Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Protocol Treatment Interventions

Following randomization women in the intervention groups arranged an appointment with the study acupuncturist based at the in vitro fertilization (IVF) centers, or at close proximity to the IVF centers. The acupuncturists were registered with a national professional association, and were required to have a minimum of two years clinical experience.

The treatment protocol used in the study was developed using a Delphi method, with treatment characteristics retained on reaching 80% group consensus. Two rounds of the Delphi process, achieved a 80% consensus to be achieved for individual items to be included in the treatment protocol[1]. Nineteen acupuncturists participated in this process, with practitioners from Australia (6), China (2), Denmark (1), Sweden (1), the United States (4), and the United Kingdom (1).

The first visit to the acupuncturist was undertaken on days 6 to 8 of the stimulated IVF cycle. At this initial visit all women underwent a traditional Chinese medicine diagnosis, by the study acupuncturist. The initial diagnosis and treatment too k60 to 90 minutes. Two treatments were subsequently administered immediately before and after the day of the scheduled embryo transfer. No other treatments other than acupuncture were administered during the study visits.

Acupuncture Group

First treatment

Treatment was based on the traditional Chinese medicine style of acupuncture. All standard acupuncture points were used[2]. The initial treatment included five core points administered to all women in the treatment group comprising of: Guilai ST-29, Guanyuan Ren-4, Qihai Ren-6, Sanyinjiao SP-6, Xuehai SP- 10. Up to five additional points based on a traditional Chinese medicine pattern differentiation could also be administered. The treatment protocol detailed additional points to be administered for the study participant from the following traditional Chinese medicine syndromes:

Kidney Yang Xu: KD13, KD3, BL23, BL32, CV3, GV4, LU7, KD6.
Kidney Yin Xu: CV7, KD3, KD13, KD6, BL52.
Kidney Jing: BL23, ST27, KI12.
Blood Xu: ST36, KD13, BL20, BL23, BL17, Zigong.
Damp/Phelgm: CV3, Zigong, ST28, SP9, CV9, LU7 (right), KD6 (left), ST30, KD4, BL32.
Liver Qi Stagnation: LR3, GB34, TH6, CO4, KD14, SP4 (right), PC6 (left).
Blood Stasis: LR3, GB34, BL17, PC6, TH6, SP4 (right), PC6 (left), KD14, KD6 (right), LU7 (left).
Heat: LI11, KD2, LR3, PC3, BL17, LU7, KD6, CO4.
Heart Qi Stagnation: Bl 15, Bl 14, Ren 17, Ren 15, Du 14, St 36, PC 4, PC 6.
Heart Qi Xu: HT7, HT6, CV14.
Spleen Qi Xu: ST36, SP3, BL20, BL21, CV12.

On the day of embryo transfer

Two subsequent treatments were administered on the day of embryo transfer, pre and post transfer. Points administered on the day of embryo transfer included:

Pre-embryo transfer
Diji SP-8, Xuehai SP-10, Taichong LR-3, Guanyuan Ren-4, Guilai ST-29, auricular point Zhigong, plus choose one point from; Shenmen HT-7, Neiguan PC-6, or YinTang.

Post-embryo transfer
Baihui DU-20, Taixi KD-3, Zusanli ST-36, Sanyinjiao SP- 6, Neiguan PC-6, and auricular points Shenmen and Zhigong.

Manual acupuncture was performed with disposable stainless needles (0.22x40mm, 0.20x12mm Vinco) inserted. Needles were inserted using the Park device, a supporting tube that facilitates maintenance of blinding for the participant. Needles were inserted to a depth of not greater than 2 cm and retained for 25 minutes at each treatment. The insertion of the acupuncture needle into an acupuncture point typically generates a range of sensations called ‘de qi’, this sensation was maintained during the initial treatment on days 6 to 8, and during the pre-embryo treatment only. Needles were inserted into points bilaterally except for the acupuncture points located on the Ren and Du points and YinTang[2].

