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ACUPUNCTURE TO IMPROVE LIVEBIRTHS FOR WOMEN UNDERGOING IVF: FINDINGS FROM A RANDOMISED CONTROLLED TRIAL

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DECLARATIONS

- Caroline Smith declares; 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 to the design of the acupuncture treatment used in this study. As a medical research institute, the National Institute of Complementary Medicine 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.

ACUPUNCTURE AND INFERTILITY

- complementary health approaches used by 30-60% women undergoing ART
- acupuncture a frequently used adjunctive treatment during IVF
- used to improve fertility, overall health and wellbeing and quality of life
- best treatment estimate from systematic reviews (2008) suggested a benefit with improving livebirths (OR 1.91, 95% CI 1.19- 3.06).
- updated Cochrane systematic review acupuncture performed around the time of embryo transfer found no significant difference in live births between acupuncture and sham control (OR 1.03, 95% CI 0.67 to 1.58, p= 0.88, I^2 = 72%, 5 trials, n=1,656), low risk of bias found in 4 trials
- benefit from acupuncture compared with usual care (OR 1.55, 95% CI 1.14 to 2.12, p=0.006, 3 trials, n=849).

AIMS

- to determine the clinical efficacy of acupuncture compared with a sham control using a non penetrating needle for women undergoing a fresh IVF cycle on livebirths
- secondary aims:
  - to determine the personal and social context of acupuncture in IVF patients, explain the reasons why the acupuncture may or may not have worked, and identify other effects of acupuncture.

RANDOMISED CONTROLLED TRIAL

- recruitment undertaken at 16 IVF centres in Australia & New Zealand
- inclusion criteria
  - < 43 years and undergoing a fresh IVF or ICSI cycle
- exclusion criteria
  - previously randomised to the study
  - planning pre-implantation genetic diagnosis
  - receiving donor eggs
  - currently having acupuncture

RCT - POWER

- to detect a 7% increase in the proportion of women that report a live birth between the treatment and placebo control, with 80% power at the 5% significance level will require 449 women per group
- we allowed for a loss of 30% due to cancelled cycles, or no embryo transfer
- sample size of 1168 women required

- ethics approved by Western Sydney University Ethics Review Committee, plus HREC associated with IVF units

STUDY TREATMENT PROTOCOLS

- all women received standard ovarian stimulation, egg retrieval, fertilisation and embryo transfer as determined by their treating clinician
- acupuncture treatment protocol developed using a Delphi consensus (Smith et al 2012)
- 3 treatments of manual acupuncture, first treatment administered between day 6–8 of ovarian stimulation, 2 treatments on the day of embryo transfer (immediately before and after ET).
- needling sensation de qi obtained following insertion, and needles stimulated midway through 25 minute treatment

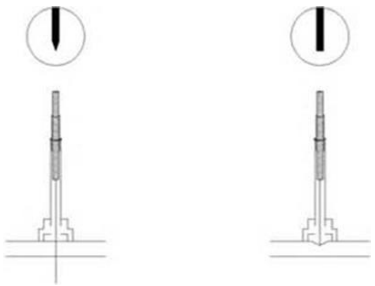
ACUPUNCTURE AND SHAM CONTROL

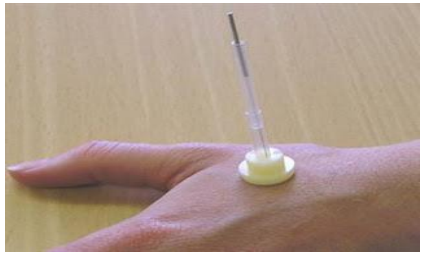
Acupuncture

- first treatment comprised of 5 standard points plus up to 5 additional points based on a TCM diagnosis
- on the day of embryo transfer: initial treatment administered prior to transfer: 6 points
- post transfer 5 points administered

Sham control

- needle has a retractable needle shaft, a blunt tip, and is supported by a plastic ring and a guide tube, with a double sided adhesive ring
- skin penetration did not occur, control points placed in the vicinity of the acupuncture points away from acupuncture points



