



Research Article

Effect of Acupuncture on Psychological Well-Being, Vascular Biomarkers and Pregnancy Outcomes in Women Undergoing IVF

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Citation: Jackson BT, Huang JC, Orlando J, Zhang Y, Garos S, et al. (2022) Effect of Acupuncture on Psychological Well-Being, Vascular Biomarkers and Pregnancy Outcomes in Women Undergoing IVF. J Community Med Public Health 6: 272. DOI: 10.29011/2577-2228.100272

Received Date: 18 November, 2022; **Accepted Date:** 30 November, 2022; **Published Date:** 05 December, 2022

Abstract

Objective: The objectives of this pilot study were (1) to assess the impact of acupuncture on the psychological well-being of women undergoing IVF, (2) to determine the effects of acupuncture on tissue perfusion using vascular tone (represented as the ratio of urinary prostacyclin to thromboxane), and (3) to assess pregnancy outcomes in women receiving acupuncture versus controls. **Design:** Prospective, Randomized Controlled Trial. **Setting:** Academic fertility center. **Patient(s):** Sixty women undergoing IVF. **Intervention(s):** Subjects were randomized to either the acupuncture or control group. The acupuncture group received three acupuncture sessions (one during ovarian stimulation, one pre-embryo transfer and one post-embryo transfer). The control group received standard care. Participants completed standardized self-perceived stress questionnaires and provided urine samples at the three time points. **Main Outcome Measure(s):** Self-perceived stress levels, urinary prostacyclin and thromboxane, pregnancy outcomes. **Result(s):** There were no significant differences in self-perceived stress levels, urinary prostacyclin, urinary thromboxane or pregnancy outcomes between groups. **Conclusion(s):** Acupuncture did not affect the stress levels, urinary vascular biomarkers or pregnancy outcomes in patients undergoing IVF.

Keywords: IVF; Acupuncture; Prostacyclin; Thromboxane; Stress

Introduction

Patients undergoing treatment for infertility often seek benefits from complementary and alternative medicine such as acupuncture [1]. Clinical studies observing the use of acupuncture in patients undergoing IVF have shown mixed results, and only a few are conducted as randomized, controlled trials [2,3]. However

meta-analysis studies conclude that a therapeutic effect does exist, but that further investigation is needed to elucidate a mechanism of action [4]. For patients noting positive results and improved success after IVF the mechanism of action is usually of little concern, however the ability to isolate the effect would be of great clinical use. Finding the correct experimental parameters to isolate this effect have proven difficult. Not only is the primary mode of therapy not known (psychological, stress reduction, vascular effect, etc.), but the addition of compounding variables, such as the use of 'sham acupuncture' in control groups to replicate

perceived placebo effects, may further confuse the interpretation of the effects of acupuncture on IVF outcomes by replicating some psychological effects of treatment [5]. These variables make the perceived effects of treatment impossible to compare to a true control group and the ability to begin and isolate the effects much more difficult. This study attempts to elaborate the efficacious effects reported by IVF patients undergoing acupuncture with a combination of vascular biomarkers, psychological well-being questionnaires, and recording IVF success.

Several proposed mechanisms by which acupuncture may benefit women undergoing IVF include reduced stress levels, reduced perceived pain, or increased perfusion to the pelvic organs [5-7]. Prostacyclin (PGI₂), a member of the eicosanoid family of prostaglandins produced by vascular epithelium, inhibits platelet activation and induces vasodilation [8]. Thromboxane A₂ (TXA₂) is a hormone released from platelets that induces platelet aggregation and arterial constriction. Both signaling molecules are formed from products of COX-1/2 oxygenation of arachidonic acid, and therefore produced upon interaction of platelets with vascular endothelium. Under physiological concentrations of lipid peroxides, PGI₂ synthase activity is high enough as to repel platelets from the lumen of the vessel. However, under low concentrations of lipid peroxides, PGI₂ is irreversibly inhibited, causing platelets to stick to the vascular lumen, TXA₂ to be generated, and thrombi to form. The balance between prostacyclin and thromboxane production has been proposed as an important indicator of circulating lipid epoxide levels, tissue perfusion, and normal circulation [9]. These markers can be easily tracked using urinary metabolites such as 6-k-PGF₁α for PGI₂ and Tx B₂ for TXA₂.

