Somatosensory stimulation and assisted reproduction

David Carr

Correspondence to
Dr David Carr, UCL Institute for Women's Health, University College London, 86–96 Chenies Mews, London WC1E 6HX, UK; davidcarr@doctors.org.uk

Accepted 12 December 2014

To cite: Carr D. *Acupunct Med* 2015;**33**:2–6.

The role of somatosensory stimulation (acupuncture and related techniques) as an adjunct to assisted reproductive technology (ART) has been hotly debated over the past decade. In the last 6 years there have been no fewer than 12 meta-analyses of 34 randomised controlled trials (table 1). Systematic and narrative reviews of the literature often report conflicting findings and opinions. Despite this controversy, subfertility remains one of the most common reasons that women consult an acupuncturist.[47] Meta-analysis of acupuncture trials is often challenging due to methodological diversity, and this is especially true for in vitro fertilisation (IVF) due to marked differences in timing (treatment given during the follicular phase, at the time of oocyte retrieval and/or embryo transfer (ET), and/or as luteal phase support) and the variety of interventions including manual acupuncture, electroacupuncture (EA), transcutaneous electrical acupuncture point stimulation (TEAS) and laser acupuncture. Various outcome measures have been used ranging from biochemical pregnancy rate to live birth rate (LBR), depending on the duration of follow-up. LBR ('take home baby rate') is considered to be the ideal primary outcome measure and is clearly most important to patients. Interestingly, concordance between studies with respect to point location is relatively high. The acupuncture points targeted generally correspond anatomically to the segmental innervation of the uterus and ovaries, irrespective of whether the primary approach to point selection is traditional or neurophysiological.

The paper by Shuai *et al*[48] used TEAS rather than needle acupuncture and examined its efficacy and mechanisms of action in women undergoing frozen-thawed ET. TEAS significantly increased the clinical pregnancy rate (CPR) and LBR relative to a sham intervention (mock TEAS). To date there has been one other (positive) trial of TEAS in IVF[43] and a third is currently underway.[49] Regarding the underlying mechanism, it has been hypothesised that acupuncture-like interventions improve endometrial receptivity, based on the observations of Stener-Victorin *et al*[50] and Ho *et al*[34] that EA reduces impedance to flow in the uterine arteries. It is often inferred, rightly or wrongly, that enhanced uterine blood flow equals improved endometrial blood flow. In support of this assumption, acupuncture has been shown to increase endometrial thickness compared with sham acupuncture and standard care.[44] However, Shuai *et al*[48] are the first to have shown positive effects on contemporary ultrasound markers of endometrial receptivity (three-dimensional endometrial and subendometrial vascularisation index and presence of a triple-line pattern) plus HOXA10 protein expression, a novel molecular marker. Interestingly, all these studies have used serial treatments that incorporate the follicular phase of the cycle. The most recent systematic review by Shen *et al*[12] only found evidence of benefit when follicular phase treatment was combined with treatment around ET, and not when timed around ET alone. It is argued that the latter approach, which typically consists of a single treatment before and one after ET (variations of the Paulus protocol[14]), is insufficient in duration and 'dose' to have any major effect on endometrial receptivity and/or blood flow, and that putative effects on pregnancy rates in this context may be due to inhibition of post-transfer uterine contractions[51] and/or reduction of patient anxiety,[52] both of which may adversely affect pregnancy rates.[53 54]

The efficacy of TEAS suggests that penetration of the skin or muscle is not required in order to effect endometrial receptivity and pregnancy rates, and this is supported by experiments on anaesthetised rats, wherein a measurable increase in uterine blood flow was observed during noxious pinching and innocuous brushing of the hind limb and perineum (regions innervated by the sacral segments).[55] This

Table 1 Randomised controlled trials and meta-analyses of acupuncture as an adjunct to assisted reproduction