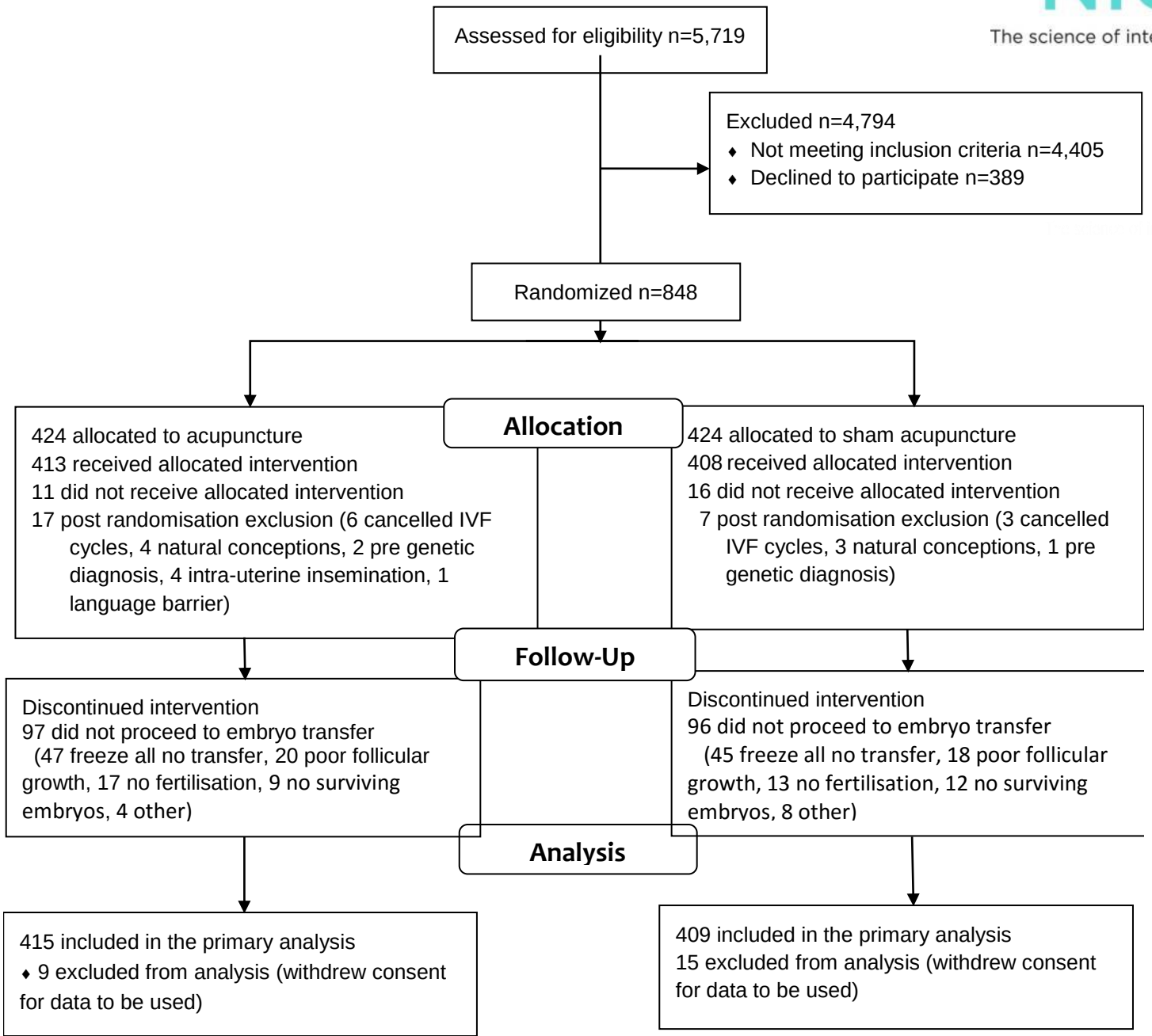


DATA COLLECTION POINTS

- primary outcome: live birth defined as the delivery of one or more living infants, with greater than 20 weeks gestation or at least 400 grams birth weight
- secondary endpoints: clinical pregnancy; total dose of FSH stimulation, numbers of oocytes aspirated and fertilised, stage of embryo development at transfer, pregnancy loss, gestational age, birthweight, congenital abnormality, adverse events