Many PCOS patients report the IVF process to be one of the more stressful events in their lives, requiring both a large time and resource commitment. Stress can have a negative impact on the patient's health and wellbeing. This can be exacerbated by any chronic stressors the patient may have, which have been shown to lead to decreased oocyte formation, collection, and pregnancy success during IVF treatment [10]. The fourteen-item Perceived Stress Scale (PSS) questionnaire was designed to reliably record stress experienced from life events, social anxieties, and chronic disease and accurately predict negative symptomatic outcomes [11]. This made it a great choice in attempting to record how all the various life stressors presented from IVF treatment affected the patient and what therapeutic impact acupuncture may have.

The objectives of this pilot study were 1) to assess the impact of acupuncture on the psychological wellbeing of women undergoing IVF treatment, 2) to determine the effects of acupuncture on tissue perfusion using vascular tone (represented as the ratio of urinary 6-k-PGF₁α to TxB₂) as a surrogate, and 3) to compare pregnancy outcomes in women receiving IVF versus

controls using a Delphi consensus acupuncture treatment protocol developed by the investigators [12].

Materials and Methods

Setting and Design

The study was conducted at the Center for Fertility and Reproductive Surgery at Texas Tech University Health Sciences Center (Lubbock, TX). Following Institutional Review Board (IRB) approval, women who were eligible for the study were invited to participate. After obtaining appropriate consent, study participants were randomized to a computer-generated assigned treatment group kept in numbered, sealed envelopes.

Protocol

Sixty women, ages 21 to 42 years, who were seeking *In-Vitro* Fertilization and Embryo Transfer (IVF-ET) were enrolled the study. Women were excluded if they were currently using alternative therapies such as acupuncture, meditation, herbal supplements or had a contraindication to needle insertion (such as psoriasis, neuropathy or coagulopathies) at the established acupoints. Fifty participants were enrolled and were randomized by computer to either treatment or control.

Those assigned to the treatment group received three sessions of acupuncture during the IVF-ET process; those in the control group received standard IVF treatment. The three sessions of acupuncture occurred on day 6, 7 or 8 of gonadotropin stimulation, and pre- and post-embryo transfer. At each of the above time points, all participants completed a 10-question validated self-perceived stress questionnaire prior to each acupuncture session and provided urine samples for the determination of 6-keto prostaglandin F₁α (6-k-PGF₁α, a stable metabolite of prostacyclin, PGI₂) and thromboxane B₂ (TxB₂, a stable metabolite of thromboxane A₂).

Acupuncture was performed by one clinician following a protocol adapted from a Delphi Consensus process developed specifically for patients undergoing IVF [12]. Three semi-standardized sessions of manual acupuncture treatment were administered during the IVF cycle. Each session was conducted at the Center for Fertility and Reproductive Surgery clinic and lasted approximately 30 minutes. The detailed protocol is published elsewhere [12].

The first acupuncture treatment session included core points ST29 bilateral, CV4, CV6, SP6 bilateral, SP10 bilateral, and 5 de-stressed points (LI11, LU4, LI4, HT7 and ST36 unilateral, Figure 1) adapted from the clinical set points protocol of Miriam Lee, a pioneer of acupuncturists in the United States [13]. This 13-point session was administered between days 6 and 8 of gonadotropin stimulation of the IVF cycle.