	Manheimer 2008[1]	Ng 2008[2]	El-Toukhy 2008[3]	El-Toukhy 2009[4]	Cheong 2008[5]	Cheong 2010[6]	Qu 2012[7]	Zheng 2012a[8]	Zheng 2012b[9]	Cheong 2013[10]	Manheimer 2013[11]	Shen 2014[12]
Stener-Victorin *et al*[13]		✓	✓	✓	✓	✓	✓	✓	✓	✓		
Paulus *et al*[14]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Zhang *et al*[15]												✓
Stener-Victorin *et al*[16]		✓	✓	✓	✓	✓	✓	✓	✓	✓		
Paulus *et al*[17]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Zhang *et al*[18]												✓
Humaidan and Stener-Victorin[19]		✓	✓	✓	✓	✓	✓	✓	✓	✓		
Gejervall *et al*[20]		✓	✓	✓	✓	✓	✓	✓		✓		
Dieterle *et al*[21]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Westergaard *et al*[22]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Smith *et al*[23]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sator-Katzenschlager *et al*[24]		✓	✓	✓	✓	✓	✓	✓	✓	✓		
Domar *et al*[25]*	✓		✓		✓							
Benson *et al*[26]	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓
Cui *et al*[27]												✓
Craig *et al*[28]*			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cui *et al*[29]								✓	✓			
Fratterelli *et al*[30]								✓	✓	✓	✓	✓
Domar *et al*[31]*				✓		✓	✓	✓	✓	✓	✓	✓
So *et al*[32]				✓		✓	✓	✓	✓	✓	✓	✓
Chen *et al*[33]							✓	✓	✓			
Ho *et al*[34]								✓	✓	✓		✓
Magarelli *et al*[35]								✓				
So and Ng[36]								✓	✓	✓	✓	✓
Andersen *et al*[37]							✓	✓	✓	✓	✓	✓
Madaschi *et al*[38]								✓	✓	✓	✓	✓
Omodei *et al*[41]											✓	✓
Arnoldi *et al*[40]								✓	✓		✓	
Feliciani *et al*[41]											✓	
Moy *et al*[42]							✓	✓	✓	✓	✓	✓
Zhang *et al*[43]												✓
Villahermosa *et al*[44]												✓
Rashidi *et al*[45]												
Craig *et al*[46]*												

Evidence matrix showing 12 meta-analyses of acupuncture and 34 primary randomised controlled trials, illustrating the variation with respect to included studies and the evolution of the evidence base over time. For simplicity, only first author names and year of publication are presented. Trials and reviews that report at least one positive outcome are coloured green while negative studies are coloured red.
*Indicate duplicated data where conference abstracts have subsequently been published in full.

calls into question the validity of sham controls that elicit strong cutaneous stimuli, such as the Streitberger needle, which is not generally considered to be physiologically inert.[56] In their recent meta-analysis, Zheng *et al*[8] performed subgroup analyses comparing pregnancy rates of patients receiving verum acupuncture versus non-Streitberger controls and demonstrated a significant increase in CPR (OR 1.34, 95% CI 1.08 to 1.67) and LBR (OR 1.63, 95% CI 1.16 to 2.30). When trials using Streitberger controls were included the effects on LBR disappeared and the effects on CPR were smaller, albeit still statistically significant (OR 1.22, 95% 1.01 to 1.47). The relevance of sham-controlled trials in IVF research has been debated at length (see Manheimer[57] for a comprehensive overview), particularly in view of the fact that pregnancy is an objective outcome measure for which blinding is less critical.[58–61]

