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The relationship between perceived stress, acupuncture, and pregnancy rates among IVF patients: a pilot study

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Abstract

The aim of this paper was to determine the effect of acupuncture on perceived stress levels in women on the day of embryo transfer (ET), and to determine if perceived stress levels at embryo transfer correlated with pregnancy rates. The study was an observational, prospective, cohort study based at the University IVF center.

Patient(s)—57 infertile patients undergoing IVF or IVF/ICSI

Interventions(s)—Patients were undergoing Embryo Transfer with or without acupuncture as part of their standard clinical care

Main outcome measure(s)—Perceive Stress Scale scores, pregnancy rates

Result(s)—women who received this acupuncture regimen achieved pregnancy 64.7%, whereas those without acupuncture achieved pregnancy 42.5%. When stratified by donor recipient status, only non-donor recipients potentially had an improvement with acupuncture (35.5% without acupuncture vs. 55.6% with acupuncture). Those who received this acupuncture regimen had lower stress scores both pre-ET and post-ET compared to those who did not. Those with decreased their perceived stress scores compared to baseline had higher pregnancy rates than those who did not demonstrate this decrease, regardless of acupuncture status.

Conclusions(s)—The acupuncture regimen was associated with less stress both before and after embryo transfer, and it possibly improved pregnancy rates. Lower perceived stress at the time of embryo transfer may play a role in an improved pregnancy rate.

Keywords

Acupuncture; infertility; perceived stress

Introduction

Acupuncture is a therapy of inserting, manipulating and retaining very fine needles in specific "acupoints". It appears to be helpful in improving the success rate of assisted reproductive techniques, although not all studies are positive [1–5]. A recent systematic review and meta-analysis concluded that preliminary evidence suggests a role for acupuncture in infertility[6]. The mechanisms by which acupuncture affects pregnancy rates are not known.

Currently at our institution (Magee-Womens Hospital), women are given the option to undergo acupuncture at the time of embryo transfer and/or earlier during the IVF cycle, and patients either self-select acupuncture or they self-select to not have acupuncture. In this pilot study, we compare subjects undergoing embryo transfer without acupuncture to those who have embryo transfer in conjunction with acupuncture to evaluate whether acupuncture improves stress levels, and whether either acupuncture or stress levels are associated with improved pregnancy rates.

The Perceived Stress Scale, which is a 10-item questionnaire is a valid and reliable tool that measures the degree to which situations in one's life are appraised as stressful[7]. The PSS is sensitive to both stress from expectations concerning future events and to chronic stress deriving from ongoing life circumstances, both of which are potentially relevant for the IVF population. We hypothesized that an increased perception of stress at the time of embryo transfer could lead to lower IVF success rates, potentially through a sympathetic activation pathway, although the mechanism was not specifically studied in this pilot study.

Stress and anxiety are very common in infertility patients, especially those undergoing IVF8. Anxiety and depression are considered causes of early drop-out after the first IVF cycle and are related to lower pregnancy rates 9–11. Acute and chronic stress in patients undergoing assisted reproduction affects biologic end points (i.e. number of oocytes retrieved and fertilized), as well as pregnancy, live birth delivery, birth weight and multiple gestations[12, 13]. Thus, reducing stress and anxiety can be helpful in IVF patients. True acupuncture decreases anxiety levels when compared to sham acupuncture14, {Kober, 2003 #38}.

We aimed to determine if acupuncture affects the levels of perceived stress at the time of embryo transfer, and whether either acupuncture or changes in stress levels play a role in the success rate in IVF. We chose to measure stress levels at the time of embryo transfer for several reasons. We postulated that reducing stress at the time of embryo transfer could result in less vasoconstriction and improved uterine receptivity. Embryo transfer data collection was logistically feasible; in addition, because all participants were receiving the same embryo transfer procedure, the study groups were fairly homogenous, with one key difference between groups being whether or not acupuncture was performed. To keep the group receiving acupuncture homogenous, the protocol used for all acupuncture patients was the same, that described by Paulus, which involves acupuncture before and after embryo transfer, on the day of embryo transfer[1]. This same protocol was found to improve pregnancy rates in a later study by a different investigator[15]. We chose this protocol because we have found, both within the University of Pittsburgh, and in the community, this is the common acupuncture approach used in conjunction with embryo transfer. Paulus notes that he chose the points based on "acupuncture points that relax the uterus according to the principles of TCM."