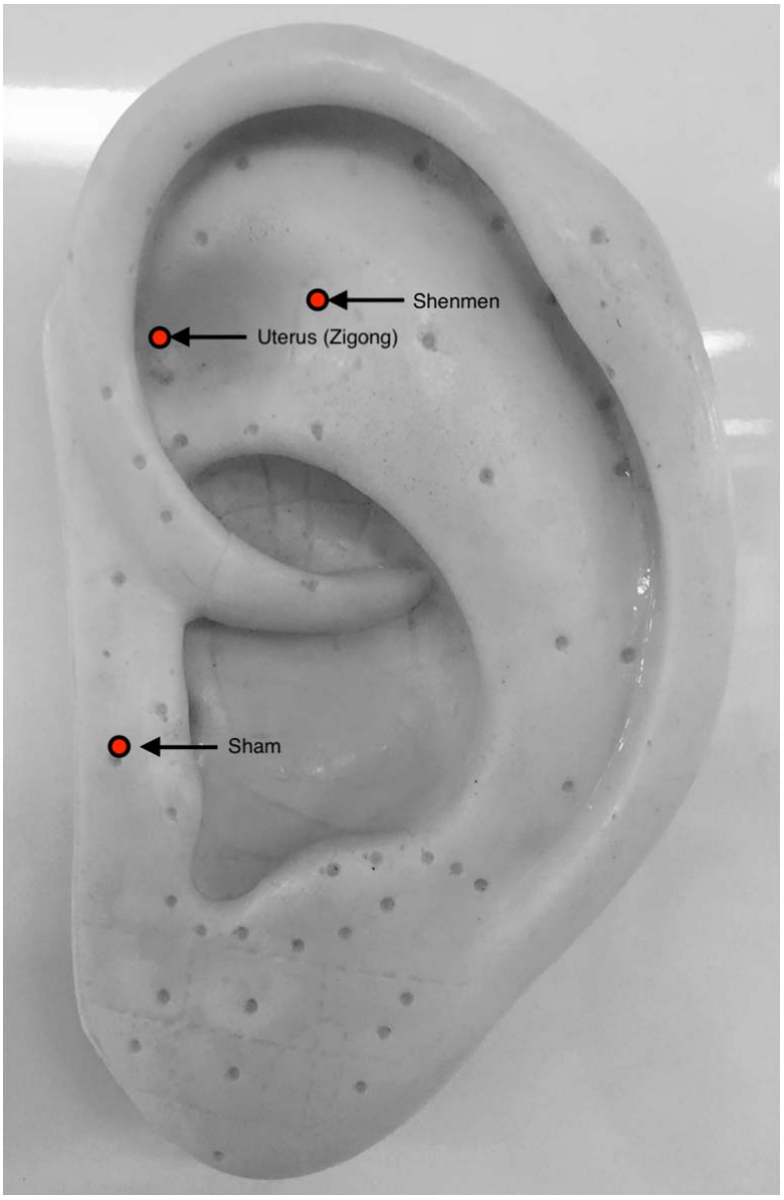
Sham acupuncture control

This acupuncture control group received placement of non-invasive Park sham needles[3]. The Park needle has been shown to be an effective device for blinding in RCT. These needles have a retractable needle shaft, a blunt tip, and skin penetration does not occur, and the needles have a supporting device. The acupuncturist was instructed to hold the 'needle' in place with one hand, while moving the handle of the needle with the other hand, so that the shaft of the needle disappeared into the handle. The needle was inserted through Park supporting device. The location of sham non-acupuncture points were away from real points and were described in relation to anatomical landmarks and relationship to acupuncture channels. The duration of needling and treatment session was the same as for the acupuncture group.