When sham-controlled trials are included, the three latest systematic reviews demonstrate no pooled benefit of acupuncture[10–12] although Shen *et al*[12] did find evidence of benefit with follicular phase treatment plus treatment around ET. Manheimer *et al*[11] reported that acupuncture treatment appears to be more successful in studies with lower baseline pregnancy rates. Their subgroup analysis appears to have been heavily influenced by one particular negative (and grossly underpowered) trial by Craig *et al*,[28 46] in which the baseline pregnancy rate in the untreated control group was extraordinarily high at 69.6% while the rate following acupuncture (Paulus protocol) was similar to previous studies using the same methodology (43.8% vs 42.5%,[14] 43.0%[17] and 43.8%[32]). However, assuming that the relationship is a genuine one, there are some potential explanations. Hypothetically, if an IVF unit could maximise its pregnancy rate from a biological perspective, there would be limited scope for acupuncture to increase it further as it is unlikely to have supra-physiological effects. However, in the presence of a 'performance gap' between actual and achievable pregnancy rates, there may be a greater potential for a shift. Alternatively, this observation may represent a statistical artifact as the lower the baseline pregnancy rate, the smaller the sample size required to show a difference (figure 1). Advanced maternal age has a powerful influence on baseline pregnancy rates; IVF success rates range from 1.9% in the over-45s to 32.2% in the under-35s (Human Fertilisation and Embryology Authority 2010 data).

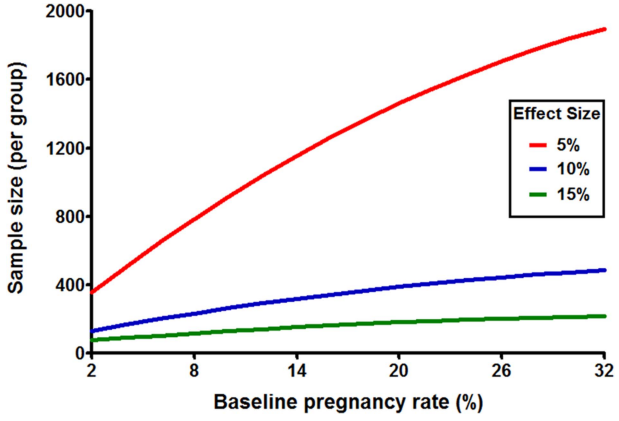

Figure 1 Effect of baseline pregnancy rate on sample size calculations. The graph shows the relationship between the baseline pregnancy rates in clinical trials and the number of patients required per group to show a significant difference (at 90% power and significance level of p<0.05) at three fixed effect sizes of 5%, 10% and 15%, respectively. Sample size calculation was performed using freely available power calculators for binary outcome superiority trials (http://www.sealedenvelope.com).

Ultimately, further research is required before somatosensory stimulation techniques such as acupuncture or TEAS can be widely adopted for ART. Meanwhile, agreement is needed about the validity of sham controls, which may otherwise obscure the evidence.

Twitter Follow David Carr at @IntegratedOBGYN

Competing interests None.

Provenance and peer review Commissioned; internally peer reviewed.

REFERENCES

1 Manheimer E, Zhang G, Udoff L, *et al*. Effects of acupuncture on rates of pregnancy and live birth among women undergoing in vitro fertilisation: systematic review and meta-analysis. *BMJ* 2008;336:545–9.
2 Ng EH, So WS, Gao J, *et al*. The role of acupuncture in the management of subfertility. *Fertil Steril* 2008;90:1–13.
3 El-Toukhy T, Sunkara SK, Khairy M, *et al*. A systematic review and meta-analysis of acupuncture in in vitro fertilisation. *BJOG* 2008;115:1203–13.
4 El-Toukhy T, Khalaf Y. The impact of acupuncture on assisted reproductive technology outcome. *Curr Opin Obstet Gynecol* 2009;21:240–6.
5 Cheong YC, Hung Yu Ng E, Ledger WL. Acupuncture and assisted conception. *Cochrane Database Syst Rev* 2008;(4):CD006920.
6 Cheong Y, Nardo LG, Rutherford T, *et al*. Acupuncture and herbal medicine in in vitro fertilisation: a review of the evidence for clinical practice. *Hum Fertil (Camb)* 2010;13:3–12.
7 Qu F, Zhou J, Ren RX. Effects of acupuncture on the outcomes of in vitro fertilization: a systematic review and meta-analysis. *J Altern Complement Med* 2012;18:429–39.
8 Zheng CH, Huang GY, Zhang MM, *et al*. Effects of acupuncture on pregnancy rates in women undergoing in vitro fertilization: a systematic review and meta-analysis. *Fertil Steril* 2012;97:599–611.
9 Zheng CH, Zhang MM, Huang GY, *et al*. The role of acupuncture in assisted reproductive technology. *Evid Based Complement Alternat Med* 2012;2012:543924.
10 Cheong YC, Dix S, Hung Yu Ng E, *et al*. Acupuncture and assisted reproductive technology. *Cochrane Database Syst Rev* 2013;7:CD006920.
11 Manheimer E, van der Windt D, Cheng K, *et al*. The effects of acupuncture on rates of clinical pregnancy among women undergoing in vitro fertilization: a systematic review and meta-analysis. *Hum Reprod Update* 2013;19:696–713.