The second acupuncture treatment session included points

SP8 bilateral, SP10 bilateral, LR3 bilateral, ST29 bilateral, CV4, one selected from HT7/PC6/ EX-HN3 (depending on symptom presentation of the patient), and auricular acupuncture points Shenmen and Zigong (left side). This 12-point session was performed on the day of embryo transfer (at least 1 hour prior to the transfer). Needling sensation, *De qi*, is a composite of unique sensations interpreted as the flow of Qi or 'the arrival of vital energy' and was elicited during the first and second acupuncture sessions. Eliciting methods include local point rubbing before the needle insertion and/or needle rotation after needle insertion. Either the patient's description of *suau* (aching or soreness), *ma* (numbness or tingling), *zhang* (fullness, distention, or pressure), and *zhong* (heaviness) or the acupuncturist's feeling of needle grasping as tense, tight, and full at the needling region was considered as *De qi* [14]. No other stimulation was elicited during needle retention.

The third acupuncture treatment session included GV20, KI3 bilateral, ST36 bilateral, SP6 bilateral, PC6 bilateral and auricular acupuncture points Shenmen and Zigong (right side). This 11-point session was performed within 48 h post-embryo transfer. Main points are shown in Figure 1, and all points were located based on the WHO Standard Acupuncture Point Locations 2008 [15]. Disposable stainless-steel acupuncture needles (0.16 × 15 mm, 0.18 × 30 mm and 0.20 × 40 mm, DBC Spring Ten, Korea) were used. Needles were inserted manually to a depth varying from 10 ± 5 mm to 25 ± 5 mm at the acupoints depending on the location and patient's physical figure. Needle retention time was approximately 25 min. A laminated acupuncture protocol describing the timing and acupoints for each session was stored with all acupuncture equipment so the acupuncturist could check and ensure consistency and accuracy during each treatment.

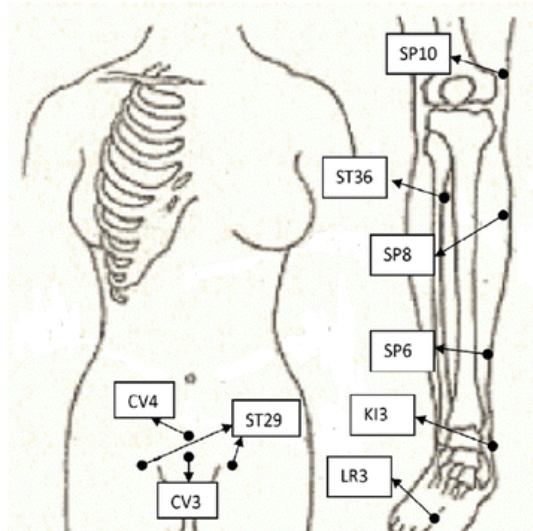


Figure 1: Main body acupoints used in acupuncture protocol [10].

The 6-k-PGF₁α (Urinary Prostacyclin Elisa, ENZO Life Sciences, Farmingdale, NY) and TxB₂ (11-dehydro Thromboxane B₂ Elisa Kit – Monoclonal; Cayman Chemical, Ann Arbor, MI) in the urine were determined using ELISA kits according to the manufacturer's protocol with samples run in duplicate. Standards and controls were also run in duplicate on each day the assay was performed. The vascular tone (expressed as the ratio of 6-k-PGF₁α to TxB₂) was used as a surrogate for tissue perfusion.

The stress levels were analyzed using a standardized global measure of perceived stress test [11]. Pregnancy outcomes observed included positive blood pregnancy test, singleton gestation, twin gestation or early pregnancy loss. (NCT02591186)

Statistical Methods

A 2 × 2 repeated-measures Analysis of Variance (ANOVA) was used to compare stress levels between groups (acupuncture vs. control) and across time points (visit 1 vs. visit 2 vs. visit 3). Spearman's rho correlation coefficients were used to assess the association between stress scores and the Prostacyclin to Thromboxane ratio (P/T ratio) at each visit. A repeated-measures ANOVA was used to compare Prostacyclin to Thromboxane ratio between groups (acupuncture vs. control), chronic effect across time points (visit 1 vs. visit 2 vs. visit 3), and acute effect within sessions (pre vs. post). Bonferroni-adjusted pairwise comparisons were used to assess simple effects as appropriate. Pregnancy outcomes between the two groups were determined using Chi-square test for pregnancy status and Mantel-Haenszel Chi-square test for pregnancy outcomes. Significance level was set at 0.05 for all comparisons.