Materials and methods

This study was an observational prospective cohort study comparing stress levels of In Vitro Fertilization (IVF) patients either receiving acupuncture or not receiving acupuncture on the day of their embryo transfer. The inclusion criteria were that the subjects were receiving an embryo transfer in the Reproductive Endocrinology and Infertility (REI) office at Magee-Womens Hospital of the University of Pittsburgh Medical Center. The only exclusion criterion was that gestational carriers, ie surrogates, were not enrolled. All acupuncture was conducted by a physician acupuncturist and licensed in the state of Pennsylvania. The study was approved by the University of Pittsburgh Institutional Review Board prior to initiating the study. Study procedures conform to the Declaration of Helsinki for Medical Research involving Human Subjects.

A total of 57 subjects were recruited for this study. The REI nurses and physicians approached patients regarding the study upon arrival to the office on the day of the ET. When patients agreed to participate, they signed an informed consent form prior to initiation of any study procedures. The nurses and physicians explained that the study involved completing a 10-item questionnaire twice, once before ET and once after ET. All patients undergoing ET were eligible with the exception of gestational carriers. As part of each patient's IVF protocol, patients self- selected into the acupuncture group or to the non-acupuncture group prior to the day of ET. There were no attempts to manipulate either the self-selection of acupuncture or the IVF protocols as part of this research study.

After informed consent was signed, the patient was given the Perceived Stress Scale[7] to fill out. Those patients in the acupuncture group completed the Perceived Stress Scale (PSS), and then had acupuncture for 25 minutes before undergoing embryo transfer. The acupuncture regimen used in this study is described in Paulus et al, 2002[1]. Those patients in the non-acupuncture group completed the Perceived Stress Scale and then rested for 25 minutes prior to embryo transfer. All patients underwent embryo transfer using their physician's standard procedure.

Once embryo transfers were completed, patients returned to the recovery room. After emptying their bladders, they either received 25 more minutes of acupuncture according to the Paulus protocol[1] followed by completion of the PSS, or they were given the PSS to complete if they were not receiving acupuncture. All patients were at bedrest for 30 minutes after ET. Once the questionnaire was completed it was returned to the nurse and placed in an envelope marked with the patient's study number and placed with her previously completed stress scale and informed consent. These were kept in a locked file cabinet.

Statistical analysis

The primary outcome variable is the change in stress level before and after embryo transfer, as measured by the perceived stress scale (PSS), described in Cohen et al, 1983[7]. A change of 7.5 on the PSS is considered to be clinically significant. Our sample size analysis determined that with an alpha of 0.05 and a beta of .2 (80% power), we needed twenty subjects in each group to detect this level of change. In order to recruit both acupuncture and non-acupuncture patients during the same time period, without specifically selecting for the acupuncture group, we enrolled subjects until we had 20 subjects in the acupuncture group. To enroll 20 acupuncture subjects, we projected that roughly 35 non-acupuncture subjects would need to be enrolled, for a total enrollment of approximately 55. We stopped enrollment when 20 acupuncture subjects were enrolled, regardless of the number of control subjects.

We defined good quality embryos as those that were 6cell, grade A, and better, as determined by the embryologists' standard clinical practice. Poor prognosis embryos were those that were

6B or worse. Endometrial lining thickness was the last ultrasound measurement prior to embryo transfer. All transfers were on day 3.

Differences in the mean score for the Perceived Stress Scale in each group (acupuncture and non-acupuncture) before and after embryo transfer were evaluated using paired t-tests. The chi-squared test was used to evaluate the pregnancy rates between the two groups. Pearson correlation coefficients were used to compare continuous variables, such as the relationship between age and stress scores. We used a t-test to compare stress levels between those who achieved pregnancy and those who did not, and multivariate logistic regression was used to evaluate the relation between acupuncture and stress to pregnancy rates independent of relevant covariates.

Results

A total of 57 women were included in the study. Two women had more than one embryo transfer; we included only the cycle with acupuncture or the last cycle if all were conducted with acupuncture. The characteristics of the subject population are displayed in Table I.

