined as demonstration of a gestational sac on ultrasound scan and calculated as a per-

centage of the total embryos transferred), ongoing pregnancy rate at 18 weeks, adverse events, and health status according to the MOS 36 Short Form Health Survey (SF36) (11).

Assessment of health status at the time of trial entry and after ET was made with the SF36. The SF36 is a multi-item scale measuring eight key health concepts: physical functioning, role limitation due to physical health problems, bodily pain, general health, vitality, social functioning, role limitation due to emotional problems, and mental health well-being. The possible score range is 0–100, with 100 being the best possible score. The posttreatment questionnaire included an evaluation of any adverse effects and an assessment of which group subjects thought they were allocated to.

The power analysis was based on data presented by Paulus et al. (5), which reported a pregnancy rate of 42.5% in the treatment group and 26% in the control group. For women undergoing IVF at Repromed, the pregnancy rate was 30% (12); this figure was used for the control group pregnancy rate. A trial of 114 women per group would detect a difference between groups, assuming a power of 80%, two-sided testing at the 5% significance level.

Data were analyzed with commercial software (Statistical Package for the Social Sciences 11.5.1; SPSS, Chicago, IL). The initial analysis examined the demographic and baseline characteristics of women randomized to the trial. Any differences in prognostic variables were taken into account in subsequent analyses of the major outcome variables. The main analyses undertook an “intention-to-treat” approach and compared differences in the primary study outcome measure between the two groups. Comparisons were made between groups with χ^2 tests and by constructing relative risks (RRs); 95% confidence intervals (CIs) were based on differences between groups. Levels of significance were reported at $P < .05$ and $P < .01$.

RESULTS

Of the 469 women assessed for eligibility, 215 declined to participate, and a small number were identified as being ineligible (Fig. 1). Of the 228 subjects randomized, an intention-to-treat analysis was performed on the primary endpoint, pregnancy outcome. Thirty-six women (15%) were unable to comply with the treatment protocol because their cycle was cancelled or the ET was not undertaken. Seven women with a cancelled cycle were excluded from analysis of the primary endpoint.

The mean age of women participating in the trial was 36 years (Table 1). The majority of subjects were receiving their first fertility cycle, had a body mass index in the overweight category, were nonsmokers (90%), were currently drinking alcohol (67%), were employed outside the home (85%), and had finished high school (83%). The majority of women (69%) had not received acupuncture previously. More than 50% of women reported a history of infertility >2 years,

with the most common reasons for infertility attributed to male infertility and tubal factors. The SF36 scores were lower for women in the study cohort on the social function, vitality, mental health, and emotional role function domains compared with the South Australian population; however, higher scores were seen on the physical function and physical role function domains compared with the South Australian population (9). No differences existed between the two groups, suggesting that the randomization produced comparable groups at baseline.

Pregnancy Outcome

Table 2 presents the primary and secondary outcomes. Grading was performed on all embryos with the score developed by Cummins et al. 1986 (13). No difference in the grading of embryos was found between groups. The pregnancy rate, defined as fetal heart rate on ultrasound scan, was 31% in the acupuncture group and 23% in the control group. For those subjects receiving acupuncture, the odds of achieving a pregnancy was 1.5 higher than the control group but again did not reach statistical significance. The pregnancy rate was also not found to differ between groups among women aged <35 years (50% vs. 33%, $P < .11$). The ongoing pregnancy rate at 18 weeks was higher in the treatment group, but the difference was not statistically significant (28% vs. 18%).

Subjects' health status did not differ between groups. Overall, however, the SF36 scores declined over the study intervention for the physical function, bodily pain, mental health, and vitality domains.

No difference was found between groups for other study endpoints: number of oocytes retrieved (weighted mean difference 0.84, 95% CI -0.64 to 2.32), fertilization rate (RR 1.08, 95% CI 0.99 to 1.17), number of embryos transferred (weighted mean difference 0.04, 95% CI -0.17 to 0.25), and biochemical pregnancy rate (RR 1.16, 95% CI 0.87 to 1.56).