12 Shen C, Wu M, Shu D, *et al*. The role of acupuncture in in vitro fertilization: a systematic review and meta-analysis. *Gynecol Obstet Invest*. Published Online First 16 May 2014.
13 Stener-Victorin E, Waldenstrom U, Nilsson L, *et al*. A prospective randomized study of electro-acupuncture versus alfentanil as anaesthesia during oocyte aspiration in in-vitro fertilization. *Hum Reprod* 1999;14:2480–4.
14 Paulus WE, Zhang M, Strehler E, *et al*. Influence of acupuncture on the pregnancy rate in patients who undergo assisted reproduction therapy. *Fertil Steril* 2002;77:721–4.
15 Zhang M, Huang G, Lu F, *et al*. Effect of acupuncture on rate of pregnancy among women undergoing embryo transfer. *Zhongguo Zhen Jiu* 2002;22:507–9.
16 Stener-Victorin E, Waldenstrom U, Wikland M, *et al*. Electro-acupuncture as a peroperative analgesic method and its effects on implantation rate and neuropeptide Y concentrations in follicular fluid. *Hum Reprod* 2003;18:1454–60.
17 Paulus WE, Zhang M, Strehler E, *et al*. Placebo-controlled trial of acupuncture effects in assisted reproduction therapy. *Hum Reprod* 2003;18:18–19.
18 Zhang M, Huang G, Lu F, *et al*. Effect of acupuncture on rate of pregnancy among women undergoing embryo transfer: a prospective randomized placebo controlled trial. *Zhongguo Zhen Jiu* 2003;23:3–5.
19 Humaidan P, Stener-Victorin E. Pain relief during oocyte retrieval with a new short duration electro-acupuncture technique: an alternative to conventional analgesic methods. *Hum Reprod* 2004;19:1367–72.
20 Gejervall AL, Stener-Victorin E, Moller A, *et al*. Electro-acupuncture versus conventional analgesia: a comparison of pain levels during oocyte aspiration and patients' experiences of well-being after surgery. *Hum Reprod* 2005;20:728–35.
21 Dieterle S, Ying G, Hatzmann W, *et al*. Effect of acupuncture on the outcome of in vitro fertilization and intracytoplasmic sperm injection: a randomized, prospective, controlled clinical study. *Fertil Steril* 2006;85:1347–51.
22 Westergaard LG, Mao Q, Krogslund M, *et al*. Acupuncture on the day of embryo transfer significantly improves the reproductive outcome in infertile women: a prospective, randomized trial. *Fertil Steril* 2006;85:1341–6.
23 Smith C, Coyle M, Norman RJ. Influence of acupuncture stimulation on pregnancy rates for women undergoing embryo transfer. *Fertil Steril* 2006;85:1352–8.
24 Sator-Katzenschlager SM, Wolfler MM, Kozek-Langenecker SA, *et al*. Auricular electro-acupuncture as an additional perioperative analgesic method during oocyte aspiration in IVF treatment. *Hum Reprod* 2006;21:2114–20.
25 Domar A, Meshay I, Keliher J, *et al*. The impact of acupuncture on IVF outcome. *Fertil Steril* 2006;86(Suppl 2):S378–9.
26 Benson M, ElKind-Hirsch K, Theall A, *et al*. Impact of acupuncture before and after embryo transfer on the outcome of invitro fertilization cycles: a prospective single blind randomised study. *Fertil Steril* 2006;86(Suppl 2):S135.
27 Cui W, Sun W, Liu L, *et al*. Effects of electroacupuncture on patients undergoing in vitro fertilization and embryo transplantation. *Zhongguo Fu You Bao Jian* 2006;22:3403–5.
28 Craig LB, Criniti AR, Hansen KR, *et al*. Acupuncture lowers pregnancy rates when performed before and after embryo transfer. *Fertil Steril* 2007;88(Suppl 1):S40.
29 Cui W, Sun W, Liu L, *et al*. Study of the effect of electro-acupuncture treatment on the patients undergomg in vitro-fertilization and embryo transfer. *Chin Matern Child Health* 2007;22:403–5.
