

The effects of acupuncture on the secondary outcomes of anxiety and quality of life for women undergoing IVF: A randomized controlled trial

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Abstract

Introduction: Studies have shown in vitro fertilization (IVF) treatment to have a significant impact on women's quality of life. In addition, anxiety is experienced during IVF treatment and prior to knowing the outcome from a treatment cycle. Although support services are available at many IVF clinics, the uptake of these opportunities may not be high. Acupuncture is used by women undertaking IVF treatment in the belief that it improves their reproductive outcomes, and some studies suggest that it may reduce anxiety. The objective of this study was to examine the effects of acupuncture compared with sham acupuncture on quality of life and anxiety for women undergoing an IVF cycle.

Material and methods: A multicenter randomized controlled trial was conducted in Australia and New Zealand. Women were eligible if they were aged 18-42 years, undergoing a fresh IVF cycle and not using acupuncture. Recruitment occurred between June 2011 and October 2015. Women were randomized to acupuncture or a sham acupuncture control group and three treatments were administered, the first treatment between day 6 and 8 of ovarian stimulation, and two treatments were given on the day of embryo transfer. The primary outcome was livebirth. Secondary outcomes included quality of life and anxiety, and were assessed at baseline, on the day of embryo transfer and 14 weeks from trial entry.

Results: In all, 848 women were randomized to the trial, 608 women underwent an embryo transfer, of which 526 (86%) received all three treatments. Adjusted analysis found that women receiving acupuncture reported reduced anxiety following embryo transfer (mean difference [MD] -1.1, 95% CI -2.2 to -0.1, $P = 0.03$). Unadjusted analysis of quality of life did not differ between groups following embryo transfer. Adjusted analyses by per protocol found a significant positive change for the acupuncture group for the general health MOS Short Form 36 (SF36) domain (MD 2.6, 95% CI 0.5-4.7, $P = 0.01$) following embryo transfer. The benefit was not sustained at 14 weeks (MD 0.1, 95% CI -2.7 to 2.9).

Conclusions: Acupuncture may reduce anxiety at embryo transfer. Quality of life did not differ between the groups. Women experience reduced emotional well-being 3 months following the IVF cycle, highlighting ongoing unmet psycho-social needs.

KEYWORDS

acupuncture, anxiety, in vitro fertilization, quality of life, randomized controlled trial

1 | INTRODUCTION

A lack of control and feeling of uncertainty are highlighted as two of the most difficult aspects of infertility treatment experienced by women and have been shown to contribute to reduced well-being while undergoing infertility treatment.¹ Longitudinal studies examining depression and anxiety before and during infertility treatment have found that between 10% and 25% of women are at risk of clinical distress following in vitro fertilization (IVF) treatment.^{2,3} Furthermore, evidence shows that IVF cycle failures have been found to predict late psychological distress.⁴ It has been proposed that intervention support to reduce stress and enhance coping are important to reduce the emotional distress but also to reduce the likelihood of patients stopping treatment prior to achieving their goals for a family.⁴⁻⁶ Although support services are available at many IVF clinics, they may not be widely used.⁷ The reasons for this are varied; some women may not recognize the need for support particularly during early treatment, and some services may not be offered to women until more obvious signs of psychological distress become more obvious. Studies have also shown infertility treatment to have a more general effect on reducing women's quality of life.^{8,9}

Complementary health approaches are frequently used by women undergoing fertility treatment,¹⁰⁻¹⁴ and studies have found that women report an increased sense of well-being from these treatments.^{15,16} Acupuncture is frequently used,¹⁴ and women describe positive effects including having a greater sense of confidence, sense of well-being, coping, feeling relaxed and less stressed,¹⁷ and increased self efficacy¹⁸ following treatment. An 8-week randomized controlled trial (RCT) examined the effect of acupuncture on psycho-social outcomes for women experiencing infertility and found there were benefits with reducing infertility stress.¹⁹ Furthermore, women reported a sense of relaxation and calmness, and significant trends were observed with reduced anxiety.

We recently reported on a randomized controlled trial (RCT) of a short course of acupuncture compared with a sham control as an adjunct to IVF which found no difference in the primary outcome of live birth and pregnancy outcomes between groups.²⁰ The objective of this study is to report on the secondary outcomes from this same trial examining the effects of acupuncture compared with sham acupuncture on quality of life measures and anxiety.