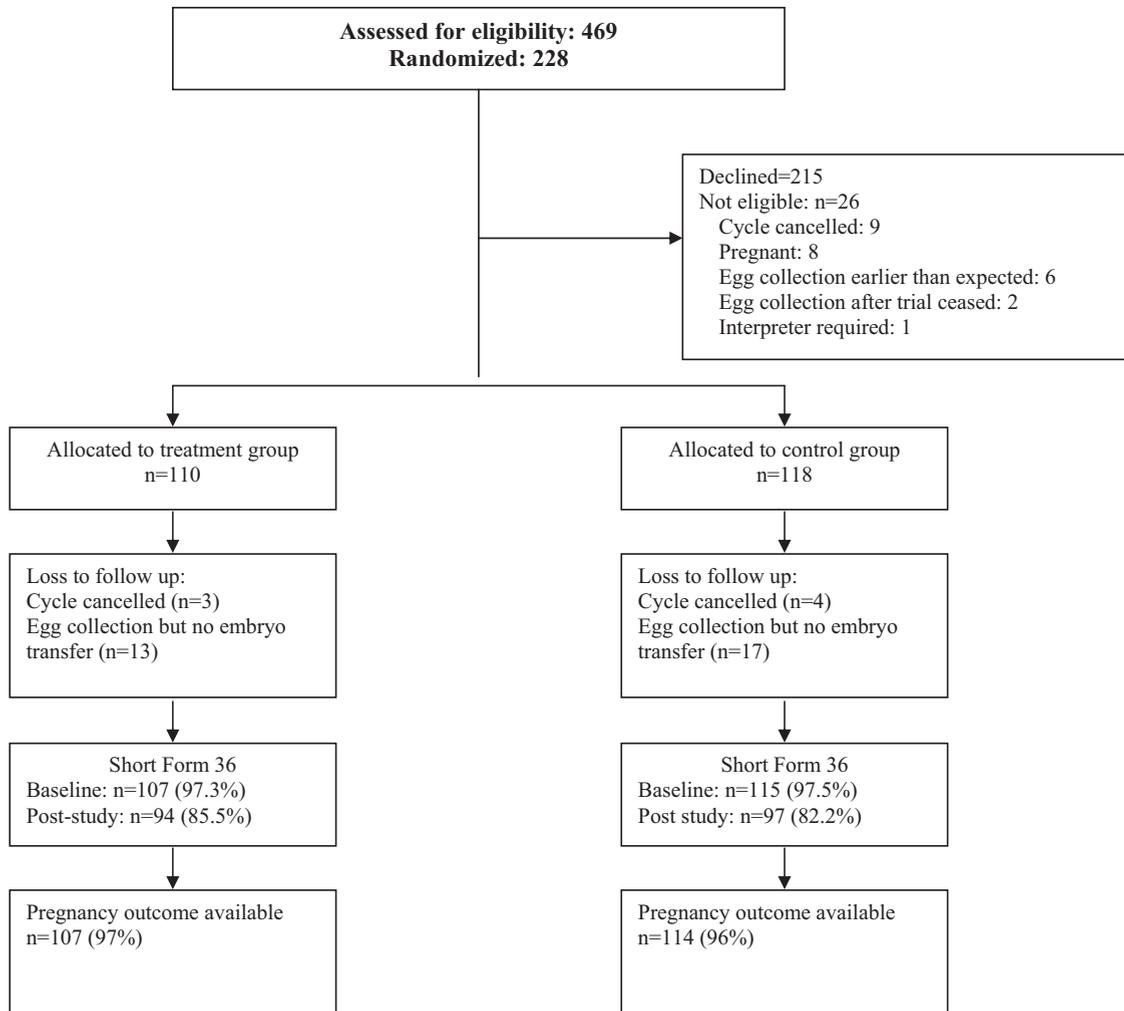
Side Effects

Subjects were asked whether they had experienced any side effects after any of their treatments. These were categorized into positive and negative side effects. The most frequently reported side effects were relaxation (51% vs. 67%), feeling calm and peaceful (55% vs. 64%), or feeling energized (10% vs. 12%). Subjects in the control group were more likely to report relaxation as a side effect of acupuncture ($P < .05$).

To examine the effect of blinding, subjects were asked which group they thought they had been allocated to. Twenty-six subjects (11%) correctly guessed their group allocation (Table 3). Of the 16 subjects who correctly guessed that they were in the treatment group, the reasons given included feeling positive, calm, relaxed, or better (6 women); gut feeling (3); positive thinking (3); point location (e.g., time taken to locate the points, accuracy in placement of needles) (2); and 1 subject guessed her group allocation. Of the 10 subjects who correctly guessed that they were in

FIGURE 1

Subject flow chart.