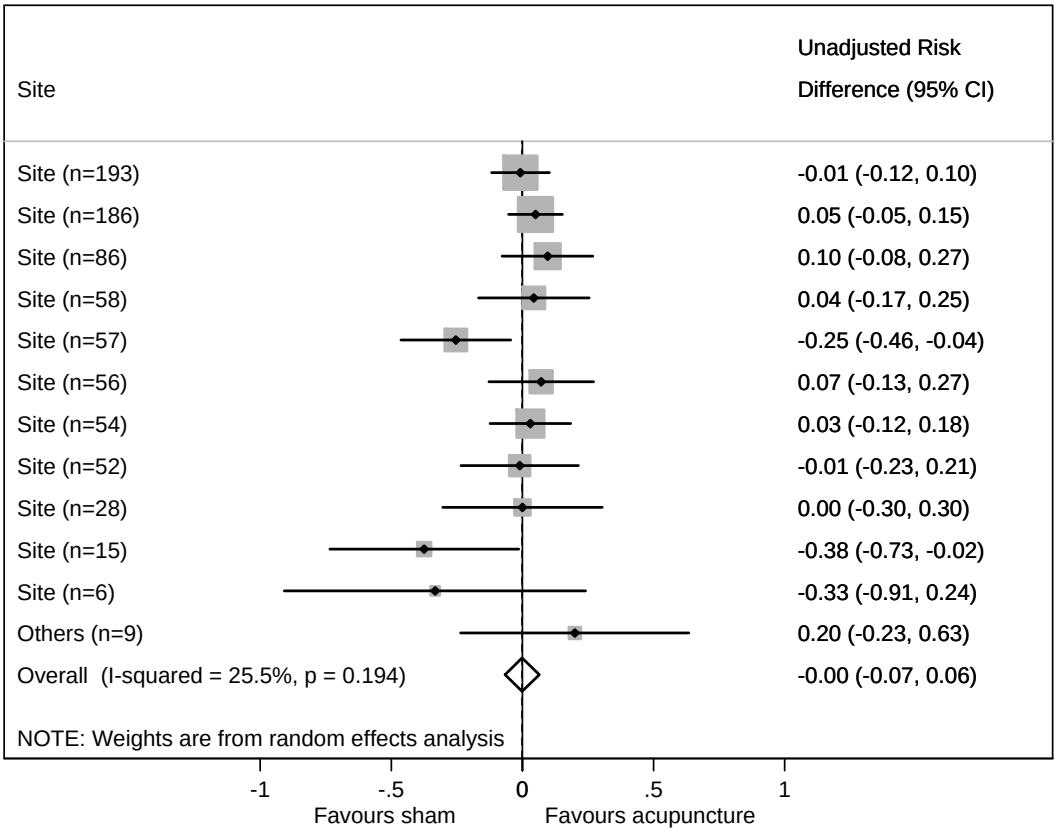
Sham points for the acupuncture control

At the first treatment the non-penetrating needle was placed at six standardised acupuncture control points placement of six sham points. At visits two and three, the **f**irst pre-embryo transfer treatment required six of seven points to be selected. The second post embryo transfer administered all six points. The location of the sham acupuncture control points are described in eTable 1 and eFigure 1.

eFigure 1. Location of Sham Ear Points



eFigure 2. Unadjusted Risk Difference of Live Birth by Study Site



Footnote:
Others represents the combined results of 4 sites who contributed 4, 3, 1 and 1 participants each.
The results for each site are presented as unadjusted risk differences with 95% confidence intervals. The size of the data markers is proportional to the relative weight of information (sample size and inverse variance) of each site. The individual risk differences are combined using a random effects model fitted using the method of DerSimonian and Laird. Heterogeneity between sites is described by the I^2 statistic which indicates the percentage of variation between the studies which is due to heterogeneity rather than due to chance. Values above 50% are often interpreted as indicative of clinically important heterogeneity. This is accompanied by a Cochran's Q chi-squared test for homogeneity where p-values less than 0.05 indicate statistically significant evidence of heterogeneity between sites.

