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Impact of Whole Systems Traditional Chinese Medicine on In Vitro Fertilization Outcomes

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Abstract

Patients undergoing IVF patients may receive either acupuncture or whole-systems traditional Chinese medicine (WS-TCM) as an adjuvant IVF treatment. WS-TCM is a complex intervention that can include acupuncture, Chinese herbal medicine, dietary, lifestyle recommendations, or both. In this retrospective cohort study, 1231 IVF patient records were reviewed to assess the effect of adjuvant WS-TCM on IVF outcomes compared among three groups: IVF with no additional treatment; IVF and elective acupuncture on day of embryo transfer; or IVF and elective WS-TCM. The primary outcome was live birth. Of 1069 non-donor cycles, WS-TCM was associated with greater odds of live birth compared with IVF alone (adjusted odds ratio [AOR] 2.09; 95% confidence interval [CI] 1.36 to 3.21), or embryo transfer with acupuncture only (AOR 1.62; 95% CI 1.04 to 2.52). Of 162 donor cycles, WS-TCM was associated with increased live births compared with all groups (odds Ratio [OR] 3.72; 95% CI 1.05 to 13.24, unadjusted] or embryo transfer with acupuncture only (OR 4.09; 95% CI: 1.02 to 16.38, unadjusted). Overall, IVF with adjuvant WS-TCM was associated with greater odds of live birth in donor and non-donor cycles. These results should be taken cautiously as more rigorous research is needed.

Keywords

acupuncture; Chinese herbal medicine; traditional Chinese medicine; whole systems; in vitro fertilization; live births; embryo transfer

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Introduction

Women undergoing IVF commonly pursue adjuvant complementary and alternative health approaches to support their cycles. Given that early studies have found that acupuncture significantly improves IVF pregnancy rates, patients increasingly choose adjuvant acupuncture to optimize their chances of pregnancy and live birth (de Lacey *et al.*, 2009). Utilization rates are unclear. In a survey of 428 Northern Californian couples, 22% reported using acupuncture (Smith *et al.*, 2010), but of 118 Boston-area women surveyed, 47% women reported using acupuncture and 17% used herbs during their assisted reproduction technique cycle (Domar *et al.*, 2012). Another survey of 77 patients found that 92% reported using acupuncture to support their IVF cycle (Aelion *et al.*, 2009). A patient may seek an acupuncturist's support by self-referral, or her IVF physician may refer her, but it is also possible that IVF physicians may not be aware of patient use of these additional therapies (Boivin and Schmidt, 2009).

Investigations into the effect of acupuncture on IVF outcomes largely focus on a limited number of standardized treatments, usually two, on or around embryo transfer compared with no acupuncture, sham acupuncture or a placebo needle. Initial studies suggested that acupuncture on or around embryo transer improved IVF outcomes (Paulus *et al.*, 2002; Dieterle *et al.*, 2006; Smith *et al.*, 2006; Westergaard *et al.*, 2006), and, in a meta-analysis of seven trials, acupuncture increased the odds of clinical pregnancy by 65% (Manheimer *et al.*, 2008). As more trials were completed, the effects of this narrow dose of only two or three acupuncture sessions were equivocal to controls. In a review of 14 trials, two to three acupuncture treatments administered around embryo transfer did not improve clinical pregnancy rates compared with controls (Cheong *et al.*, 2013b). Another review of 16 trials confirmed these findings, but the covariate of baseline pregnancy rate was found to be a significant mediator of acupuncture's effect (Manheimer *et al.*, 2013). Additionally, a clear need exists for an adequate acupuncture control, as penetrating or non-penetrating ‘sham or placebo’ acupuncture controls are likely to be impractical and may have physiological effects (Manheimer, 2011; Vickers *et al.*, 2012).

With the advent of two standardized acupuncture sessions as a complete investigational intervention, acupuncture providers thereby question whether it is a sufficient dose (Craig *et al.*, 2014; Shen *et al.*, 2014). In clinical practice, acupuncture treatment is not standardized and instead considers the patient singularly; treatment is individualised. A course of treatment can range from six to 24 treatments depending on the complexity of the case. Furthermore, if an IVF patient seeks adjuvant acupuncture treatment in the period before the day of embryo transfer, it is possible that the patient, her parnter, or both, will receive a complex intervention at the acupuncturist's office, such as whole-systems traditional Chinese medicine (WS-TCM). This is a multi-dimensional intervention that can include any combination of modalities classified under the system of traditional Chinese medicine. These include any combination of acupuncture (the insertion of sterile, filiform needles in the body) (Cochrane *et al.*, 2014), moxibustion (the burning of processed herb, *artemesia argyi*, on or near the body) (Nedeljkovic *et al.*, 2013), Chinese herbal medicine (Ried and Stuart, 2011; Tan *et al.*, 2012; Cao *et al.*; 2013), Chinese medical massage with a tool (guasha) or without (tuina), Chinese medicine-based dietary recommendations, breathing

exercises (Qi Gong), or movement exercises (Tai Chi) (Noll and Wilm, 2009). It may also include recommendations for vitamins, supplements, or both, depending on the training and licensure of the provider. Beyond a published case study (Hullender Rubin, 2010) and expert texts (Liang, 2003; Lyttleton, 2004; Noll and Wilm, 2009), the effectiveness of the multi-dimensional WS-TCM approach on IVF outcomes is unclear.