Smith. RCT of acupuncture at ET. Fertil Steril 2006.

the control group, the reasons included the placement of needles (e.g., focus on feet, placement of needles, and points used) (6); gut feeling (1); never had acupuncture before (1); to avoid disappointment (1); and 1 subject guessed her group allocation.

After the third treatment, a difference was found between subjects' perception of their group allocation ($P < .05$). Of the 24 subjects who correctly guessed that they were in the treatment group, the reasons for their decision included feeling good, relaxed, calm, positive, happier, warm, or better (12); the treatment itself (e.g., points chosen, time to locate points, sense of accuracy in the method or care of treatment administration) (4); positive thinking (4); and other reasons (4). Of the 10 subjects who correctly guessed that they were in the control group the reasons for their decision included a lack of sensations (4); needle placement (3); and other reasons (3).

We examined whether previous experience of acupuncture would lead subjects to correctly identify their group allocation. This analysis was based on 71 subjects (32 in the treatment group and 39 in the control group). After the first treatment 73% of subjects were unsure of their group allocation, and after the third treatment 68% were unsure of their group allocation. Participants with previous acupuncture experience were not more likely to be able to correctly guess their group allocation ($P > .05$).

DISCUSSION

The results from this study did not show a significant increase in the pregnancy rate between acupuncture and sham acupuncture groups; however, a smaller treatment effect can not be excluded. Our results suggest that acupuncture was safe for women undergoing ET.

TABLE 1**Participant demographic and baseline characteristics.**

Characteristic	True acupuncture (n = 110)	Noninvasive sham acupuncture (n = 118)	P
Age (y)	35.9 (4.7)	36.1 (4.8)	NS
No. of cycles			
1	55 (50)	54 (45)	NS
2	24 (21)	31 (26)	
3	12 (10)	12 (10)	
4	7 (6)	8 (6)	
5+	12 (10)	13 (11)	
Parity			
0	79 (71)	94 (79)	NS
≥1	31 (28)	24 (20)	
BMI	25.4 (4.2)	26.0 (5.6)	NS
Currently smoking	9 (8)	15 (12)	NS
Currently drink alcohol	78 (70)	76 (64)	NS
Employed outside the home	92 (83)	103 (87)	NS
Finished high school	96 (87)	94 (79)	NS
Completed tertiary education	25 (22)	32 (27)	NS
Duration of infertility (y)			
<2 y	42 (38)	60 (51)	NS
2–4	51 (46)	38 (32)	
5+	17 (15)	19 (16)	
Reason for infertility			
Male factor	45 (40)	60 (51)	NS
Tubal	51 (46)	38 (32)	NS
Unexplained	29 (26)	22 (18)	NS
Endometriosis	26 (76)	28 (76)	NS
Other	36 (32)	46 (39)	NS
Previous interventions used			
Clomiphene citrate	21 (19)	23 (19)	NS
IUI alone	11 (10)	9 (7)	NS
IUI with ovarian stimulation	25 (22)	24 (20)	NS
IVF	70 (63)	69 (58)	NS
Health status (SF36)			
Physical functioning	88.9 (16.7)	90.0 (17.7)	NS
Role–physical	85.7 (27.7)	85.2 (31.5)	NS
Bodily pain	91.0 (21.8)	94.9 (20.0)	NS
General health	68.2 (17.7)	68.4 (16.2)	NS
Vitality	53.9 (21.6)	56.9 (18.2)	NS
Social functioning	80.8 (24.7)	81.5 (22.5)	NS
Role–emotional	76.6 (33.7)	78.8 (36.0)	NS
Mental health	72.0 (15.8)	71.9 (16.0)	NS

Note: Values are mean (SD) or n (%).

Smith. RCT of acupuncture at ET. Fertil Steril 2006.

The study might have been underpowered, with the sample size calculation based on the effect size of the Paulus study. Our results suggest a smaller treatment effect from acupuncture with a post hoc power effect of 27.4%, requiring a sample size of 484 subjects. Our study can not be directly compared with the Paulus study (5): our study protocol included a first treatment administered before

egg collection, transfer of embryos of varying quality (the Paulus study transferred good-quality embryos only), and there were also minor variations in treatment protocol.