Results

Sixty women were enrolled in the study. Sixty women completed self-perceived stress questionnaires. Twenty-nine participants were randomized to the acupuncture group; 31 were randomized to the control group. Forty-five participants were included in the analytic sample (25 in the acupuncture group, 20 in the control group). Fifteen participants did not complete the study due to cancellation of the embryo transfer, patient choice or lack of one or more key personnel to complete the protocol. There was no significant difference in mean age of the acupuncture group (32 years; range 24-39 years) versus the control group (34 years; range 22-41). Reported race was similar between the acupuncture group (23 white, 4 Hispanic, 1 black, 1 other) and the control group (26 white, 1 Hispanic, 1 black, 3 other).

Self-perceived stress

From the ANOVA results, there were no differences in stress between acupuncture or control groups [F(1,36)=0.50, p=0.484] nor between visits [F(2,72)=2.06, p=0.135], and there was no

significant interaction between both factors [$F(2,72)=1.50, p=0.229$] (Table 1).

	Acupuncture (n=21)	Control (n=17)
Stress		
Visit 1	2.32 (0.38)	2.21 (0.39)
Visit 2	2.27 (0.36)	2.14 (0.29)
Visit 3	2.11 (0.36)	2.17 (0.3)
P/T ratio		
Visit 1 Pre	2.37 (4.12)	2.68 (5.08)
Visit 1 Post	2.31 (2.92)	3.20 (6.11)
Visit 2 Pre	1.56 (1.94)	2.15 (3.91)
Visit 2 Post	2.43 (3.4)	1.70 (1.47)
Visit 3 Pre	2.38 (3.48)	1.42 (0.85)
Visit 3 Post	2.47 (3.77)	1.22 (0.56)
All values are mean (SD).		

Table 1: Stress scores and Prostacyclin to Thromboxane ratio (P/T ratio) at each visit.

Urinary Prostacyclin/Thromboxane ratio

No statistically significant correlations were found between P/T ratio and stress at any visit (Table 2). None of the ANOVA effects showed significant differences in P/T ratio and no significant interactions between factors were determined. No effect between treatments was found, $F(1,36)=0.04, p=0.840$. Time effect (visits) was not statistically significant, $F(2,72)=1.60, p=0.210$, and interaction between visit and treatment was not significant, $F(2,72)=1.66, p=0.197$. The acute effect of treatment (pre to post difference) on P/T ratio at each visit was not statistically significant for both control (visit 1: 0.527, $p=0.286$; visit 2: -0.447, $p=0.570$; visit 3: -0.194, $p=0.447$) and acupuncture (visit 1: -0.067, $p=0.879$; Visit 2: 0.87, $p=0.223$; visit 3: 0.091, $p=0.691$) groups.

	Acupuncture (n=21)		Control (n=17)	
	P/T ratio pre	P/T ratio post	P/T ratio pre	P/T ratio post
Stress at visit 1	0.15 (0.519)	0.21 (0.364)	-0.36 (0.154)	-0.32 (0.201)
Stress at visit 2	-0.10 (0.656)	0.06 (0.785)	-0.25 (0.337)	-0.15 (0.558)
Stress at visit 3	-0.16 (0.484)	-0.26 (0.256)	-0.11 (0.688)	-0.21 (0.418)
All values are Spearman's rho (p-value).				

Table 2: Correlations (Spearman's rho) between stress and Prostacyclin to Thromboxane ratio at each visit.

Pregnancy outcome

There was no statistically significant differences between the acupuncture and control groups for pregnancy status ($\chi^2= 0.16$, $p= 0.69$) or pregnancy outcomes ($\chi^2=0.72$, $p= 0.53$) (Table 3).