Given this background, we sought to compare the reproductive outcomes of women who elected WS-TCM treatment in addition to their usual IVF care, and compared them with those who received the usual IVF care alone and to those who received two standardized acupuncture treatments on the day of embryo transfer acupuncture only. Our main objective was to compare the three groups on the primary outcome of live birth.

Materials and methods

Study design

This was a retrospective cohort study of WS-TCM effects on IVF reproductive outcomes compared with two groups: those who received acupuncture treatments only on the day of embryo transfer (ACU); and those who received IVF usual care alone. The Oregon College of Oriental Medicine Institutional Review Board approved this study on 11 January 2011 (IRB reference number 09-028). Reproductive outcomes data were obtained from a single, private IVF centre, the Northwest Center for Reproductive Sciences (NCRS), Kirkland, Washington.

Patient criteria

Of 1509 patient charts, only NCRS patients who underwent IVF with fresh donor or non-donor embryos transferred between August 2005 and December 2010 were included, regardless of embryo quality. Additionally, women who underwent pre-implantation genetic screening testing or intracytoplasmic sperm injection cycles were also included. To further reduce selection bias, all biomedical diagnoses were included. Diminished ovarian reserve was diagnosed if FSH was 12 mIU/ml or more, antral follicle count total less than 10, and anti-Müllerian hormone less than 1.0 ng/ml, or any combination of these measures. Since the mean age of the WS-TCM was higher than the other groups, this most likely accounted for the increased incidence of diminshed ovarian reserve diagnosis. All patients who underwent transfers with frozen embryos (n = 251) or embryos from frozen oocytes (n = 27, research cycles) were excluded.

All included patient data (n = 1231) were reviewed to identify patients who received ACU, and then reviewed a second time to identify and tabulate patients who received WS-TCM, as all WS-TCM patients received ACU as part of their treatment plans. The data were de-identified and assigned unique identifiers. The key was only available to the primary investigator. Visit data were then independently abstracted from acupuncture clinic financial records and confirmed via scheduling calendars by two research assistants. A third party was consulted to resolve any conflicts.

Interventions

Usual care

Non-donor: IVF cycle management was individualized to each patient according to biomedical diagnosis. In general, patients were treated with either a gonadotrophin-releasing hormone (GnRH) agonist (Cramer *et al.*, 1999) or antagonist (Felberbaum *et al.*, 1995; Olivennes *et al.*, 1998) IVF protocol. Oral contraceptive pills were taken on the first day of menses and continued from 1–3 weeks. Once ovarian suppression was confirmed, ovarian stimulation was initiated. Gonadotrophin medications were administered twice daily in variable doses based on age and antral follicle count, for up to 12 days, and included follitropin alpha (Gonal-f, EMD Serono, Geneva, Switzerland), follitropin beta injection (Follistim; Merck, New Jersey, US), injectable menotropins (Menopur, Ferring, Saint-Prex, Switzerland), or both. When three to four lead follicles measured a minimum of 17–18 mm on ultrasound, a patient was triggered with HCG (HCG; Novarel; Ferring, Siat-Prex, Switzerland). Within 36 h of trigger, transvaginal ultrasound-guided oocyte retrieval was carried out under conscious sedation. Once recovered from retrieval, patients were administered intramuscular progesterone in oil injections (Watson Laboratories, Parsippany, NJ, USA; West-Ward Pharmaceutical, Eatontown, NJ, USA; or Fresenius Kabi, Lake Zurich, IL, USA), 50 mg/ml twice daily until embryo transfer.

All recovered oocytes were fertilized within the embryology laboratory by either conventional insemination or intracytoplasmic sperm injection. Fertilization was visually confirmed by the presence of two pronuclei 17–22 h after fertilization. Embryos were cultured in 5% oxygen incubators and were evaluated every 24 h before embryo transfer. All embryos were individually cultured in 20–30 μl droplets of Global Medium (IVF Online, Guildford, CT, USA), supplemented with 10% human serum albumin and covered with 5.5 ml of equilibrated oil. Embryo culture was carried out in 35 mm Nunc dishes (Thermo Scientific Fisher, San Rafael, CA, USA). For blastocyst culture, embryos were moved to new culture dishes on day 3 of development. Day of embryo transfer was based on the cause of patient infertility, number and quality of embryos, as well patient age. Blastocyst culture and transfer was attempted whenever possible. When pre-implantation genetic diagnosis or screening was planned, blastomere biopsy was carried out on cleavage-stage embryos on day 3 of development, and embryo transfer occurred on day 5.

Day 3 embryo(s) or day 5 blastocyst(s) embryo transfer was undertaken with all patients with a full bladder using a Wallace catheter (Smiths Medical International, Kent, UK) with ultrasound guidance by one out of four physicians and according to SART guidelines (SART and ASRM, 2006; SART and ASRM, 2008; SART and ASRM, 2009). After transfer, Prometrium (progesterone, AbbVie Inc., Chicago, IL, USA), 200 mg suppositories were inserted vaginally twice daily. Serum HCG was collected to determine pregnancy 14 days after retrieval. If pregnant, progesterone supplementation continued to gestational week 10. If not pregnant, progesterone was discontinued.