30 Fratterelli JL, Leondires MR, Fong K, *et al*. Laser acupuncture before and after embryo transfer improves ART delivery rates: results of a prospective randomized double-blinded placebo controlled five-armed trial involving 1,000 patients. *Fertil Steril* 2008;90(Suppl 1):S105.
31 Domar AD, Meshay I, Kelliher J, *et al*. The impact of acupuncture on in vitro fertilization outcome. *Fertil Steril* 2009;91:723–6.
32 So EW, Ng EH, Wong YY, *et al*. A randomized double blind comparison of real and placebo acupuncture in IVF treatment. *Hum Reprod* 2009;24:341–8.
33 Chen J, Liu LL, Cui W, *et al*. Effects of electroacupuncture on in vitro fertilization-embryo transfer (IVF-ET) of patients with poor ovarian response. *Zhongguo Zhen Jiu* 2009;29:775–9.
34 Ho M, Huang LC, Chang YY, *et al*. Electroacupuncture reduces uterine artery blood flow impedance in infertile women. *Taiwan J Obstet Gynecol* 2009;48:148–51.
35 Magarelli PC, Cridennda DK, Cohen M. Changes in serum cortisol and prolactin associated with acupuncture during controlled ovarian hyperstimulation in women undergoing in vitro fertilization-embryo transfer treatment. *Fertil Steril* 2009;92:1870–9.
36 So EW, Ng EH. Acupuncture in reproductive medicine. *Womens Health (Lond Engl)* 2010;6:551–63.
37 Andersen D, Lossl K, Nyboe Andersen A, *et al*. Acupuncture on the day of embryo transfer: a randomized controlled trial of 635 patients. *Reprod Biomed Online* 2010;21:366–72.
38 Madaschi C, Braga DP, Figueira Rde C, *et al*. Effect of acupuncture on assisted reproduction treatment outcomes. *Acupunct Med* 2010;28:180–4.
39 Omodei U, Piccioni G, Tombesi S, *et al*. Effect of acupuncture on rates of pregnancy among women undergoing in vitro fertilization. *Fertil Steril* 2010;94:S170.
40 Arnoldi M, Diaferia D, Corbucci MG, *et al*. The role of acupuncture in patients at unfavourable reproductive prognosis in IVF: a prospective randomised study. *Hum Reprod* 2010;25 (Suppl 1):i257.
41 Feliciani E, Ferraretti AP, Paesano C, *et al*. The role of acupuncture in ART: preliminary results of an ongoing prospective randomized study. *Hum Reprod* 2011;26:i230.
42 Moy I, Milad MP, Barnes R, *et al*. Randomized controlled trial: effects of acupuncture on pregnancy rates in women undergoing in vitro fertilization. *Fertil Steril* 2011;95:583–7.
43 Zhang R, Feng XJ, Guan Q, *et al*. Increase of success rate for women undergoing embryo transfer by transcutaneous electrical acupoint stimulation: a prospective randomized placebo-controlled study. *Fertil Steril* 2011;96:912–16.
44 Villahermosa DI, Santos LG, Nogueira MB, *et al*. Influence of acupuncture on the outcomes of in vitro fertilisation when embryo implantation has failed: a prospective randomised controlled clinical trial. *Acupunct Med* 2013;31:157–61.
45 Rashidi BH, Tehrani ES, Hamedani NA, *et al*. Effects of acupuncture on the outcome of in vitro fertilisation and intracytoplasmic sperm injection in women with polycystic ovarian syndrome. *Acupunct Med* 2013;31:151–6.
46 Craig LB, Rubin LE, Peck JD, *et al*. Acupuncture performed before and after embryo transfer: a randomized controlled trial. *J Reprod Med* 2014;59:313–20.
47 Hopton AK, Curnoe S, Kanaan M, *et al*. Acupuncture in practice: mapping the providers, the patients and the settings in a national cross-sectional survey. *BMJ Open* 2012;2:e000456.
48 Shuai Z, Lian F, Li P, *et al*. Effect of transcutaneous electrical acupuncture point stimulation on endometrial receptivity in