2 | MATERIAL AND METHODS

A multicenter parallel RCT was conducted in Australia and New Zealand comparing acupuncture with a sham acupuncture control. The methods have been previously described.²¹ The

Key message

Anxiety and low quality of life are experienced by women during and following an IVF cycle. Acupuncture reduced anxiety compared to sham acupuncture. No differences in quality of life were found between acupuncture and the sham acupuncture groups.

randomization sequence was computer-generated with stratification by the number of previous embryo transfer cycles (0-1, 2-6 and >6), woman's age (<38, and 38-42 years), and study site. Allocation concealment was ensured using a centralized telephone computer program. Study participants, fertility specialists and nurses, and the analyst were blinded to group allocation. The clinical trial coordinator and acupuncturists were not blinded to group allocation. Study site research nurses who were blind to group allocation enrolled women into the study and collected clinical outcome data. Blinding was maintained until completion of analysis.

Women were recruited from 16 IVF units across Australia and New Zealand and were eligible if they met the following criteria; aged 18-42 years, undergoing a fresh IVF or intracytoplasmic sperm injection cycle, and not currently using acupuncture. Exclusion criteria were women undergoing a frozen embryo transfer, previous randomization to the study, planning pre-implantation genetic diagnosis or receiving donor eggs. Recruitment occurred between June 2011 and October 2015. Randomization commenced prior to the start of the IVF treatment. It was intended that all women would receive standard IVF treatment protocols of ovarian stimulation, egg retrieval, fertilization and embryo transfer as determined by their treating clinician.

2.1 | Interventions

Following randomization, women made an appointment with the study acupuncturist onsite at the IVF centers or nearby. The first treatment was administered between days 6 and 8 of ovarian stimulation, and two treatments were given on the day of embryo transfer. The acupuncturists had a minimum of 2 years clinical experience, was a member of a national professional association, and were registered with the national Australian Health Practitioner Regulation Agency. All acupuncturists were trained in the treatment protocol with annual refresher training provided. The acupuncture protocol was developed using a Delphi method, with treatment characteristics retained on reaching 80% group consensus.²²

A short treatment protocol was administered. The treatment strategy was based on traditional Chinese medicine. The first treatment involved core points Guilai ST-29, Guanyuan Ren-4, Qihai Ren-6, Sanyinjiao SP-6 and Xuehai SP-10. In addition, up to five additional points based on the traditional Chinese medicine diagnosis were selected from a semi-standardized protocol. Manual acupuncture was applied, the needling sensation *de qi* was attained, and needles were re-stimulated midway through the 25-minute treatment. On the day of embryo transfer, an initial treatment was administered within 1 hour prior to embryo transfer and comprised points Guilai ST-29, Diji SP-8, Xuehai SP-10, Taichong LR-3, Guanyuan Ren-4, one point from Shenmen HT-7, Neiguan PC-6 or YinTang, and auricular point Zhigong. Following embryo transfer, the second acupuncture treatment was administered comprising points Baihui DU-20, Taixi KD-3, Zusanli ST-36, Sanyinjiao SP-6, Neiguan PC-6, and auricular point ShenMen. Needles were applied using the Park device²³ of a plastic ring and a guide tube, with a double-sided adhesive ring to facilitate maintenance of blinding for the participant.

The sham control group received non-insertive acupuncture using the Park sham needle supported by the Park device.²³ This needle has a retractable needle shaft and a blunt tip. We used sham points at locations away from known acupuncture points and with no known function.²⁴ Sham acupuncture was administered at six points for each of the treatments. Needle placement duration was the same as for the acupuncture group.²¹

2.2 | Outcomes and analysis

Secondary outcomes included anxiety and quality of life. These outcomes were assessed at baseline following the last treatment (day of embryo transfer) and 14 weeks from trial entry. To measure anxiety we used the shortened 10-item version of the State Trait Anxiety Inventory (STAI).²⁵ This instrument has good psychometric properties and has been used extensively in research. Quality of life was assessed using the MOS Short Form 36 (SF36).²⁶ At baseline we assessed women's sense of coping with infertility using the infertility self-efficacy scale.²⁷ This scale included items that are preceded by the phrase "I am confident that I can..." and are anchored by a nine-point Likert-type scale from one (not at all confident) to nine (totally confident). The total score of 144 is achieved by summing up all individual item scores. Following the final study treatment, data were collected on the empathy demonstrated by the study practitioner. Empathy was assessed as a process clinical encounter using the validated CARE questionnaire.²⁸ This instrument comprises 10 items rated over a 6-point scale (poor to excellent).