Donor: Egg donors underwent ovarian stimulation using similar protocols as non-donors. Donor egg recipients underwent an endometrial development cycle timed to correspond to the ovarian stimulation of the donor. Donor recipients began the oral contraceptive pill on

the first day of their menses and continued from 1–3 weeks. Once suppression was confirmed, Vivelle-Dot patches (Novartis, Basel, Switzerland) and Estrace (Bayer-Schering, Berlin, Germany) were incrementally increased for up to 11–15 days depending on oestrogen levels and endometrial thickness. Once the endometrial thickness achieved 8 mm or thicker, and the donor eggs were retrieved, the donor recipient proceeded with the same progesterone protocol and embryo transfer as non-donor patients.

Acupuncture group—In addition to the IVF usual care, patients could elect to receive two standardized acupuncture treatments on the day of embryo transfer (ACU). The IVF nurse notified patients that acupuncture treatment was available to them. All ACU treatment protocols were based on previous published research (Paulus *et al.*, 2002; Craig *et al.*, 2014), and the treatment methods were previously described (Hullender Rubin *et al.*, 2012a; 2012b; Hullender Rubin *et al.*, 2013c). Patients received two standardized acupuncture treatments on the same day as the embryo transfer.

Treatments were administered onsite at the IVF centre by one of nine state-licensed acupuncturists, certified in acupuncture by the National Certification Commission of Acupuncture and Oriental Medicine (NCCAOM). The acupuncturists' experience ranged from 1–9 years. All were trained to carry out the treatments in the same manner, and a treatment manual was provided. Refresher training to ensure continuity of methods occurred annually.

The first acupuncture session took place 1 h and 15 min before embryo transfer, and the second no more than 30 min after the embryo transfer. The Craig acupuncture protocol was used on both cycle types between 2005 and 2007 (Craig *et al.*, 2014), and the following points were needled. Before embryo transfer: GV-20/Baihui; PC-6/Neiguan; CV-6/Qihai; ST-29/Guilai; SP-8/Diji; LR-3/Taichong; right ear (uterus, endocrine); left ear (Shenmen, Brain) After embryo tranfer: LI-4/Hegu; SP-10/Xuehai; ST-36/Zusanli; SP-6/Sanyinjiao; KI-3/Taixi; right ear (Shenmen, Brain); and left ear (uterus, endocrine). Between 2008 and 2009, the modified Craig protocol was used in both cycle types, with the only modification being acupoint KI-3/Taixi was removed from the protocol (Hullender Rubin *et al.*, 2012a; 2012b). In 2010, the acupuncture protocol was adjusted according to cycle type owing to preliminary retrospective analysis suggesting fresh, non-donor cycles benefitted from the modified Craig (Hullender Rubin *et al.*, 2012a), and donor cycles benefitted from the Craig protocol (Hullender Rubin *et al.*, 2012b; 2013a). Patients could also elect to listen to soft music or a guided meditation during the acupuncture sessions. No other recommendations were provided.

Whole-systems traditional Chinese medicine group—In addition to the usual IVF care and acupuncture on the day of embryo transfer as described above, patients could elect to pursue adjuvant whole-systems traditional Chinese Medicine (WS-TCM) treatment. Patients were either referred by the IVF doctor or self-referred. Flyers describing care with the acupuncturist were available in the IVF clinic lobby.

One of three Washington state-licensed acupuncturists with 3–4 years of master's level training in acupuncture and Chinese herbal medicine provided the WS-TCM treatment. All

three acupuncturists were nationally certified by the NCCAOM in acupuncture, one (LHR) was NCCAOM certified in herbs, and one was certified in herbs by the California state licensing exam. All pursued postgraduate continuing education in reproductive medicine and infertility, and one (LHR) was board certified in reproductive medicine by the American Board of Oriental Reproductive Medicine.

At the initial visit, the patient's biomedical chart was reviewed. The patient was assessed according to TCM theory, an accepted form of medicine (WHO, 2007). A detailed WS-TCM treatment plan was provided outlining the dose and frequency of acupuncture, electro-acupuncture, Chinese medicine-based dietary suggestions, lifestyle recommendations, and any recommended nutritional supplements.

Patient visits were typically once a week and increased in frequency to twice a week from the start of IVF suppression medications to oocyte retrieval. Needles sizes ranged from 0.18 mm to 0.25 mm in diameter and 30–40 mm in length for body points, and 0.16 mm × 15 mm for ears. Size and length were selected based on patient's tolerance, acupoint location and body size. Needles used were Vinco brand (China), Sierin brand (Japan), and DBC brand (Korea). Electroacupuncture stimulator used was ES-2 (Heliomed, China) between 2005 and 2007, and Electrostimulator 4c.Pro (Pantheon Research, Venice, CA, USA) was used between 2007 and 2010. Treatment could also include the following modalities: warming Far Infrared Mineral lamp (TDP CQ-27, FIRARD II, China), Chinese medical massage (tuina) and indirect moxibustion stick (Hoist Wuyan Jiutiao, Smokeless Moxa Stick, China). All customized Chinese herb formulas were dispensed in granular form and manufactured by KPC herbs (Taiwan). All herbal tablets were made of standardized Chinese herbal formulas and manufactured by Golden Flower Chinese Herbs (Taiwan). Recommended nutritional supplements included prenatal vitamins, essential fatty acids, antioxidants and probiotics.