eTable 1. Location of Sham Points for the Sham Acupuncture Control

Point	Patient position	Anatomical landmark	Point location	Relationship to channel
First treatment				
1. Arm 1	Supine	Between cubital crease and axillary fold	Anterior upper arm, 5 cun proximal to cubital crease, 4 cun below axillary fold, on the bulge of the biceps brachii	2 cun below PC2, 5 cun above PC3 0.5 cun lateral to PC channel
2. Forearm	Supine		On the forearm, about 6 cun proximal to the transverse wrist crease, medial to m. Palmaris longus	1 cun medial and 1 cun proximal to PC4, about 1 cun lateral to heart channel
3. Forearm	Supine	Lateral epicondyle of the humerus	On the extensor surface of the forearm	Midway between LI and TH channels, one cun distal and one cun lateral to LI11
4. Abdomen	Supine	Navel	2 cun above naval and 5 cun lateral	1 cun lateral to spleen channel
5.Abdomen	Supine	Navel	3 cun lateral to the midline,	Between the levels of CV6 and CV7.
6. Back *Start or finish with this point insert and retain for 5 minutes.*	Prone	T 12	5 cun lateral to T12	2 cun lateral to outer BL line
Second treatment				
1. Abdomen	Supine	Navel	2 cun above naval and 5 cun lateral	1 cun lateral to spleen channel
2. Abdomen	Supine	Navel	1 cun above naval, 5 cun lateral	1 cun lateral to spleen channel
3.Arm	Supine		2 cun from the wrist crease above the radial artery.	Between the Lung and Pericardium meridians
4. Foot	Supine	Anterior surface	Anterior to the junction of the 3rd and 4th metatarsals of the foot.	
5. Leg	Supine, knee partly flexed	Anterior crest of tibia	On the anterior crest of the tibia, 7 cun below the base of the patella	1 cun distal and 1.5 cun medial to St 37
6. Leg	Supine	Patella rectus femoris	On the bulge of the rectus femoris, 5 cun above the middle of the superior border of the patella	2 cun lateral and 3 cun proximal to SP10, 3 cun proximal and 2 cun medial to St32.
7. Ear	Supine		Middle of tragus	

Point	Patient position	Anatomical landmark	Point location	Relationship to channel
1. Arm	Supine		2 cun from the wrist crease above the radial artery.	Between the Lung and Pericardium meridians
2. Foot	Supine	Anterior surface	Anterior to the junction of the 3rd and 4th metatarsals of the foot.	
3. Leg	Supine	Lower leg, crest of the tibia	4 cun below the lateral knee-eye point, two fingerbreadths lateral to the crest of the tibia	Midway between Gall Bladder and Stomach meridian
4. Leg	Supine	Lower leg	2 cun above KD3,	midway between the Spleen and Kidney meridians
5.Face	Supine	Eyebrow	2 cun superior to the middle of the eyebrow, directly above the pupil	Between BL4 and GV meridian

