

The impact of acupuncture on in vitro fertilization outcome

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Objective: To replicate previous research on the efficacy of acupuncture in increasing pregnancy rates (PR) in patients undergoing IVF and to determine whether such an increase was due to a placebo effect.

Design: Prospective, randomized, controlled, single blind trial.

Setting: Private, academically affiliated, infertility clinic.

Patient(s): One hundred fifty patients scheduled to undergo embryo transfer.

Intervention(s): Subjects were randomized to either the acupuncture or control group. Acupuncture patients received the protocol, as first described by Paulus and his colleagues, for 25 minutes before and after embryo transfer. Control subjects laid quietly. All subjects then completed questionnaires on anxiety and optimism. The IVF staff remained blind to subject assignment.

Main Outcome Measure(s): Clinical PRs, anxiety, optimism.

Result(s): Before randomization both groups had similar demographic characteristics including age and psychological variables. There were no significant differences in PRs between the two groups. Acupuncture patients reported significantly less anxiety post-transfer and reported feeling more optimistic about their cycle and enjoyed their sessions more than the control subjects.

Conclusion(s): The use of acupuncture in patients undergoing IVF was not associated with an increase in PRs but they were more relaxed and more optimistic. (Fertil Steril® 2009;91:723–6. ©2009 by American Society for Reproductive Medicine.)

Key Words: Infertility, IVF, acupuncture, placebo effect

Acupuncture has been used for the treatment of numerous medical and psychological conditions in China for thousands of years. Some of the first reports on the use of acupuncture for the treatment of infertility were published in the 1960s (1). There have been numerous published anecdotal reports on the positive impact of acupuncture on fertility rates in both men and women, as well as nonrandomized studies with the same claims.

In 2002, Paulus and his colleagues (2) published the first randomized, controlled, prospective study on the impact of before and after embryo transfer acupuncture on pregnancy rates (PR) in 160 IVF patients with good quality embryos. The women who received 25 minutes of acupuncture before and again 25 minutes after embryo transfer had a 42.5% clinical PR compared to a 26.3% rate ($P=.03$) in the control subjects who laid quietly for an equivalent amount of time. This study received widespread coverage in the national

and international media and the subsequent demand for acupuncture treatment by infertility patients worldwide has escalated.

Interestingly, the investigators of this study conducted a subsequent study using the same protocol as the first study but instead of having the control group lie quietly for an equivalent amount of time, the control subjects received placebo acupuncture (3). The PR for the real acupuncture patients was 43% and for the placebo patients it was 37% ($P=.39$). They proposed that the placebo needles might have induced an “acupressure effect,” thus leading to a higher PR in those patients. They did not otherwise address the lack of significance between the two groups. This study is in abstract form but has not been published as an article.

Since that time several more randomized, controlled, prospective studies have been published (4–6), all of which have shown higher PRs in women who received acupuncture during their IVF cycle. This effect was maintained even in the studies that used sham acupuncture (4, 5).

Thus, the mechanism for the potential positive impact of acupuncture on PRs in IVF patients remains unclear. It is possible that the effect is caused by the placebo effect on the part of the patient, the health care team, or a combination of the two.

The purpose of this study was to replicate the original Paulus study and to assess the potential contribution of a placebo

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effect on the part of the patient, but to control for the placebo effect on the part of the health care team.

MATERIALS AND METHODS

Setting and Design

This prospective randomized trial was conducted at Boston IVF, a large private academically affiliated fertility clinic in the Boston area, from January to June 2006. During that time all patients who were scheduled to have a fresh embryo transfer on weekends using nondonor eggs were invited to participate. A brochure describing the study was distributed to all potentially eligible patients before discharge after their oocyte retrieval. When patients were called by the IVF nurse coordinator to be informed of their fertilization rate and the time of their embryo transfer, they were asked whether they planned to participate in the study. Patients who responded affirmatively were asked to come to the clinic an hour earlier than patients not participating in the study.

This study received institutional review board (IRB) approval.