Acupuncture and herbal treatment was based on TCM pattern diagnosis and phase of menstrual cycle. According to Chinese medicine, regulating the menstrual cycle is considered a central treatment approach to female reproduction (Cochrane *et al.*, 2014). This approach was previously described in several case studies (Hullender, 2009; Hullender Rubin; 2010; 2013b; Hullender Rubin and Marx, 2012), but in general, treatment was divided into four phases: menses (cycle days 1–4, follicular [cycle days 5–11], ovulation [cycle days 12–16], and luteal [cycle days 17 to onset of menses]). During menses, treatment was directed at regulating menses and reducing of dysmenorrhoea pain, if present (Smith *et al.*, 2011). Follicular phase treatment was directed at regulating reproductive hormones (Chen, 1997; Napadow *et al.*; 2008), and endometrial (Stener-Victorin *et al.*, 1996) and follicular development (Rashidi *et al.*, 2013). Ovulation phase treatment was directed at inducing ovulation (Jedel *et al.*, 2011; Stener-Victorin *et al.*, 2012; Johansson *et al.*, 2013; Johansson and Stener-Victorin, 2013). Luteal phase treatment focused on regulating hormones (Cochrane *et al.*, 2014). Throughout the entire cycle, treatment had a sub-aim of reducing stress (de Lacey *et al.*, 2009; Kovarova *et al.*, 2010; Madaschi *et al.*, 2010). During the IVF cycle, WS-TCM treatments were individualized according to patient needs and TCM pattern diagnosis, but aimed to support the goals of the IVF phase. Treatment could also include Chinese medicine-based dietary and lifestyle recommendations. During down-

regulation and ovarian stimulation, treatment was aimed to improve ovarian and uterine blood flow (Stener-Victorin *et al.*, 1996; Magarelli *et al.*, 2009), improve oocyte quality (Rashidi *et al.*, 2013) and reduce stress. Acupuncture was optional on the day of oocyte retrieval to manage pain (Gejervall *et al.*, 2005; Stener-Victorin, 2005; Humaidan *et al.*, 2006), or postoperative nausea, vomiting, or both (Cheong *et al.*, 2013a), which was used by only six patients. One more visit was suggested 5–7 days after oocyte retrieval to reduce stress.

Outcome measures

The primary outcome measure was live birth after 24 weeks' gestation. Secondary outcome measures were biochemical pregnancies, spontaneous abortions, ectopic pregnancies, gestational age, singleton, twin and triplet pregnancy. Biochemical pregnancy was defined as a positive serum beta-HCG and pregnancy that failed to develop to the clinically identifiable stage on ultrasound evaluation. Spontaneous abortion is defined as the spontaneous loss of a pregnancy with an ultrasound-confirmed gestational sac before 20 gestational weeks.

Statistical analysis

Treatment groups were counted and differentiated by donor or non-donor cycle type. Demographics and descriptive statistics were computed by group in the following variables for non-donor cycles: age, FSH, primary infertility, cause of infertility, cycle number, method of fertilization, pre-implantation genetic screening, total antral follicle count, number of days stimulated, total gonadotrophin dose, peak oestradiol, endometrial thickness, number of mature oocytes obtained, number of embryos transferred, day of embryo transfer (day 3 or 5), ovarian hyperstimulation syndrome (OHSS) and gestational age. For donor cycles, the same covariates were compared with the exception of age, FSH, total antral follicle count, number of days stimulated, total gonadotrophin dose and OHSS.

Outcomes of live birth, biochemical pregnancy, spontaneous abortion, singleton, twins and triplet pregnancy were tabulated by group and cycle type. Differences in outcomes were calculated using logistic regression and adjusted by covariates associated with outcomes.

Data were analysed in the following ways: (i) comparability of demographics between group; (ii) differences in outcomes with chi-squared (when groups numbered 10 or greater) or Fisher's exact (when groups numbered less than 10). Means were compared via analysis of variance and proportions were compared by chi-squared; (iii) in order to control for potential confounding, the magnitude of effects on pregnancy outcomes was assessed using multivariable logistic regression analyses and presented as adjusted odds ratios (AOR) with 95% confidence intervals (CI). Results were considered statistically significantly different if $P < 0.05$. Stata. (StataCorp, 2011, USA) was used to carry out all tests.

Results

A total of 1231 fresh cycles took place, in which an embryo transfer occurred. Non-donor cycles numbered 1069 and donor cycles numbered 162 (Table 1). In the non-donor cycles, 580 patients were in the usual care group, 370 in the ACU group and 119 in the WS-TCM

group. The mean (± SD) number of WS-TCM visits was 12.0 (± 12.4). The three groups were comparable on all reproductive variables at the start of the cycle, except diagnosis of diminished ovarian reserve ($P = 0.01$), diagnosis of cause of infertility as 'other' ($P = 0.03$); cycle number ($P = 0.004$) and total antral follicle count ($P = 0.0497$). Significant differences were found in cycle characteristics: number of mature oocytes obtained ($P = 0.02$); number of embryos transferred ($P = 0.003$) (Table 2).