The sample size was informed by our previous pilot study, evidence from the systematic reviews and clinical advice, and was determined in relation to the primary outcome livebirth. We estimated that a 7 percentage point increase in the proportion of live births would be clinically important.^{29,30} To obtain 80% power at a 5% significance level for a 2-sided test, we assumed a proportion of 13.4%³⁰ live births in the control group and 20.4% live births in the acupuncture group, requiring

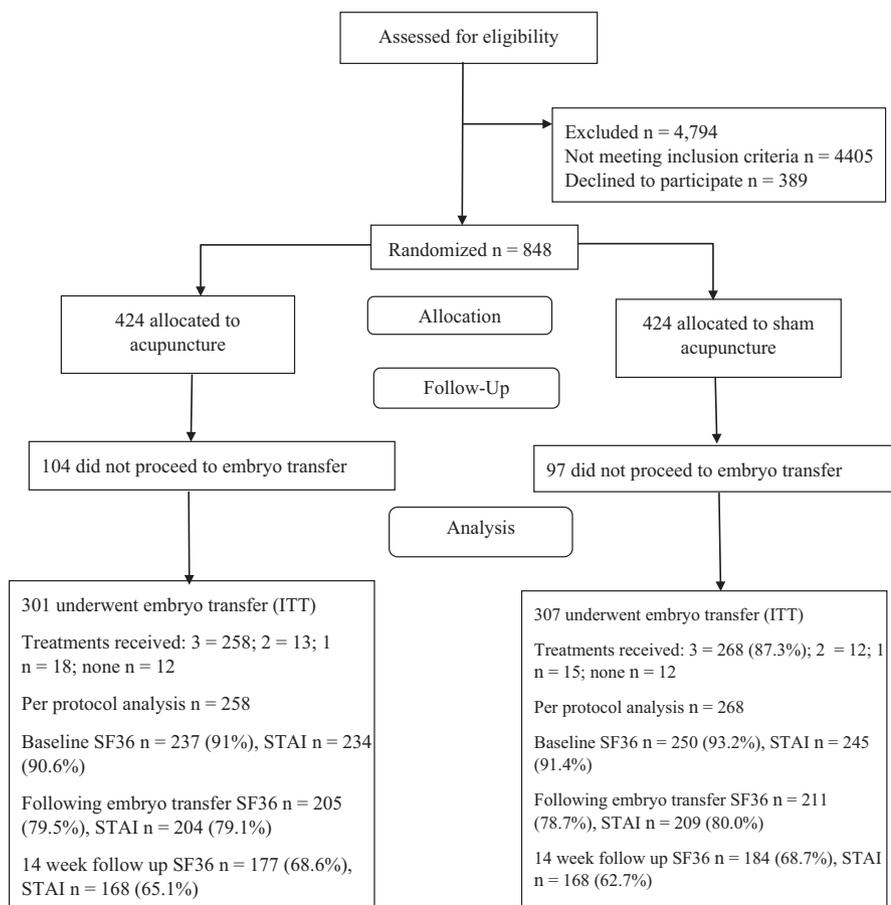


FIGURE 1 Flow of participants through study. ITT, intention-to-treat; SF36, MOS 36-Item Short Form Health Survey; STAI, State Trait Anxiety Inventory

449 participants per group. Allowing for 30% attrition from the study due to cancelled cycles or no embryo transfer and study withdrawal, 1168 women were required. For the secondary analyses reported here, 449 women per group would provide 90% power to detect a 0.21 standard deviation difference in means on independent samples *t* test. According to Cohen's criteria this implies that the study would be adequately powered to detect even small treatment effects.