women undergoing frozen-thawed embryo transfer: a single-blind prospective randomised controlled trial. *Acupunct Med* 2015;33:9–15.
49 Zheng CH, Zhang J, Wu J, *et al*. The effect of transcutaneous electrical acupoint stimulation on pregnancy rates in women undergoing in vitro fertilization: a study protocol for a randomized controlled trial. *Trials* 2014;15:162.
50 Stener-Victorin E, Waldenstrom U, Andersson SA, *et al*. Reduction of blood flow impedance in the uterine arteries of infertile women with electro-acupuncture. *Hum Reprod* 1996;11:1314–17.
51 Kim J, Shin KH, Na CS. Effect of acupuncture treatment on uterine motility and cyclooxygenase-2 expression in pregnant rats. *Gynecol Obstet Invest* 2000;50:225–30.
52 Isoyama D, Cordts EB, de Souza van Niewegen AM, *et al*. Effect of acupuncture on symptoms of anxiety in women undergoing in vitro fertilisation: a prospective randomised controlled study. *Acupunct Med* 2012;30:85–8.
53 Balk J, Catov J, Horn B, *et al*. The relationship between perceived stress, acupuncture, and pregnancy rates among IVF patients: a pilot study. *Complement Ther Clin Pract* 2010;16:154–7.
54 Fanchin R, Righini C, Olivennes F, *et al*. Uterine contractions at the time of embryo transfer alter pregnancy rates after in-vitro fertilization. *Hum Reprod* 1998;13:1968–74.
55 Hotta H, Uchida S, Shimura M, *et al*. Uterine contractility and blood flow are reflexively regulated by cutaneous afferent stimulation in anesthetized rats. *J Auton Nerv Syst* 1999;75:23–31.
56 Lundeberg T, Lund I, Sing A, *et al*. Is placebo acupuncture what it is intended to be? *Evid Based Complement Alternat Med* 2011;2011:932407.
57 Manheimer E. Selecting a control for in vitro fertilization and acupuncture randomized controlled trials (RCTs): how sham controls may unnecessarily complicate the RCT evidence base. *Fertil Steril* 2011;95:2456–61.
58 Wood L, Egger M, Gluud LL, *et al*. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008;336:601–5.
59 Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med* 2001;344:1594–602.
60 Hrobjartsson A, Gotzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev* 2010;(1):CD003974.
61 Kaptchuk TJ, Stason WB, Davis RB, *et al*. Sham device v inert pill: randomised controlled trial of two placebo treatments. *BMJ* 2006;332:391–7.

Somatosensory stimulation and assisted reproduction

David Carr

Acupunct Med 2015 33: 2-6 originally published online January 20, 2015
doi: 10.1136/acupmed-2014-010739