The proportion of live births was significantly higher in the WS-TCM group (61.3%) compared with either the usual care (48.2%) or ACU groups (50.8%, $P = 0.03$ (Table 3). Fewer spontaneous abortions ($P = 0.02$) occurred in the WSTCM group compared with the other groups. On the outcome of biochemical pregnancies, there was no difference between groups, but WS-TCM trended toward significantly fewer than the other groups ($P = 0.05$). No ectopic pregnancies occurred in the WS-TCM group, but this was not a significant difference than compared with the usual care or ACU groups. Mean gestational age, and the proportions of live birth on or after 37 gestational weeks, singleton, twin and triplet pregnancies were not different between groups.

The WS-TCM group was associated with more live births compared with both groups when adjusted for the covariates of previous IVF cycle, age, and gonadotrophin dosage (adjusted odds ratio [AOR] 1.93; 95% confidence interval [CI] 1.27 to 2.92) (Table 4). More live births were associated with WS-TCM compared with embryo transfer acupuncture only, adjusted for age and gonadotrophin dosage (AOR 1.62; 95% CI 1.04 to 2.52), and when compared with IVF alone, adjusted for previous IVF and gonadotrophin dosage (AOR 2.09; 95% CI 1.36 to 3.21). Live births were not significantly affected in patients who received acupuncture only on the day of embryo transfer compared with unassisted childbirth.

When compared with both groups, WS-TCM was associated with fewer biochemical pregnancies (odds ratio [OR] 0.27; 95% CI 0.08 to 0.86). Decreased biochemical pregnancies were also associated with WS-TCM compared with embryo transfer acupuncture alone unadjusted (OR 0.25; 95% CI 0.07 to 0.82), or standard IVF when adjusted for FSH and gonadotropin dosage, (AOR 0.28; 95% CI 0.09 to 0.91). No difference was observed between the ACU and usual care groups on this outcome.

No differences were detected between groups on the outcomes of spontaneous abortion, ectopic pregnancies, singleton, twin, triplet pregnancies or gestational age.

Of the donor cycles, 104 recipients usual care group received an embryo transfer, 37 in the ACU group and 21 in the WS-TCM group. The mean (± SD) number of WS-TCM visits was 10.6 (± 13.6). The three groups were comparable on the variables of incidence of primary infertility; cause of infertility due to male factors; diagnosis of diminished ovarian reserve; endometriosis; ovulatory dysfunction; tubal issues; uterine issues; unknown reasons; other diagnosis; male only factors; female only factors; male and female factors; cycle number; incidence of pre-implantation genetic screening; fertilization method; number of days stimulated; peak oestradiol; endometrial thickness; day 3 or day 5 embryo transfer (Tables 1 and 2). Groups were different for the following variables: multiple diagnoses ($P = 0.02$) and number of mature oocytes obtained ($P = 0.005$).

On the outcome of live births, 85.7% of the WS-TCM group, 62.5% of the usual care and 59.5% of the ACU group had a live birth (Table 3). No differences were observed between groups for biochemical pregnancies or spontaneous abortions. No ectopic pregnancies occurred in the WS-TCM group for this cycle type, but this was not significantly fewer than usual care or ACU groups. Gestational age, singleton, twin, and triplet pregnancies were also not different between groups.

Significantly greater odds of live birth was associated with adjuvant WS-TCM compared with all groups (OR 3.72; 95% CI 1.05 to 13.24), and when compared with the ACU group (OR 4.09; 95% CI 1.02 to 16.38). When WS-TCM was compared with usual care, an association of increased odds trended towards significance (OR 3.6; 95% CI 1.00 to 13.01, unadjusted). The small sample size and exceedingly broad confidence intervals, however, indicate the weaknesses of these associations. No difference was found between the ACU and usual care groups on this outcome.

Outcomes of biochemical pregnancy or spontaneous abortion was not significantly affected by WS-TCM, regardless of comparison group in the donor cycles.

Discussion

To the best of our knowledge, this is the first adequately powered study of the effect of adjuvant WS-TCM on IVF reproductive outcomes. This is meaningful for its public health impact on infertility treatment and management, preliminary evidence of the need for an optimized acupuncture dose and demonstration that WS-TCM, a multidisciplinary intervention that includes acupuncture, was associated with more live births than two standardized acupuncture treatments on the day of embryo transfer or usual IVF care alone. These findings suggest WS-TCM could make significant contributions to the public health issue of infertility (Macaluso *et al.*, 2010; CDC, 2010; CDC, 2014), if provided an effective dose. Although IVF live births increase with advances in patient management and laboratory procedures, success is not guaranteed. Couples often must undergo several IVF cycles engendering extensive emotional distress and economic costs (Cousineau and Domar, 2007).