When eligible patients presented for the study, they were led into the recovery room and a curtain was drawn so that none of the nurses or physicians could see which group they were being randomized to. The acupuncturist (J.K.) explained the purpose and procedures and then each subject was asked to read and sign the informed consent form. Subjects then completed a demographic questionnaire, the Spielberger State Trait Anxiety Inventory (STAI) (7), and the Life Orientation Test-revised (LOT-R) (8). The STAI is the most widely used and reliable measure of both state and trait anxiety. The LOT-R was developed to assess individual differences in optimism and pessimism.

Randomization was accomplished by using a computer-generated random numbers table. Each acupuncture subject received 25 minutes of acupuncture with the same 22-needle protocol as the one described in the original Paulus study (2). These points were chosen for their sedative effect as well as to increase uterine blood flow. The control subjects lay quietly for 25 minutes. Each subject was asked to not reveal their group assignment to the nurses or to the physician performing the embryo transfer, although in a few cases, one of the recovery room nurses came into the curtained area and was able to see if the patient was receiving acupuncture or not. However, for the majority of cases, this did not happen. After embryo transfer, each subject had another identical 25-minute session. A nurse who was blind to subject assignment collected the postprocedure forms from each subject: the STAI-State and several questions designed for this study to assess optimism and opinion of their sessions (Table 1).

The PR data were obtained from each subject's electronic medical record by the study research assistant (I.M.). The accuracy of these data was double checked by another research assistant who was blind to subject assignment. The

STAI and LOT-R were hand-scored by a study research assistant and approximately 20% were randomly chosen to be double checked by yet another research assistant. All hand-scoring was performed by individuals who were blind to group assignment.

Pregnancy was noted if the β -hCG was more than 15 IU 11 days after embryo transfer. Clinical pregnancy was defined as the presence of at least one normal gestational sac with a fetal heartbeat.

Statistical Methods

The χ^2 test was used to compare qualitative variables and Student's *t*-test, to compare quantitative variables. The statistical package SPSS (SPSS, Inc., Chicago, IL) was used for this analysis.

RESULTS

A total of 150 women were recruited into the study and each read and signed the informed consent form. Four of these patients did not proceed with the study for various reasons (embryo transfer cancelled, patient changed her mind, not enough time to complete session before embryo transfer), leaving 146 subjects in the study. Seventy-eight were randomized into the acupuncture group and 68 to the control group.

There were no significant differences before randomization between the two groups for any of the variables studied (Table 2).

There were no significant differences between the two groups on β -hCG or clinical PRs. The acupuncture subjects had a 50.0% positive β -hCG test compared to a 42.6% rate in the control group ($P=.47$) and a 30.8% ultrasound-confirmed clinical PR compared to a 33.8% rate in the controls ($P=.69$). The chemical pregnancy (loss) rate (positive β -hCG but no ultrasound-confirmed clinical pregnancy) did not differ significantly between the two groups as well.

Because the Paulus study used only subjects with good quality embryos, a separate analysis was performed on subjects who had at least one good quality embryo transferred. The acupuncture patients in this subgroup had a 42% clinical PR and the control subjects had a 47% rate (P =not significant [NS]).

The acupuncture patients reported significantly less anxiety after embryo transfer than the control subjects, enjoyed their sessions more, and felt more relaxed (Table 3). The acupuncture patients reported feeling significantly more optimistic about their chance for conception, but not to feel more confident about the outcome. It is interesting to note that subjects in general were highly confident that their cycle would be successful. The average subject predicted her chance of success in the 50%–60% range, which, in fact, was twice the actual rate for this sample.