The analysis used an intention-to-treat analysis excluding those women who did not undergo an embryo transfer. A per protocol analysis was undertaken of those women who underwent embryo transfer and received all three study treatments. The reproductive and demographic characteristics of the women randomized to each treatment group were summarized using counts and percentages for categorical variables, and means and standard deviations for numeric variables. For the differences between groups we used independent samples *t* tests and reported mean differences (MD) with associated 95% confidence intervals (CI). For discrete data, Pearson's Chi-square test and Fisher's exact test were used to examine differences between groups. Two-sided *P* values <0.05 indicated statistical significance. A post-hoc secondary analysis using a logistic regression was undertaken examining the effect of treatment adjusted for the baseline SF36 total score and pregnancy outcome from the IVF cycle defined as not pregnant, pregnant and miscarried, on quality of life and anxiety. The analysis was undertaken using SAS version 9.4 (SAS Institute, Cary, NC, USA).

2.3 | Ethical approval

Ethics approval was obtained from the Western Sydney University Human Ethics Committee (approval H8936) and at the respective sites. All women gave written informed consent. The trial is registered with the Australian New Zealand Clinical Trials Registry (ANZCTR): 12611000226909 (www.anzctr.org.au).

3 | RESULTS

In all, 848 women were randomized to the trial (Figure 1). A total of 201 women discontinued the intervention due to the IVF cycle being cancelled with no embryo transfer. An intention-to-treat analysis was undertaken on 301 women receiving acupuncture and 307 receiving control acupuncture. Of the 608 analyzed as intention-to-treat (ITT), 526 (86%) women received all three acupuncture treatments (treatment per protocol), 25 (4.1%) two treatments and 28 (4.6%) one treatment only.

The mean age of women in the study was 35 years, 71% had experienced infertility for over 2 years, over 74% had no children and 47% had undergone two or more IVF cycles (Table 1). These characteristics were balanced between groups with only modest differences in highest level of education and previous acupuncture use. The mean infertility self-efficacy scale did not differ between the groups and indicated that the women had moderate coping skills.

TABLE 1 Baseline characteristics of trial participants

	Acupuncture (n = 301)	Sham (n = 307)	<i>P</i>
Age at randomization ^a	35.7 (4.3)	35.7 (4.2)	0.83
Duration of infertility (n = 606) ^b			
<2 years	81 (27.0)	92 (30.1)	0.41
2-5 years	138 (46.0)	145 (47.4)	
>5 years	81 (27.0)	69 (22.6)	
Fertility diagnosis ^b			
Male factor	99 (32.9)	89 (29.0)	0.30
Tubal	21 (7.0)	29 (9.5)	0.27
Unexplained	116 (38.5)	111 (37.2)	0.54
Endometriosis	28 (9.3)	36 (11.7)	0.33
Other includes polycystic ovarian syndrome	83 (27.6)	83 (27.0)	0.88
Parity nulliparous ^b	228 (75.8)	227 (73.9)	0.61
Number of IVF cycles ^b			
0	85 (28.2)	84 (27.4)	0.49
1	68 (22.6)	82 (26.7)	
≥2	148 (49.2)	141 (45.9)	
Previous acupuncture use (n = 607) ^b	171 (56.8)	150 (49.0)	0.055
Employed full time (n = 607) ^b	186 (61.8)	195 (63.7)	0.62
Highest education ^b			
Primary or high school	38 (12.6)	58 (18.9)	0.034
Vocational or University	263 (87.4)	249 (81.1)	
Race ^{b,c}			
White	232 (77.1)	250 (81.4)	0.37
Asian	45 (15.0)	35 (11.4)	
Other ^c	24 (8.0)	22 (7.2)	
Infertility self-efficacy scale (n = 537) ^b	93.8 (20.9)	91.8 (20.5)	0.26
Acupuncture treatments received (n = 600) ^d			
0	8 (2.7)	8 (2.6)	0.93
1	18 (6.1)	15 (5.0)	
2	13 (4.4)	12 (4.0)	
3	258 (88.9)	268 (88.5)	

^aMean (SD).

^bData are n (%).

^cRace: other includes Aboriginal and Torres Strait Islander, Maori, Polynesian.

^dPer protocol analysis.