Acupuncture on or around day of embryo transfer does significantly reduce stress in IVF patients in both randomized controlled trials (RCTs) (Smith *et al.*, 2006; Domar *et al.*, 2009; Isoyama *et al.*, 2012) and observational studies (de Lacey *et al.*, 2009; Balk *et al.*, 2010). Initial RCTs found that acupuncture improved IVF pregnancy rates (Paulus *et al.*, 2002; Dieterle *et al.*, 2006; Westergaard *et al.*, 2006). As more studies were conducted, the effect became less clear as subsequent studies failed to reproduce those outcomes, with one RCT finding live births were lower in the acupuncture group compared with control (Craig *et al.*, 2014). Craig *et al.* (2014) suspected the location of treatment offsite from the IVF centre and study population of acupuncture naïve women may have contributed to this finding(2014). Further, two standardized acupuncture sessions administered on day of embryo transfer alone were in insufficient acupuncture dose to improve IVF birth outcomes in two of the most recent systematic reviews (Cheong *et al.*, 2013b; Manheimer *et al.*, 2013).

We observed that, in addition to embryo transfer acupuncture, an average of 12 WS-TCM visits for non-donor cycles and 11 visits for donor cycles were associated with greater odds of live birth. The combined approach of WS-TCM treatment before starting IVF with the two treatments on the day of embryo transfer acupuncture may be an optimal intervention to improve IVF birth outcomes in addition to stress reduction. An increased acupuncture dose, ie. more acupuncture sessions, is consistent effectiveness reported in other studies. Uterine blood flow was improved with eight electro-acupuncture sessions (Stener-Victorin *et al.*, 1996). Nine electro-acupuncture sessions plus embryo transfer day acupuncture were correlated with an increase in serum cortisol and prolactin and improved IVF outcomes in prospective clinical trial (Magarelli *et al.*, 2009). Fourteen sessions of low-frequency electro-acupuncture significantly reduced androgens and improved menstrual frequency over physical exercise or no treatment in women with polycystic ovary syndrome in an RCT (Jedel *et al.*, 2011). Ovulation was induced in another RCT with 24 visits over 3 months in women with polycystic ovary syndrome (Johansson *et al.*, 2013) using the same intervention described by Jedel *et al.* (2011).

In our study, every patient undergoing WS-TCM received a multidisciplinary intervention, of which all patients received acupuncture, electro-acupuncture, or both, in addition to lifestyle and dietary recommendations in this group. Prenatal vitamins, essential fatty acids, antioxidants, probiotics, and Chinese herbs were also commonly suggested. Because of the nature of individualized care, recommendations were tailored to the patient's need and varied considerably within the group. Further, some patients elected to only pursue acupuncture to support their cycles. This is representative of TCM treatment in the real world. An objective of whole-systems research is to evaluate the combined effects of a complex intervention (Ritenbaugh *et al.*, 2003; Elder *et al.*, 2006). It is not intended to evaluate the single ingredients of a complex intervention, as it may over or underestimate the single ingredient's influence and cannot account for the confounding or mediating effects of the other component(s).

This retrospective study has three limitations. First, owing to the nature of a retrospective cohort study, there is limited internal validity. Study groups were not randomly allocated, so the groups differed on several variables. We attempted to minimize potential bias from these differences by adjusting for covariates associated with pregnancy outcomes through multivariable logistic regression analysis. Further, women elected which treatment to pursue. Women who elected WS-TCM, ACU, or both, could differ in unknown ways that may affect outcomes. It was also possible that women in the usual care groups received WS-TCM or day of embryo transfer acupuncture at another site, or patients in the ACU group received WS-TCM elsewhere leading to misclassification bias. Complementary and alternative medicine use is common in IVF patients (Smith *et al.*, 2010) and not always reported to their IVF practitioners (Boivin and Schmidt, 2009). Such bias, however, would have been towards the null suggesting that our estimates of effect would only underestimate the actual effect of WS-TCM.

Finally, embryo quality may have differed between groups. Although embryo quality is a known predictor of IVF success (Vernon *et al.*, 2011; Heitmann *et al.*, 2013), only the highest quality embryos available were selected for transfer. As more women in the WS-

TCM group were diagnosed with diminished ovarian reserve, it is more likely that the WS-TCM group would have had lower quality embryos, which may mean the effect of WS-TCM is underestimated by our study.

In conclusion, despite these potential limitations, this study provides evidence that the addition of WS-TCM to non-donor IVF cycles may increase the odds of achieving a live birth over usual IVF care alone or two standardized treatments administered around embryo transfer. The effects of WS-TCM were less clear compared with usual donor IVF care alone but showed a non-significant trend towards increased odds of a live birth in this cycle type. This retrospective cohort study suggests that WS-TCM as an adjuvant IVF treatment may be associated with improved live birth rates. More rigorous, comparative effectiveness research is needed to substantiate these findings and determine an optimal number of WS-TCM visits compared with an adequate and validated time-attention control, such as a mind–body programme to confirm these findings.

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Biography

Lee Hullender Rubin, DAOM, MS, LAc, FABORM, is a clinician and researcher specializing in reproductive medicine, women's health and vulvar pain. She graduated with her master's degree from Bastyr University in 2001, and her doctorate from the Oregon College of Oriental Medicine (OCOM) in 2009. Dr Hullender Rubin was OCOM's first postdoctoral research fellow funded by a National Institutes of Health educational grant. She teaches the doctoral infertility module and is Adjunct Research Faculty at OCOM, and Visiting Research Faculty at Oregon Health and Science University. She currently practices at her clinic, the Portland Acupuncture Studio, in Portland, Oregon.