Women with acupuncture tended to be older compared to women with no acupuncture. They were more likely to have had donor eggs transferred which, as expected, tended to be of better quality. Women with acupuncture at the time of embryo transfer had lower levels of perceived stress before and after acupuncture compared to women with no acupuncture. Both groups had less perceived stress after embryo transfer, but there was no difference in the mean change in scores between the two groups (p=0.66) nor in the likelihood of having a reduction in stress >= 2 points (p=0.76). Age was the only factor that was significantly correlated with the mean change in perceived stress scores (r=−0.28, p=0.04), as shown in Figure I. In these data, stress levels decreased as maternal age increased. Differences in stress according to acupuncture group, however, were unchanged when adjusted for maternal age.

Overall, 28 women (49.1%) achieved pregnancy following embryo transfer. Women with acupuncture tended to achieve pregnancy more often compared to women without acupuncture (64.7% vs. 42.5%, p=0.13). There was no difference, however, in the change in perceived stress among women who did and did not achieve pregnancy (−0.93 vs. −0.45, p=0.52). However, women with perceived stress scores that were reduced by 2 or more points compared to baseline (21% of the study group) had higher pregnancy rates than those with more modest reductions or increases in perceived stress (75.0% vs. 42.2%, p=0.04). Although precision was compromised when results were stratified by donor egg status, the effect of acupuncture on pregnancy rates appeared to be limited to those without donor eggs (35.5% without acupuncture vs. 55.6% with acupuncture, p=0.28; Table 2). In addition, stress reduction in women with or without acupuncture was not different according to donor egg status.

Acupuncture was associated with a 3.0 fold increased rate of pregnancy (95% CI 0.8, 8.0). Although estimates were quite imprecise due to limited sample size, this relation appeared to be independent of embryo quality, uterine lining thickness, maternal age and changes in perceived stress measured before and after embryo transfer (OR 3.4, 95% CI 0.6, 18.6).

Discussion

Overall, our study confirms that the chosen acupuncture regimen appears to increase pregnancy rates in IVF patients. When we model the relationship of this acupuncture regimen to pregnancy success, women with acupuncture were 3.0-times more likely to become pregnant. However, the confidence interval is extremely large and overlaps 1 CI (0.5–17.9). One commonly reported action of acupuncture is stress reduction. Given that a stress response causes vasoconstriction[16], which could acutely decrease uterine perfusion, it seems plausible that

excessive stress on the day of embryo transfer could lower pregnancy rates. It also seems that techniques that elicit the relaxation response, leading to vasodilation, at the time of ET could improve pregnancy rates. Future studies could evaluate other relaxation techniques at the time of embryo transfer.

Those who received this protocol of acupuncture had both higher rates of pregnancy, and lower levels of stress both before and after embryo transfer. The vast majority of acupuncture patients had been receiving acupuncture prior to the day of ET, which could explain why the pre-ET stress scores were lower. However, the particular acupuncture protocol we used in this study did not seem to lower stress scores significantly from before embryo transfer to after embryo transfer. Therefore, the mechanism by which pregnancies were increased with this protocol remains unknown. Because this is not an attention-controlled study, it is possible that merely having the attention from acupuncture, rather than the actual acupuncture, resulted in lower stress scores. Based on the results of this study, it would be interesting to try new acupuncture protocols targeted at reducing stress levels at the time of ET.

When subjects in either group had a significant reduction in stress from before the embryo transfer to after it, pregnancy rates increased. It is possible that those who had a reduction in perceived stress scores had that reduction because they had excellent quality embryos, whereas those who had increased stress did so because they were less optimistic about their outcome. Thus, the decrease in stress could have occurred because the chances of pregnancy were higher, not that the decrease in stress resulted in higher pregnancy rates. However, when we examined this, embryo quality was not related to the change in stress scores ($p=0.78$), the pretest scores ($p=0.97$), or the post-test scores ($p=0.91$).