eTable 2. Unadjusted Post-Hoc Secondary Study Outcomes by Study Group

Unadjusted post hoc secondary outcomes[a]	Acupuncture n=415[e]	Acupuncture sham control n=409[f]	Risk difference (%) / Mean difference (95% CI)	Relative risk (95% CI)	p-value[j]
Follicle stimulation hormone dose units [b,c](mean SD) Median IQR	2444 (1298) 2183 (1500, 3000)	2381 (1137) 2200 (1500, 3000)	62.3 (-107-232)	NA	0.72[k]
Number of oocytes aspirated[b,g]					0.82[l]
0	26 (6.3)	22 (5.4)	0.9 (-2.3, 4.1)	1.16 (0.67, 2.02)	
1-2	27 (6.5)	24 (5.9)	0.6 (-2.7, 3.9)	1.11 (0.65, 1.89)	
3-6	106 (25.5)	120 (29.3)	-3.8 (-9.9, 2.3)	0.87 (0.70, 1.09)	
7-12	153 (36.9)	150 (36.7)	0.2 (-6.4, 6.8)	1.01 (0.84, 1.20)	
>12	91 (21.9)	86 (21.0)	0.9 (-4.7, 6.5)	1.04 (0.80, 1.35)	
[d]Number of embryos transferred					
0	114 (27.5)	102 (24.9)	2.5 (-3.5,8.5)	1.10 (0.88, 1.39)	0.83
1	200 (48.2)	214 (52.3)	-4.1 (-11.0,2.7)	0.92 (0.80,1.06)	0.24
2	101 (24.3)	93 (22.7)	1.6 (-4.2,7.4)	1.07 (0.84,1.37)	0.59
Quality of embryo 1					
Excellent	150 (36.1)	164 (40.1)	-4.0 (-10.6,3.9)	0.90 (0.76,1.07)	0.24
Satisfactory	143 (34.5)	126 (30.8)	3.7 (-2.8,10.1)	1.12 (0.92,1.36)	0.26
Unsatisfactory	8 (1.9)	14 (3.4)	-1.5 (-3.7,0.7)	0.56 (0.24,1.33)	0.19
Quality of embryo 2					
Excellent	26 (6.3)	25 (6.1)	0.2 (-3.1,3.4)	1.03 (0.60,1.74)	0.93
Satisfactory	63 (15.2)	58 (14.2)	1.0 (-3.8,5.8)	1.07 (0.77,1.49)	0.69
Unsatisfactory	12 (2.9)	10 (2.4)	0.5 (-1.8,2.7)	1.18 (0.52,2.71)	0.69
Stage of embryo development					
Cleavage stage	171 (41.2)	146 (35.7)	5.5 (-1.1,12.1)	1.15 (0.97,1.37)	0.11
Blastocyst stage	130 (31.3)	161 (39.4)	-8.0 (-14.6,-1.5)	0.80 (0.66,0.96)	0.02
Pregnancy loss [h]					
Ectopic pregnancy	3/101 (3.0)	4/86 (4.7)	-1.7 (-7.2,3.9)	0.64 (0.15,2.78)	0.55
Stillbirth among clinical pregnancy	2/101 (2.0)	0/86 (0)	2.0 (-0.7,4.7)	4.26 (0.21,87.64)	0.35
Birthweight [b,i] (g)	3190.8 (560.1)	3144.9 (747)	[j] 45.9 (-170.6-260.5)	NA	0.68[k]
Gestational age at delivery[b,i] (weeks)	38.7 (2.3)	38.0 (3.0)	[m]0.77 (-0.11-1.64)	NA	0.08
Congenital abnormality	8 (2.0)	3 (0.7)	1.3 (-0.4-2.9)	2.69 (0.72,10.08)	0.14

[a] data are n and %,
[b]mean and SD
[c] n=397 acupuncture group (5 missing data and 1 woman with 0 FSH excluded), n=401) sham acupuncture control 2 missing data
[d]women undergo a transfer of 1 or 2 embryos only at the recruiting sites.
[e] 12/415 women did not proceed with IVF (3 were pregnant, 3 converted to IUI, 2 had unrelated health issues, 4 changed their minds)
[f] 6/409 women did not proceed with IVF (3 were pregnant, 3 changed their mind)
[g] n=403 n=402, (one missing in sham acupuncture control group)
[h] pregnancies due to IVF are 101 in the acupuncture group and 86 in the sham acupuncture group
[i] births due to IVF are 73 in the acupuncture group and 72 in the sham acupuncture group
[j] unless otherwise specified, this tests the hypothesis that relative risk is equal to 1.
[k] independent samples t-test testing the hypothesis that the means are equal
[l] Pearson's chi-square testing the hypothesis of no association with treatment group
[m] Mean difference

Note: Days in nursery or special care nursery (acupuncture n=15, median and range 10 (1,70), sham acupuncture n=16, median and range 6 (0.4,46).

eTable 3. Post Hoc Analyses of Selected Outcomes of Women Who Underwent an Embryo Transfer by Study Group