3.1 | Quality of life

Baseline quality of life scores for the cohort who received treatment per protocol and those who did not and the return of the SF36 forms

TABLE 2 Baseline characteristics of those who received treatment per protocol compared with those who did not

	Treatment per protocol (n = 526), mean (SD)	Treatment incomplete (n = 82), mean (SD)	Difference in means (95% CI)	P
Baseline SF36 response rate	n = 487 (92.6%)	n = 60 (73.2%)		<0.001
Baseline SF36 domains				
Physical functioning	90.5 (17.1)	92.8 (13.8)	-2.2 (-6.1 to 1.7)	0.26
Role limitations due to physical health	90.1 (25.0)	89.2 (27.8)	1.0 (-6.5 to 8.5)	0.25
Role limitations due to emotional health	84.3 (29.6)	78.9 (36.8)	5.4 (-4.4 to 15.2)	0.28
Energy/fatigue	60.5 (17.7)	58.8 (20.1)	1.7 (-3.7 to 7.1)	0.53
Emotional well-being	72.2 (15.7)	71.9 (16.6)	0.3 (-4.2 to 4.8)	0.90
Social functioning	84.2 (20.5)	81.0 (21.4)	3.1 (-2.7 to 9.0)	0.28
Pain	83.1 (18.6)	83.3 (20.5)	-0.1 (-5.7 to 5.4)	0.96
General health	75.8 (16.5)	76.5 (16.6)	-0.7 (-5.2 to 3.8)	0.75
Health change	62.8 (21.7)	57.1 (20.1)	5.8 (0.2 to 11.3)	0.04

are examined in Table 2. The completion rate of the SF36 questionnaire was significantly higher for women who received treatment per protocol than for those who did not. The "Health Change" domain of the SF36 examines "compared to 1 year ago, how would you rate your health in general now?" Those who received treatment per protocol have a slightly more positive view on how their health has changed over time ($P < 0.04$).

There were no significant differences between groups on SF36 domains. Overall, physical health scores were higher than energy and emotional functioning scores at the three time periods. There were no significant differences between the acupuncture and sham acupuncture groups who received treatment per protocol in their response rates to the SF36 at the three time points (Chi-square $P = 0.53$ at baseline, $P = 0.84$ at end of treatment, $P = 0.99$ at 14-week follow up) (Table 3).

For the 361 women, post-hoc analysis examined whose treatment was per protocol and who completed the 14-week follow up of the SF36, and the effect of the IVF reproductive outcome on their emotional well-being (Table S1). The women's reproductive status was categorized as pregnant, miscarried and no pregnancy achieved. Large differences in the quality of life domains and pregnancy outcome were observed, with the lowest scores for those women who miscarried, role limitation due to emotional health (mean 59.6, SD 39.4), emotional well-being (mean 60.0, SD 23.0) and social functioning (mean 60.5, SD 26.4). Emotional well-being was highest for women who were pregnant (mean 80.2, SD 13.2) and role limitation due to emotional health (mean 92.5, SD 24.3).

The per protocol differences in mean SF36 scores between treatment groups adjusted for baseline score and pregnancy status are presented in Table 4. This analysis was undertaken on the women who underwent an embryo transfer and received all three acupuncture treatments. A significant difference was found between the groups, with the scores indicating on average a positive change for the acupuncture group for the adjusted analysis of the

SF36 domain in general health domain (MD 2.6, 95% CI 0.5-4.7, $P = 0.01$) following treatment on the day of embryo transfer. Review of the descriptive statistics (data not shown) suggest that this effect occurred due to an improvement in average general health score in the acupuncture group coupled with no change in the control group. When women were followed up, however, this benefit was not sustained at 14 weeks (MD 0.1, 95% CI -2.7 to 2.9) with both groups' average general health scores virtually identical to baseline levels. The adjusted analysis for the baseline SF36 score and pregnancy status at the 14-week follow up found no difference on any SF36 domain between both groups.

3.2 | Anxiety

There was no significant difference between the treatment groups in the response rates to the STAI at baseline and at the 14-week follow up (chi-square $P = 0.82$ and $P = 0.78$, respectively), and no significant differences in anxiety between groups at the end of treatment and at the 14-week follow up corrected for baseline scores (Table 5). Women's assessment of practitioner empathy did not differ between the groups ($P = 0.71$).

STAI scores were adjusted for baseline STAI score and pregnancy outcome, and show that women receiving acupuncture reported slightly reduced anxiety immediately after treatment than participants who received sham acupuncture (MD -1.1 95% CI -2.2 to -0.1, $P = 0.03$) (Table 6).