ANALYSES

- intention-to-treat analysis performed excluding women who withdrew consent for use of their data
- primary and secondary outcomes analysis compared the proportions of women with livebirths in the two groups using relative risks (RR) with 95% confidence intervals (CI) for categorical measures and mean differences and 95% CI for numerical measures



	Acupuncture n=415	Acupuncture sham control n=409
Age (years)	35.4 (4.3)	35.5 (4.3)
Duration of infertility		
- **<2 years**	113 (27.3%)	119 (29.3%)
- **2-5 years**	198 (47.8%	195 (48.0%)
- **>5 years**	103 (24.9%)	92 (22.7%)
Fertility diagnosis		
- **Male factor**	130 (31.3)	117 (28.6)
- **Tubal**	28 (6.8)	40 (9.8)
- **Unexplained**	155 (37.4)	147 (35.9)
- **Endometriosis**	39 (9.4)	50 (12.2)
- **Other includes PCOS**	117 (28.2)	113 (27.6)
Parity		
- **0**	303 (73.0%)	303 (74.3%)
- **>=1**	112 (27.0%)	105 (25.7%)
Number of IVF cycles		
- **0**	127 (30.7%)	116 (28.5%)
- **1**	102 (24.6%)	106 (26.0%)
- **>=2**	185 (44.7%)	186 (45.5%)
Previous acupuncture use	225 (54.5%)	200 (49.1%)
Race (n-807)		
- **White**	314 (75.7%)	322 (79.1%)
- **Asian**	70 (16.9%)	56 (13.8%)
- **Other**	31 (7.5%)	29 (7.1%)

The average trial participant was:

- 35 years old
- Caucasian
- had infertility for greater than two years
- had no children
- undergone multiple IVF cycles
- 50% had used acupuncture previously.
- no differences between groups at baseline

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	Acupuncture n=415	Acupuncture sham control n=409	Relative risk (95% CI)	p-value
Primary outcome live birth /participant	74/405 (18.3%)	72/404 (17.8%)	1.0 (0.76-1.38)	0.83
Posthoc exploratory analyses Livebirth per participant receiving an embryo transfer	73/301 (24.3)	72/307 (23.5)	1.0 (0.78-1.37)	0.77

Clinical outcomes

- live births did not differ between groups (RR 1.0 95% 0.76-1.38; p=0.83) with 74 (18.3%) women receiving acupuncture resulted in a live birth vs 72 (17.8%) receiving the sham control.

secondary outcomes	Acupuncture n=415	Acupuncture sham control n=409	Relative risk (95% CI)	p-value
Clinical pregnancy per participant	105/408 (25.7)	88/406 (21.7)	1.19 (0.93-1.52	0.17
Posthoc exploratory analyses clinical pregnancy per participant receiving an embryo transfer	101/301 (33.6)	86/307 (28.0)	1.20 (0.94,1.52)	0.140
Miscarriage among clinical pregnancy	23/101 (22.8)	10/86 (11.6)	1.96 (0.99-3.88)	0.054

Post hoc secondary outcomes	Acupuncture n=415	Acupuncture sham control n=409	Relative risk (95% CI)	p-value
FSH dose (mean SD)	2444 (1298)	2381 (1137)	NA	0.72
oocytes aspirated (n)				0.82
0	26 (6.5)	22 (5.5)	1.16 (0.67, 2.02)	0.59
1-2	27 (6.7)	24 (6.0)	1.11 (0.65, 1.89)	0.70
3-6	106 (26.3)	120 (29.9)	0.87 (0.70, 1.09)	0.22
7-12	153 (38.0)	150 (37.3)	1.01 (0.84, 1.20)	0.95
>12	91 (22.6)	86 (21.4)	1.04 (0.80, 1.35)	0.75
Undergoing embryo transfer	301 (72.5)	307 (75.1)	0.96 (0.89,1.05)	0.41
Cleavage stage	171 (41.2)	146 (35.7)	1.15 (0.97,1.37)	0.11
Blastocyst stage	130 (31.3)	161 (39.4)	0.80 (0.66-0.96)	0.02
Ectopic pregnancy	3/101 (3.0)	4/86 (4.7)	0.64 (0.15-2.78)	0.55
Stillbirth	2/101 (2.0)	0/86 (0)	4.26 (0.21-87.64)	0.35
Birthweight (n 73/72)	3190.8 (560.1)	3144.9 (747)	NA	0.68
Gestational age at delivery (weeks)	38.7 (2.3)	38.0 (3.0)	NA	0.08
Congenital abnormality	8 (2.0)	3 (0.7)	2.69 (0.72-10.08)	0.14