TABLE 1**Post-embryo transfer optimism assessment questions. (all scored from 1–5)**

Question 1: What did you think of your 25 minute sessions? 1—liked them very much 5—hated them	4—30%-40%
Question 2: How relaxed did you feel during the sessions? 1—totally relaxed 5—not relaxed at all	3—20%-30%
Question 3: How optimistic do you feel about the outcome of this cycle? 1—very optimistic 5—not optimistic at all	7—60%-70%
Question 4: How confident do you feel that you will get pregnant this cycle? 1—very confident 5—not confident at all	8—70%-80%
Question 5: What do you think your chance is of getting pregnant? 1—0-10% 5—40%-50%	3—20%-30%
9—80%-90%	7—60%-70%

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TABLE 2**Group characteristics before randomization.^a**

	Acupuncture	Control
Age (y)	36.1	36.1
Previous IVF cycles	2.26	2.97
No. of oocytes retrieved	9.08	10.94
No. of embryos transferred	2.50	2.53
STAI-State	37.63	38.82
STAI-Trait	35.68	36.99
LOT	27.09	27.50

Note: LOT = Life Orientation Test; STAI = Spielberger Trait Anxiety Inventory.

^a All $P > .05$.

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DISCUSSION

The results from this study differ from previous research. All four randomized, controlled, prospective, published studies (2, 4–6) demonstrated higher PRs in the acupuncture group than in the control group. In one study (5), the differences did not reach statistical significance, although the odds ratio for the acupuncture subjects to achieve pregnancy were 1.5 times higher than in the control group. The actual needling protocols differed among the published studies and thus it is difficult to interpret the potential mechanisms for action. Possible causal explanations include a placebo effect on the part of the patient leading to an increased sense of relaxation and optimism that somehow increased implantation rates.

The goal of this study was to replicate the original Paulus protocol and to investigate the potential of a placebo effect. It was theorized that the acupuncture patients would have significantly higher PRs than the control subjects and that this difference could be attributed to a placebo effect on the part of the subject. It was hypothesized that the acupuncture subjects, who were not blind to subject assignment, would report far higher rates of optimism and confidence that their cycle would be successful.

TABLE 3**Psychological results between the two groups after embryo transfer.**

STAI-State	28.22	31.69	0.015
Question 1	1.63	1.99	0.016
Question 2	1.79	2.06	0.055
Question 3	1.73	2.01	0.046
Question 4	1.97	2.19	0.125
Question 5	6.26	6.26	0.990

Note: STAI = Spielberger Trait Anxiety Inventory.

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This was not the case. There were no significant differences between the two groups in PRs, thus eliminating the possibility that a placebo effect on the part of the patient led to improved outcomes. Although the acupuncture patients did report an increased sense of relaxation and reported feeling more optimistic on some of the measures, this did not have an impact on pregnancy outcomes.

How then can one explain the different results between this study and the prior ones?

There was one difference between this study and prior ones. In this study, the entire medical team (nurses in the recovery room, nurses in the operating room, and the physician performing the embryo transfer) was blinded to patient assignment. This differs from previous research. In both the Paulus and Dieterle studies (2, 4), the physician performing the embryo transfer was blind but the remainder of the healthcare team was apparently not. There was no information on staff blinding in the Smith study (5) and in the Westergaard study (6), blinding could not have taken place as the actual acupuncture sessions were conducted by the clinic nurses themselves. Thus it is possible that there could have been a placebo effect on the part of members of the healthcare team. This is somewhat doubtful, as one would think that the member of the team who has the greatest potential impact on the results of the embryo transfer would be the physician and this was controlled for in at least two of the studies.

It is also possible that acupuncture as an intervention has the most potential to be effective in patients with good quality embryos. Previous research has included mostly patients with good quality embryos. However, separately analyzing the subjects with good quality embryos did not reveal any differences in this study.

It is also possible that the acupuncture sessions themselves could differ in some way. However, the acupuncturist in this study (J.K.) has extensive clinical experience, needling points are consistent across the world, and he used the exact points as in the original Paulus study. The fact that the Westergaard study demonstrated statistically significant differences

between the groups despite the use of briefly trained nurses in the administration of acupuncture contradicts this theory as well.

There does not seem to be any readily available explanation for the contradictory results of this study. It is notable that this is the first study from the United States and perhaps there is something to the expectations or care that differs.

Further research in this area is needed to determine whether acupuncture can and should be used as a successful adjunct to traditional medical treatment with patients undergoing IVF.

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