4 | DISCUSSION

Study findings found a statistically significant reduction in anxiety for women receiving acupuncture at the time of an embryo transfer. However, this effect was not sustained at the 14-week follow up. A benefit was also reported from acupuncture on the general health

TABLE 3 Quality of life scores by group—per protocol

SF36 domains (n = 258/268)	Acupuncture, mean (SD)	Acupuncture sham control, mean (SD)	Mean difference, 95% CI	P
Baseline (n = 237/250)				
Physical functioning	92.0 (15.3)	89.1 (18.5)	2.9 (−0.1 to 5.9)	0.059
Role limitations due to physical health	91.1 (24.9)	89.2 (25.1)	1.9 (−2.5 to 6.4)	0.39
Role limitations due to emotional health	86.6 (27.2)	82.0 (31.6)	4.6 (−0.6 to 9.9)	0.08
Energy/fatigue	60.8 (17.5)	60.3 (17.9)	0.4 (−2.7 to 3.6)	0.79
Emotional well-being	72.4 (15.7)	71.9 (15.8)	0.5 (−2.30 to 3.30)	0.73
Social functioning	84.4 (21.1)	84.0 (19.9)	0.4 (−3.3 to 4.0)	0.83
Pain	84.0 (17.7)	82.3 (19.4)	1.6 (−1.7 to 5.0)	0.33
General health	74.7 (16.8)	76.8 (16.1)	−2.1 (−5.1 to 0.80)	0.16
Health change	61.9 (22.6)	63.7 (20.8)	−1.8 (−5.7 to 2.1)	0.37
Following ET (n = 205/211)				
Physical functioning	88.0 (18.6)	87.6 (19.1)	0.3 (−3.3 to 4.0)	0.85
Role limitations due to physical health	77.6 (35.4)	75.9 (37.0)	1.6 (−5.4 to 8.6)	0.65
Role limitations due to emotional health	83.6 (31.1)	80.3 (34.5)	3.3 (−3.0 to 9.6)	0.30
Energy/fatigue	58.0 (19.3)	56.3 (20.7)	1.6 (−2.2 to 5.5)	0.40
Emotional well-being	71.1 (16.1)	71.2 (16.7)	−0.1 (−3.2 to 3.1)	0.96
Social functioning	79.3 (21.2)	76.8 (25.4)	2.4 (−2.1 to 6.9)	0.29
Pain	74.1 (21.7)	73.0 (23.9)	1.1 (−3.3 to 5.5)	0.62
General health	77.2 (17.3)	76.4 (16.7)	0.8 (−2.5 to 4.0)	0.64
Health change	62.2 (21.7)	61.6 (21.3)	0.6 (−3.6 to 4.7)	0.78
14-week follow up (n = 177/184)				
Physical functioning	87.8 (17.4)	86.3 (18.9)	1.5 (−2.3 to 5.2)	0.45
Role limitations due to physical health	78.5 (35.1)	78.7 (34.3)	−0.1 (−7.3 to 7.1)	0.97
Role limitations due to emotional health	82.3 (32.8)	84.6 (32.3)	−2.3 (−9.0 to 4.4)	0.50
Energy/fatigue	53.1 (21.1)	55.1 (20.5)	−1.9 (−6.3 to 2.4)	0.38
Emotional well-being	72.7 (17.5)	73.7 (17.5)	−1.0 (−4.7 to 2.6)	0.57
Social functioning	79.2 (23.2)	80.6 (23.2)	−1.3 (−6.1 to 3.5)	0.59
Pain	81.2 (21.7)	78.6 (22.6)	2.6 (−2.0 to 7.1)	0.27
General health	74.2 (19.3)	75.5 (18.5)	−1.3 (−5.3 to 2.5)	0.50
Health change	57.3 (21.2)	60.2 (22.1)	−2.8 (−7.3 to 1.6)	0.21

domain following the last treatment on the day of embryo transfer; however, this effect was not sustained at 14 weeks. Women who underwent embryo transfer and completed all treatments held a more positive view of their health than those who did not, which may indicate this group of women invested more in their health and well-being.