Compared with other clinical trials of acupuncture, our study included a larger sample size. Other strengths of this

TABLE 2

Primary and secondary outcomes by group.				
Pregnancy outcome	True acupuncture	Noninvasive sham acupuncture	Risk ratio (95% CI)	P
Grading of embryo 1				
Excellent	32 (34)	29 (29)	0.90 (0.40–2.03)	.75
Satisfactory	42 (45)	53 (54)	0.62 (0.30–1.40)	.24
Unsatisfactory	19 (20)	15 (15)	Reference	
Implantation achieved (defined as demonstration of a gestational sac on ultrasound)				
1	29 (78)	25 (80)	Reference	
2	8 (21)	6 (19)	1.15 (0.35–3.80)	.81
Pregnancy achieved (all women) (fetal heart on ultrasound)	34 (31)	27 (23)	1.50 (0.82–2.71)	.18
Pregnancy at 18 weeks	31 (28)	22 (18)		.08
SF36 mean (SD)				
Physical functioning	87.50 (16.90)	85.36 (19.85)		.42
Role–physical	73.13 (37.78)	74.48 (37.66)		.80
Bodily pain	67.90 (20.61)	69.18 (17.18)		.64
General health	67.29 (16.43)	70.25 (16.56)		.21
Vitality	58.64 (19.44)	58.04 (18.10)		.82
Social functioning	80.16 (21.46)	80.92 (21.43)		.80
Role – emotional	83.68 (29.22)	81.44 (32.26)		.80
Mental health	74.30 (13.85)	73.60 (14.98)		.74

Note: Values are n (%) or mean (SD).

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trial include high compliance and low loss to follow-up; loss to follow-up was associated with the IVF cycle being cancelled rather than their being any association with acceptability of the research. Both groups were also comparable for sociodemographic characteristics and reproductive status at randomization.

The pregnancy rate for women in the control group of the study was lower than the overall pregnancy rate at Repromed. This might have been influenced by the age of subjects in the study and an overrepresentation of women with poor pregnancy outcomes from previous IVF cycles. Data from Repromed indicate that our study might have been

TABLE 3

Subjects' views on study group allocation.			
Perceived group allocation	True acupuncture (n = 109)	Noninvasive sham acupuncture (n = 118)	P
After first treatment			
Treatment	16 (14)	14 (11)	.42
Control	14 (12)	10 (8)	
Unsure	79 (71)	94 (79)	
After last treatment			
Treatment	24 (25)	10 (10)	.047
Control	6 (6)	10 (10)	
Unsure	63 (67)	76 (78)	

Note: Values are n (%).

Smith. RCT of acupuncture at ET. Fertil Steril 2006.

underrepresented by younger women (46.5% vs. 38.6%) and overrepresented by women aged 35–39 years (30.9% vs. 35.0%) and >40 years (22.5% vs. 26.3%), who are less likely to have a positive outcome (14).

Although there were differences in the perception of group allocation at the end of the trial, we do not think women became unblinded to their group allocation. Subjects who correctly guessed that they had received acupuncture based their decision on the fact that they felt relaxed, better, calm, or happier after the acupuncture. This reason did not relate to the way in which the treatment was administered and was not something that could be controlled for. Of the 10 people who correctly guessed that they were in the control group, only 4 cited reasons that related to the way in which the placebo acupuncture was administered.

An interesting finding in our study was an increase in relaxation reported in the control group, suggesting that the control group might have been physiologically active. Our results, however, do not support the view that a greater sense of relaxation contributed to greater blood flow to the uterus, which contributed to more successful implantation of the fetus.

The clinical implications from our research suggest that acupuncture does not have any adverse effects at the time of egg retrieval and ET. The study suggests there might be a smaller treatment effect and that acupuncture might have a promising role as an adjunctive therapy in reproductive medicine at the time of ET.

Further research is needed to evaluate the efficacy of acupuncture at the time of ET. A large trial with appropriate power is required, as well as acupuncture research to examine the physiological changes in the uterus and the reproductive system.

Acknowledgments: The authors thank all the women participating in the trial; the staff at Repromed who contributed to the implementation of the

trial; Kristyn Willson (The University of Adelaide) and Ms. Kerena Eckert (The University of South Australia) for their statistical support; and Carol Horn, acupuncturist.

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