One limitation to this study is that it is small, with only 57 subjects. Previous studies have indicated that acupuncture improves pregnancy rates; however, the selection bias for acupuncture is unknown. If poor prognosis patients tend to choose acupuncture, then an improvement in pregnancy rates is very important. If good prognosis patients choose acupuncture, then a high pregnancy rate is less impressive. We found that donor oocyte recipients were more likely to choose acupuncture when compared with non-donor oocyte patients. We believe this is due to our clinical donor program, where the patients have a one-on-one relationship with the donor coordinator, and are more likely to hear all the options available to them.

Another major limitation is that this study is not-randomized, blinded, or placebo-controlled. Given the large financial and emotional investment in IVF, it is difficult to recruit for a randomized, placebo-controlled trial. Lack of a placebo arm means that this study is testing the whole acupuncture regimen, not just needling of the specific points. Also, while the measurement of the stress scores was prospective, the chart review for the variables was retrospective. Thus, some variables, such as the use of ICSI, was not collected prospectively and was difficult to obtain reliably from a clinical chart review. Another weakness of the study is that we did not control for the amount of acupuncture that the subjects received prior to the day of ET. Some received it only on the day of ET, whereas others had multiple sessions of acupuncture. This study is too small to determine a dose-response relationship, but future studies should explore this possibility. Lastly, the acupuncture protocol used was the Paulus protocol, and it was the same used for all subjects. It is possible that individualizing acupuncture, rather than using a formulaic approach, would lead to different results. We chose this protocol because it is commonly used on the day of ET, and when modifications are made to this protocol with respect to point selection or timing of acupuncture, or the protocol is individualized based on TCM diagnosis, the results appear to be less positive than using the Paulus protocol[5, 15, 17]. Our results only refer to the acupuncture regimen chosen; other acupuncture regimens might have different results.

Although more involved questionnaires might be useful to provide additional information, we chose a short, validated questionnaire to have minimal burden on the subject and the healthcare team. This study did not have a funded research recruiter, so we needed to be able to enroll subjects with minimal disruption to clinical care. Future studies could investigate serial cortisol concentrations, anxiety measurements, and measurements of autonomic function, such as heart rate variability.

One of the strengths of this study is that it is innovative. It is the first study to investigate the effects of acupuncture on perceived stress at time of ET, and we believe it is the first study to investigate the effects of perceived stress at the time of ET on pregnancy rates. In addition, our study assessed subjects based on what is done in clinical care, where some patients choose acupuncture and others do not, although the acupuncture regimen in clinical care is not uniform for all subjects, as it was in this study.

Finally, even with our small sample size, we were able to demonstrate that acupuncture was associated with less stress both before and after embryo transfer, and that acupuncture may improve pregnancy rates. It is possible that lower perceived stress at the time of embryo transfer may plan a role in an improved pregnancy rate. Future studies should investigate a dose-response relationship, mechanisms of action, and the types of biases and directions of the biases that may confound the relationship between acupuncture and pregnancy success.