An assessment of quality of life has been highlighted as vital when assessing the efficacy of any infertility treatment.³¹ This remains an under-reported outcome. In this trial the outcome was assessed on two occasions during the IVF cycle, and for the first time 3 months following from the onset of the IVF cycle. No consistent beneficial effect on quality of life was found from acupuncture vs

	Following ET		14-week follow up	
	Mean difference (95% CI)	P	Mean difference (95% CI)	P
Adjusted for baseline score	Acupuncture n = 194 Sham control n = 199		Acupuncture n = 168 Sham control n = 176	
SF36 domains				
Physical functioning	-0.9 (-4.3 to 2.6)	0.62	0.8 (-2.9 to 4.6)	0.66
Role limitations due to physical health	3.1 (-3.3 to 9.5)	0.34	-0.4 (-7.5 to 6.7)	0.90
Role limitations due to emotional health	2.6 (-3.3 to 8.5)	0.38	-2.6 (-9.3 to 4.2)	0.45
Energy/fatigue	1.8 (-1.2 to 4.8)	0.25	-1.8 (-5.6 to 2.1)	0.36
Emotional well-being	1.0 (-1.5 to 3.5)	0.44	-0.5 (-3.8 to 2.8)	0.79
Social functioning	3.4 (-0.7 to 7.6)	0.11	-0.9 (-5.6 to 3.7)	0.70
Pain	0.8 (-3.3 to 4.9)	0.71	2.6 (-1.8 to 7.0)	0.25
General health ^a	2.6 (0.5 to 4.7)	0.01	0.1 (-2.7 to 2.9)	0.94
Health change	1.8 (-1.7 to 5.4)	0.31	-2.7 (-7.1 to 1.6)	0.21
Adjusted for baseline score and pregnancy status			Acupuncture n = 168 Sham control n = 176	
SF36 domains				
Physical functioning	n/a		1.4 (-2.0 to 4.8)	0.41
Role limitations due to physical health			0.9 (-5.7 to 7.6)	0.78
Role limitations due to emotional health			-2.0 (-8.6 to 4.6)	0.54
Energy/fatigue			-1.1 (-4.8 to 2.5)	0.55
Emotional well-being			-0.2 (-3.3 to 2.9)	0.89
Social functioning			-0.1 (-4.6 to 4.5)	0.98
Pain			3.6 (-0.7 to 7.9)	0.10
General health			0.3 (-2.5 to 3.2)	0.82
Health change			-2.7 (-7.1 to 1.7)	0.23

^aAcupuncture group scores increased more than the sham control on average.

sham acupuncture and these findings are consistent with our earlier acupuncture RCT with women undergoing IVF.³⁰ We did not use a specific fertility-related quality-of-life instrument such as the FertilQoL³²; however, no differences in women's quality of life have been reported in a study examining the impact of repeated IVF cycles.³³ The finding of no change in quality of life after supportive interventions during an IVF cycle may not be surprising,

as women reported discomfort, fatigue and mood changes from the IVF procedures and injections.³¹ Trial findings indicate similar SF36 scores 3 months on from the start of the trial, highlighting the potential for quality of life to impact on the burden of IVF treatment.

There was an effect on anxiety from acupuncture. This finding differs from two RCT studies using a similar short duration

TABLE 4 Quality of life scores by per protocol treatment group adjusted for baseline score and pregnancy status

TABLE 5 Anxiety and practitioner empathy by study group

STAI	Acupuncture (n = 301), mean (SD)	Acupuncture sham control (n = 307), mean (SD)	Mean difference (95% CI)	P
Baseline n = 234/245	19.3 (5.9)	19.6 (6.1)	-0.3 (-1.4 to 0.7)	0.54
Following last treatment on the day of embryo transfer, n = 204/209	19.5 (5.7)	20.5 (6.3)	-1.0 (-2.2 to 0.02)	0.09
14-weeks follow up, n = 168/168	19.1 (6.0)	19.4 (6.0)	-0.3 (-1.6 to 1.0)	0.65
Practitioner empathy (210/234)	43.1 (8.1)	43.4 (8.2)	-0.3 (-1.8 to 1.2)	0.71

TABLE 6 STAI scores per protocol treatment group adjusted for baseline score and pregnancy status