	Acupuncture	Acupuncture sham control	Risk difference % (95% CI)	Relative risk (95% CI)	p-value
Women undergoing cleavage embryo transfer					
Number with livebirth	34/171 (19.9)	30/146 (20.5)	-0.7 (-9.5,8.2)	0.97 (0.62,1.50)	0.88
Clinical pregnancy achieved(confirmed by sac on ultrasound)	48/171 (28.1)	38/146 (26.0)	2.0 (-7.8,11.8)	1.08 (0.75,1.55)	0.68
Number with miscarriage	12/171 (7.0)	5/146 (3.4)	3.6 (-1.2,8.4)	2.05 (0.74,5.68)	0.17
Women undergoing blastocyst embryo transfer					
Number with livebirth	39/130 (30.0)	42/161 (26.1)	3.9 (-6.5,14.3)	1.15 (0.79,1.65)	0.46
Clinical pregnancy achieved(confirmed by sac on ultrasound)	53/130 (40.8)	48/161 (29.8)	11.0 (0.0,22.0)	1.37 (1.00,1.87)	0.051
Number with miscarriage	11/130 (8.5)	5/161 (3.1)	5.4 (-0.1,10.8)	2.72 (0.97,7.64)	0.057
Women with 0-1 IVF cycles					
Number with livebirth	48/153 (31.4)	48/166 (28.9)	2.5 (-0.8,12.5)	1.09 (0.78,1.52)	0.63
Clinical pregnancy achieved(confirmed by sac on ultrasound)	64/153 (41.8)	53/166 (31.9)	9.9 (-0.1,20.5)	1.31 (0.98,1.75)	0.07
Women with 2+ IVF cycles					
Number with livebirth	25/148 (16.9)	24/141 (17.0)	-0.1 (-8.8,8.5)	0.99 (0.60,1.65)	0.98
Clinical pregnancy achieved(confirmed by sac on ultrasound)	37/148 (25.0)	33/141 (23.4)	1.6 (-8.3,11.5)	1.07 (0.71,1.61)	0.75
Women with 0 or 1 treatment session					
Number with livebirth	5/29 (17.2)	8/22 (36.4)	-19.1 (-43.5,5.2)	0.47 (0.18,1.25)	0.13
Clinical pregnancy achieved(confirmed by sac on ultrasound)	9/29 (31.0)	8/22 (36.4)	-5.3 (-31.6,20.9)	0.85 (0.39,1.85)	0.69
Women with 2+ treatment sessions					
Number with livebirth	68/272 (25.0)	64/285 (22.5)	2.5 (-4.5,9.6)	1.11 (0.83,1.50)	0.48
Clinical pregnancy achieved(confirmed by sac on ultrasound)	92/272 (33.8)	78/285 (27.4)	6.5 (-1.2,14.1)	1.24 (0.96,1.59)	0.10

[1]15 women received 0 treatments and data is missing for one woman.

eTable 4. Assessment of Blinding Using the Bang Blinding Index

	Treatment guess after completing treatment (n %)			
Group	**Acupuncture**	**Sham control**	**not answered**	**Bang blinding index[e] P value**
Acupuncture	180/415 (43.4)[a]	104/415 (25.1)	131/415 (31.6)	0.183[h] <0.001[c]
Sham control	142/409 (34.7)	168/409* (41.1)[b]	99/409 (24.2)	0.064 0.139[d]
Acupuncture	**Treatment guess after completing treatment**			**Response bias[f] P value**
				Z=2.08 0.03
	Treatment guess two weeks after embryo transfer (n %)			
	true	**sham**	**not answered**	**Bang blinding index P value**
Acupuncture	158/415 (38.1)[a]	108/415 (26.0)	149/415 (35.9)	0.120[i] 0.002[c]
Sham control	134/409 (32.8)	139/409* (34.0)[b]	136/409 (33.3)	0.012 0.762[d]
Acupuncture	**Treatment guess two weeks after embryo transfer**			**Response bias[g] P value**
				Z=1.96 0.05

[a]Women who received acupuncture who guessed they received acupuncture
[b]Women who received the sham control who guessed they received the sham control
[c]Women receiving acupuncture were more likely to guessthey received acupuncture.
[d]Women receiving the sham control were not more likely to guess they received the sham control.
[e]The Bang Blinding index represents the proportion of participants making a correct treatment guess beyond chance. A positive index represents a correct guess, and a negative index represents a guess in the opposite direction. A score of 0 is consistent with perfect blinding, The Bang Index suggest that significant unblinding in one group but not the other may be caused by an overall response bias,
[f,g]A response bias was calculated for at the two time periods. The response bias indicated respondents were slightly more likely to believe they are on active treatment than sham.[h,i]Interpretation of the Bang Index and response bias by Bang et al[4] indicates, that a value of >2 as suggestive of unblinding. The acupuncture group returned a statistically significant result although the values were less than the 2 cut off.

eReferences

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