	Acupuncture	Control	p-value
Pregnancy status			0.69
Pregnant	11(44)	10(50)	
Not pregnant	14(56)	10(50)	
Pregnancy outcome			0.53
Singleton	6(24)	6(30)	
Twins	2(8)	3(15)	
Chemical loss	3(12)	1(5)	
Not pregnant	14(56)	10(50)	

Table 3: Pregnancy outcomes.

Discussion

The cost, emotional stress, and time commitment required to complete an IVF cycle drive many patients to seek alternative therapies to potentially increase the chance of success. Although acupuncture has been practiced for thousands of years, only recently has it become popular in Western medicine, and even more recently as adjuvant therapy in reproductive medicine. Mixed results from systematic reviews of acupuncture treatment in IVF have shown that it increases both clinical pregnancy and live birth rates, but that further studies are necessary to elucidate a mechanism of action and route of delivery for the effect [4].

The results of our pilot study showed no difference in self-perceived stress levels, urinary vascular biomarkers, or pregnancy outcomes between the acupuncture and control groups. These pregnancy outcomes are not reflective of the overall trend, however a further increase in sample size may correct for this issue. The lack of a significant shift in urinary vascular markers does not totally dismiss the argument for an increase in pelvic organ circulation, but it does show that perhaps the ratio of 6-k-PGF1 α to TxB2 plays less of a role than previously thought. Likewise, the lack of a significant shift in PSS scores does not totally dismiss any potential psychological benefit or reduced stress like those reported by individual IVF patients.

This study included many strengths including a prospective, randomized approach to correlate stress levels, urinary P/T, and pregnancy outcomes in women undergoing IVF. It also tried to eliminate unnecessary variables by ensuring all acupuncture treatments were performed by one qualified individual using a set

acupuncture routine, which provided a true control that did not undergo any false or 'sham' acupuncture.

Limitations of our study included a small sample size, limitations in methodology used, and a lack of individualization of acupuncture treatment for each patient. While a power analysis on the limited number of acupuncture studies would show that 60 patients is far too few to draw any definitive conclusions from, the results of this negative data and its application to fertility medicine specifically is clinically relevant. The use of urine metabolites to track increases in vascular perfusion of skeletal and uterine muscle has been criticized as being both questionable in its accuracy, and unspecific in its tracking of organ perfusion. The immunoassay to detect urine metabolites was rare and labs have little to no experience with it. Other more well established methods, such as 3D ultrasound with power doppler, could track uterine perfusion more accurately but were passed up on due to lack of resources for this pilot study [16]. Finally, while standardizing an acupuncture protocol is appealing for research purposes, many believe that individualization of acupuncture treatment is essential for maximum efficacy based upon the patient's specific symptoms and clinical findings. Occasionally, having only one individual performing the acupuncture was a limitation if this key personnel was not available.

The multifactorial nature of IVF outcomes makes study interpretation difficult, especially when it comes to tracking the efficacy of commonly non-traditional interventions such as acupuncture. And although efficacy has been reported among IVF patients, this study found that no therapeutic benefits were seen in either muscle perfusion, relative stress, or IVF outcomes. Seeing as how larger studies continue to produce an unknown therapeutic effect, additional studies and more advanced methodology, such as those listed previously, are needed to determine how such treatments benefit patients.

Acknowledgments

Financial Support

Laura W. Bush Institute for Women's Health and University Medical Center. This study was supported in part by the Texas Tech University Health Sciences Center, Clinical Research Institute.

Accepted for Poster Presentation: Phy JL, Zhang Y, Orlando J, Prien SD, Penrose L, Garos S, Huang J. Poster, IVF Pregnancy Rates in Women Undergoing Acupuncture vs. Controls, American Society for Reproductive Medicine, Philadelphia, PA, October 2019.

Acupuncture Protocol Design (Not including data) was published by the authors: Zhang Y, Phy JL, Orlando J, Garos S, Penrose L, Prien SD, Huang J (2017). Effects of a Delphi

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