STAI score	Following last treatment on day of embryo transfer		14-week follow up	
	Mean difference (95% CI)	P	Mean difference (95% CI)	P
	Acupuncture n = 191 Sham n = 196		Acupuncture n = 158 Sham n = 161	
Adjusted for baseline score ^a	-1.1 (-2.2 to -0.1)	0.03	-0.1 (-1.2 to 1.1)	0.91
Adjusted for baseline score and pregnancy status	n/a		-0.2 (-1.3, 0.9)	0.73

^aNegative values mean the acupuncture group increased less than the sham group on average.

treatment protocol of acupuncture vs a sham acupuncture control which found no difference in anxiety between groups, although both groups demonstrated significantly reduced anxiety following the intervention.^{34,35} This finding also supports our earlier study examining the role of acupuncture treatment which was focused only on addressing psycho-social well-being compared with usual care; that study found reduced anxiety in women with infertility.¹⁹ Findings also support reduced anxiety from acupuncture compared with usual care only when performed at embryo transfer.³⁶ Our earlier research findings including observational designs^{17,18} have found a beneficial effect on anxiety from both short and longer acupuncture treatment. These observations are supported from large well-designed RCT comparing acupuncture to sham acupuncture.

Research has indicated that emotionally the most difficult time for women undertaking IVF is the waiting time between the embryo transfer and the pregnancy test.³⁷ Our study findings also show rates of pretreatment anxiety were high and remained high 3 months following the IVF cycle. It is possible that the women who chose to participate in this RCT were more chronically anxious. Our findings are consistent with Verhaak et al³⁸ who reported that women whose IVF cycles were unsuccessful experienced increased emotional distress. The study findings highlight a need to further support women with anxiety while undergoing treatment and providing follow-up post-treatment.

The overall effects from acupuncture are attributed to needling, specific non-needling components (palpation, education and diagnosis) and nonspecific components (time, attention, credibility and expectation).³⁹ The findings from efficacy RCT comparing acupuncture and sham acupuncture may be partially explained by data suggesting that these devices may not be inert⁴⁰ and that some activity may arise from sensory and psycho-social cues. Non-needling components and nonspecific effects from acupuncture⁴¹ have been proposed to explain the verum or sham acupuncture anxiolytic effect during IVF⁴² indicated by two previous acupuncture sham controlled trials.^{34,35} However, our finding of reduced anxiety from acupuncture following embryo transfer from acupuncture does not support both groups having a similar anxiolytic effect. This finding will contribute to further methodological discussions of acupuncture controls.

The strength of the study includes the large sample size and inclusion of IVF centers across Australia and New Zealand. There are some limitations. We have previously reported that the treatment protocol was based on best practice, and blinding was intact in both groups.²⁰ There was attrition with the return of questionnaires following completion of treatment and at follow up when the outcome of the IVF cycle was known; however, there was no evidence of a responder bias with no significant differences in the return of questionnaires found between the groups. Although there was some consistency with the acupuncture points used in the acupuncture protocols in clinical practice, different protocols may be individualized with variation in the characteristic of treatment components, and this treatment protocol was short in duration.²² It is possible that the practitioners may have interacted with women in a different manner; however, this is unlikely to explain our findings, as empathy was assessed as high in both groups and not statistically different between the groups.

5 | CONCLUSION

Acupuncture reduced anxiety on the day of embryo transfer, although the effects were not sustained. Further research is needed, and there is a need for ongoing psycho-social support post-treatment when completing an IVF treatment cycle.

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CONFLICT OF INTEREST

Caroline Smith declares that she has collaborated with Ms Lyttleton, a Director of one of the acupuncture clinics where some treatments were administered in this study. Ms Lyttleton, in addition to other international experts, provided clinical advice on the design of the acupuncture treatment used in this study. As a medical research institute, NICM Health Research Institute receives research grants and donations from foundations, universities, government agencies and industry. Sponsors and donors provide untied and tied funding for work to advance the vision and mission of the Institute. Michael Chapman reports that he is a shareholder in an IVF clinic. Robert Norman reports that he is a shareholder in an IVF clinic and has received grants from Ferring and travel from Merck. Neil Johnson reports personal fees from Guerbet, personal fees from Vifor Pharma, non-financial support from Bayer Pharma, non-financial support from Merck-Serono, non-financial support from Merck Sharp & Dohme (MSD) and grants from Abb-Vie, outside the submitted work. Sheryl de Lacey, Julie Ratcliffe and Paul Fahey have nothing to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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