Highlights

- Whole Systems Traditional Chinese Medicine (WS-TCM) added to IVF may be beneficial.
- WS-TCM and IVF was associated with more live births compared with acupuncture and IVF.
- WS-TCM and IVF was associated with more live births compared with IVF alone.
- WS-TCM is individualized and includes acupuncture and other TCM interventions.

Table 1

Demographic characteristics.

	WS-TCM	Usual care	ACU	*P*-value
Non-donor cycles				
Group N	119	580	370	
Age [a,b]	35.0 ± 4.0	34.3 ± 4.3	34.9 ± 4.3	NS
FSH[a,b]	10.9 ± 3.4	10.7 ± 3.1	11.2 ± 3.9	NS
Total antral follicle count[a,b,f]	8.0 ± 2.4	8.3 ± 2.5	7.9 ± 2.6	0.0497
Primary infertility[c,d]	48.0	51.4	52.7	NS
Cause of infertility[c,d]				
Male	40.0	36.6	35.4	NS
Diminished ovarian reserve	31.1	20.9	27.3	0.01
Endometriosis	10.1	11.9	12.7	NS
Ovulatory dysfunction	17.7	20.7	21.6	NS
Tubal	15.1	15.9	13.0	NS
Uterine	6.7	5.9	5.2	NS
Other[f]	13.5	7.8	6.0	0.03
Unknown	8.4	14.5	14.3	NS
Multiple diagnoses	34.5	31.4	30.8	NS
Cycle number [c,d]				
First cycle[f]	57.4	72.6	70.0	0.004
Repeated cycle[f]	42.6	27.4	30.0	0.004

	WS-TCM	Usual care	ACU	*P*-value
Doner cycles				
Group N	21	104	37	
Primary infertility[c,d]	47.6	34.6	45.9	NS
Cause of infertility				
Male[c,e]	19.0	16.3	10.8	NS
Diminished ovarian reserve[c,d]	81.0	92.3	89.2	NS
Endometriosis[c,e]	0.0	16.3	10.8	NS
Ovulatory dysfunction[c,e]	9.5	1.0	2.7	NS
Tubal[c,e]	9.5	6.7	5.4	NS
Uterine[c,e]	9.5	7.6	5.4	NS
Other[c,e]	4.8	9.6	8.1	NS
Unknown[c,e]	0.0	0.0	0.0	NS
Multiple diagnoses[c,e,f]	28.6	42.3	24.3	0.02
Cycle number				
First cycle[c,e]	57.1	51.0	67.6	NS

	WS-TCM	Usual care	ACU	*P*-value
Repeated cycle[c,e]	42.9	49.0	32.4	NS

[a] Data are mean ± SD

[b] Analysis of variance

[c] Data are proportion

[d] chi-squared

[e] Fisher's exact

[f] Significant findings ($P < 0.05$).

ACU, women receiving acupuncture on day of embryo transfer; NS, not statistically significant; WS-TCM, Whole-systems traditional Chinese medicine.

Table 2

Cycle characteristics.

	WS-TCM	Usual care	ACU	*P*-value
Non-donor cycles				
Group, n	119	580	370	
Number of days stimulated[a,b]	9.8 ± 1.2	9.9 ± 1.2	9.9 ± 1.3	NS
Total gonadotrophin dose, IU[a,b]	3959.3 ± 1503.6	3721.6 ± 1515.6	3932.1 ± 1580.1	NS
Peak oestradiol, pg/ml[a,b]	3153.7 ± 1781.8	3211.0 ± 1644.0	3017.0 ± 1634.0	NS
Endometrial thickness, mm[a,b]	10.9 ± 2.4	11.2 ± 2.4	11.2 ± 2.2	NS
Number of mature oocytes obtained[a,b,f]	14.0 ± 8.7	15.7 ± 9.1	14.2 ± 8.0	0.02
OHSS [c,d]	8.4	9.5	7.1	NS
Fertilization method[c,d]				
Conventional	47.1	51.0	46.3	NS
ICSI	48.7	46.2	49.3	NS
Mixed	4.2	2.8	4.3	NS
Pre-implantation genetic screening[c,d]	13.5	9.3	6.5	NS
Number of embryos transferred[a,b,f]	2.9 ± 1.2	2.6 ± 1.1	2.8 ± 1.1	0.003
Day of embryo transfer[c,d]				
Day 3	64.7	59.7	65.7	NS
Day 5	35.3	40.3	34.3	NS
Mean number of acupuncture visits[a]	12.0 ±12.4			
Donor cycles				
Group, N	21	104	37	
Peak oestradiol, pg/ml[a,b]	4303.9 ±2130.5	4250.3 ±2035.4	4428.4 ±2660.4	NS
Endometrial thickness, mm[a,b]	9.7 ±2.0	10.5 ±2.1	10.0 ±2.0	NS
Number of mature oocytes obtained from donor[a,b,f]	18.6 ±8.0	21.7 ±8.7	26.4 ±11.2	0.005
Fertilization method				
Conventional[c,d]	57.1	60.6	67.6	NS
ICSI[c,e]	38.1	33.7	27.0	NS
Mixed[c,e]	4.8	5.8	5.4	NS
Pre-implantation genetic diagnosis Testing[c,e]	4.8	10.6	8.3	NS
Number of embryos transferred [a,b]	2.2 ±0.7	2.2 ±0.7	1.9 ±0.6	NS
Day of embryo transfer				
Day 3[c,e]	23.8	38.5	24.3	NS
Day 5[c,d]	76.2	61.5	76.7	NS
Mean number of acupuncture visits[a]	10.6 ±13.6			