Pre-specified secondary outcomes	Acupuncture n=415 %	Acupuncture sham control n=409 %	Relative risk (95% CI)	p-value
Women who reported any adverse event	87/301 (28.9)	65/307 (21.2)	1.37 (1.03-1.81)	0.029
Tiredness	44/301 (14.6)	36/307 (11.7)	1.25 (0.83-1.88)	0.293
Discomfort on day of embryo transfer	31/301 (10.3)	15/307 (4.9)	2.11 (1.16-3.82)	0.014
Dizziness drowsiness	17/301 (5.7)	14/307 (4.6)	1.23 (0.62-2.47)	0.674
Pain	15/301 (5.0)	10/307 (3.3)	1.53 (0.70-3.35)	0.288
Bruising	15/301 (5.0)	4/307 (1.3)	3.82 (1.28-11.39)	0.016
Nausea, vomiting	8/301 (2.6)	4/307 (1.3)	2.04 (0.62,6.70)	0.240
Headaches	7/301 (2.3)	7/307 (2.3)	1.02 (0.36-2.87)	0.970

OVERVIEW OF QUALITATIVE STUDY

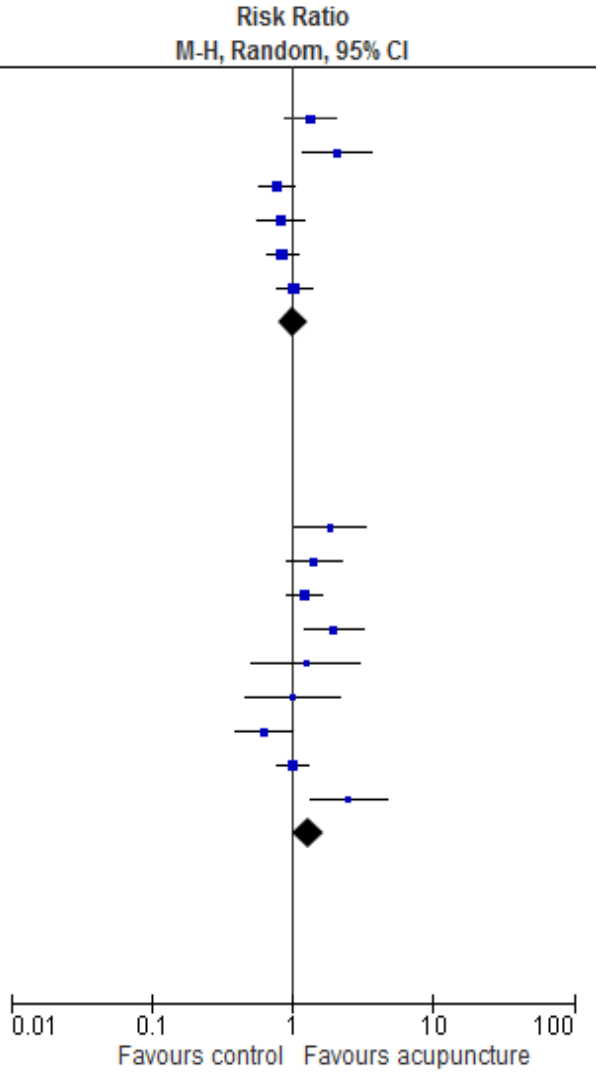
- aim to investigate women's perceptions of acupuncture during IVF and the RCT, how women thought about their use and experience of acupuncture, its effects and the outcomes
- 50 interviews were completed
- data transcribed and entered into Nvivo, coded, categorised and themes extracted.