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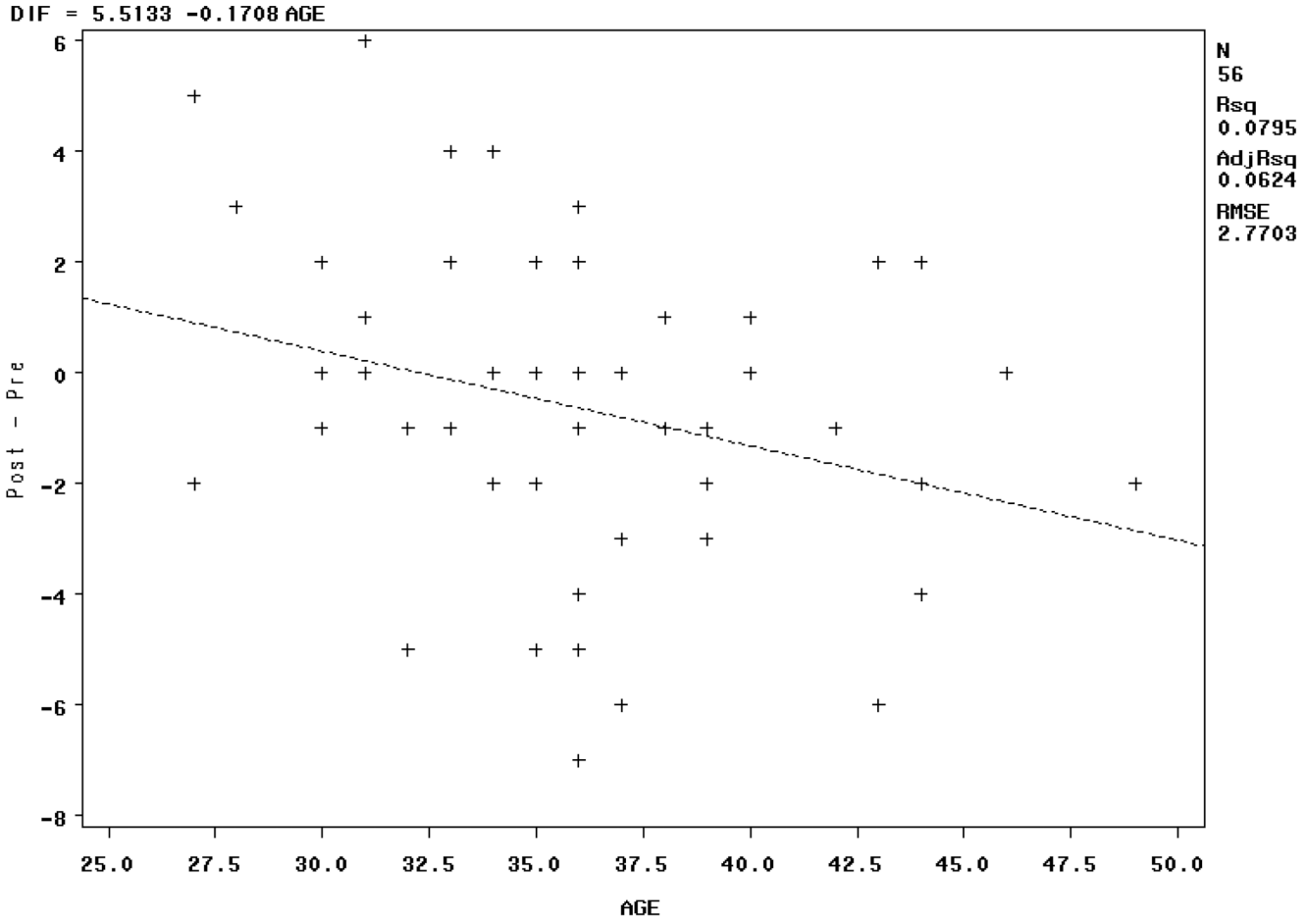

Figure I.
Relationship between change in stress score and age (r=−0.28, p=0.04)

Table 1

Characteristics of women with and without acupuncture, mean (SD) or n (percent)

	No acupuncture (n=40)	Acupuncture (n=17)	p-value[a]
Age (years)	35.8 (4.4)	37.5 (5.4)	0.21
Failed cycles (no.)	1.6 (1.7)	1.8 (1.2)	0.70
Uterine lining	11.0 (3.1)	9.9 (2.8)	0.20
Nulliparous	27 (67.5)	9 (52.9)	0.29
Good embryo quality	19 (47.5)	12 (75.0)	0.06
Donor egg	9 (22.5)	8 (47.1)	0.06
Number of embryos transferred	2.6 (0.7)	2.4 (0.9)	0.43
Pregnant	17 (42.5)	11 (64.7)	0.13
Stress pre-test	17.3 (6.3)	13.2 (3.6)	0.01
Stress post-test	16.7 (6.6)	12.4 (5.2)	0.02
Stress test difference (post-pre)	−0.56 (2.8)	−0.94 (3.1)	0.66
Stress reduction ≥ 2 points	8 (20.0)	4 (23.5)	0.76

[a] T test or chi square test

Table 2

Pregnancy rates and stress reduction among women with and without acupuncture, stratified by donor egg status

	No acupuncture	Acupuncture	p-value*
No donor egg (n=40)			
Achieved pregnancy	11/31 (35.5)	5/9 (55.6)	0.28
Stress reduction >=2	5/31 (16.1)	2/9 (22.2)	0.67
Donor egg (n=17)			
Achieved pregnancy	6/9 (66.7)	6/8 (75.0)	0.71
Stress reduction >=2	3/9 (33.3)	2/8 (25.0)	0.71

* chi square