[a] Data are mean ± SD

[b] Analysis of variance

[c] Data are proportions

[d] chi-squared

[e] Fisher exact

[f] Significant findings ($P < 0.05$)

ICSI, intracytoplasmic injection; OHSS, ovarian hyperstimulation syndrome

Table 3

Reproductive outcomes.

	WS-TCM	Usual care	ACU	*P*-value
Non-donor cycles				
Group, n	119	580	370	
Live birth[a,b,f]	61.3	48.2	50.8	0.03
Biochemical pregnancy[a,c,f]	2.5	8.4	9.5	NS
Spontaneous abortion[a,c,f]	5.8	10.7	7.3	0.02
Ectopic[a,c]	0	1.0	0.8	NS
Singleton[a,b]	60.3	63.2	57.0	NS
Twins[a,b]	38.4	33.2	40.3	NS
Triplets[a,b]	1.4	3.2	2.2	NS
Gestational age[d,e]	37.8 ± 2.7	37.8 ± 2.8	37.4 ± 3.3	NS
Live birth on or after 37.0 weeks[a,b]	64.4	72.9	67.6	NS
Donor cycles				
Group, n	21	104	37	
Live birth[c,d]	85.7	62.5	59.5	NS
Biochemical pregnancy [a,c]	4.8	8.7	8.1	NS
Spontaneous abortion[a,c]	4.8	11.5	16.2	NS
Ectopic[a,c]	0.0	1.0	0.0	NS
Singleton [a,b]	55.6	54.0	54.6	NS
Twins[a,c]	38.9	45.3	45.5	NS
Triplets[a,c]	4.8	1.6	0.0	NS
Gestational age[d,e]	37.7 ±3.3	36.9 ±3.1	36.8 ± 3.7	NS
Live birth on or after 37.0 weeks[a,b]	72.2	60.0	63.6	NS

[a] Data are proportions

[b] chi-squared

[c] Fisher's exact

[d] Data are mean ± SD

[e] Analysis of variance

[f] Significant findings ($P < 0.05$)

Table 4

Reproductive outcomes logistic regression analysis (odds ratio and 95% confidence interval).

Outcome	Cycle type	WS-TCM versus all	WS-TCM versus usual care	WS-TCM versus ACU	ACU versus usual care
Live birth	Non-donor	1.93, 1.27 to 2.92[a,h]	2.09, 1.36 to 3.21[b,h]	1.62, 1.04 to 2.52[c,h]	1.24, 0.94 to 1.64[d]
	Donor	3.72, 1.05 to 13.24[e,h]	3.6, 1.00 to 13.01[e]	4.09, 1.02 to 16.38[e,h]	0.74, 0.35 to 1.58[e]
Biochemical pregnancy	Non-donor	0.27, 0.08 to 0.86[e,h]	0.28, 0.09 to 0.91[f,h]	0.25, 0.07 to 0.82[e,h]	1.30, 0.83 to 2.03[e]
	Donor[h]	0.54, 0.07 to 4.36[e]	0.55, 0.06 to 4.74[g]	0.57, 0.06 to 5.82[e]	1.01, 0.26 to 3.90[e]
Spontaneous abortion	Non-donor[h]	0.60, 0.27 to 1.34[e]	0.50, 0.22 to 1.13[e]	0.79, 0.34 to 1.87[e]	0.72, 0.45 to 1.14[e]
	Donor[h]	0.34, 0.04 to 2.70[e]	0.38, 0.05 to 3.12[e]	0.26, 0.03 to 2.31[e]	1.67, 0.59 to 4.75[e]

[a] Adjusted odds ratio comparing WS-TCM with all groups with previous IVF, age and gonadotrophin dosage as covariates.

[b] Adjusted odds ratio comparing WS-TCM with usual care, with previous IVF and gonadotrophin dosage as covariates.

[c] Adjusted odds ratio comparing WS-TCM with ACU with age and gonadotrophin dosage as covariates.

[d] Adjusted odds ratio comparing isual care with ACU with prior IVF, age, and gonadotrophin dosage as covariates.

[e] unadjusted odds ratio.

[f] Adjusted odds ratio comparing WS-TCM with usual care, with FSH, and gonadotrophin dosage as covariates.

[g] Adjusted odds ratio comparing WS-TCM with usual care, with number of embryos transferred as covariate.

[h] Significant outcomes.

ACU, day of embryo transfer acupuncture only; usual care, usual IVF care; WS-TCM, whole-systems traditional Chinese medicine.