FINDINGS

- reasons for joining the trial: altruism, taking an opportunity to achieve a better treatment outcome
- weighed risks and benefits of trial participation and concluded they had “nothing to lose”, “something to gain” and some wanted to try everything available so they could feel they “threw everything at it”.
- beliefs about effects of acupuncture on treatment outcome included scepticism to hopefulness that it could make a positive difference

Effect of acupuncture versus control on live birth

Study or Subgroup	Acupuncture Events	Acupuncture Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.3.1 Sham control							
Paulus 2003	35	100	26	100	14.4%	1.35 [0.88, 2.06]	2003
Dieterle 2006	33	116	15	109	10.9%	2.07 [1.19, 3.59]	2006
So 2009	55	185	71	185	19.3%	0.77 [0.58, 1.03]	2008
So 2010	33	113	40	113	15.9%	0.82 [0.56, 1.21]	2010
Anderson 2010	79	314	96	321	20.6%	0.84 [0.65, 1.08]	2010
Smith 2018	74	405	72	404	19.0%	1.03 [0.76, 1.38]	2017
Subtotal (95% CI)		**1233**		**1232**	**100.0%**	**1.01 [0.80, 1.28]**	
Total events	309		320				
Heterogeneity: Tau² = 0.05; Chi² = 13.89, df = 5 (P = 0.02); I² = 64%							
Test for overall effect: Z = 0.09 (P = 0.93)							
1.3.2 No adjunctive treatment							
Paulus 2002	26	80	14	80	10.0%	1.86 [1.05, 3.29]	2002
Westergaard 2006	58	199	19	93	12.2%	1.43 [0.90, 2.25]	2006
Madaschi 2010	70	208	57	208	15.7%	1.23 [0.92, 1.64]	2010
Omodei 2010	19	44	27	124	11.8%	1.98 [1.23, 3.19]	2010
Arnold 2010	10	102	8	102	5.9%	1.25 [0.51, 3.04]	2010
Feliciani 2011	8	23	8	23	6.9%	1.00 [0.45, 2.21]	2011
Craig 2014	18	57	28	56	12.0%	0.63 [0.40, 1.00]	2014
Morin 2017	78	214	76	210	16.5%	1.01 [0.78, 1.30]	2017
Gillerman 2018	27	78	11	79	9.1%	2.49 [1.33, 4.66]	2018
Subtotal (95% CI)		**1005**		**975**	**100.0%**	**1.30 [1.00, 1.68]**	
Total events	314		248				
Heterogeneity: Tau² = 0.09; Chi² = 21.80, df = 8 (P = 0.005); I² = 63%							
Test for overall effect: Z = 1.97 (P = 0.05)							



Test for subgroup differences: Chi² = 1.95, df = 1 (P = 0.16), I² = 48.8%

DISCUSSION

- no specific effects from acupuncture at the time of ovarian stimulation and embryo transfer on live births
- results consistent with high quality meta-analyses
- safety of acupuncture assessed by miscarriage supported by the findings from the Cochrane systematic review plus studies that find no evidence that acupuncture poses any risk to the mother or unborn fetus
- meta-analysis examining placebo devices in acupuncture research, found devices not necessarily inert controls
- usual-care alone group not included in the RCT

LIMITATIONS

- did not reach sample size, 95% CI of risk difference excluded the minimal clinically important difference of 7%, suggesting the study was not underpowered
- 193 women did not complete the study due to cancelled cycle, but intention to treat analysis and per protocol analysis produced similar results
- the short protocol widely used acupuncture protocol may no longer reflect current clinical practice, treatment is individualised, variation in the dosing characteristics of acupuncture

CONCLUSION

- acupuncture has not been shown to be superior to a sham control with improving reproductive
- future research should focus on different dosing acupuncture regimens
- no further research using sham devices alone is recommended and future research now focus on research designs that assess the total effects of acupuncture

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