

The effects of acupuncture on in vitro fertilization outcomes: a systematic review of the literature and an update to the Cochrane Collaboration review

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Dedication

This work is dedicated to my fellow students.

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Abstract

Background

Infertility, or impaired fecundity, affects 11.8% of women between the ages of 15 and 44, which translates to 7.3 million women. The use of assisted reproductive techniques has doubled over the past decade, with 148,055 cycles performed during 2008 resulting in 46,326 live births and the delivery of 61,426 infants. Acupuncture has been used in China to treat numerous and disparate medical conditions for thousands of years. Many anecdotal reports and non-randomized studies have claimed that acupuncture improves fertility, but the number of high-quality randomized controlled clinical trials and cohorts is much thinner.

Objectives

To determine whether the use of acupuncture results in higher pregnancy rates in patients undergoing in vitro fertilization compared with placebo acupuncture or no treatment.

Search strategy

All randomized controlled trials and prospective cohort reports of acupuncture and assisted reproductive technology were obtained through a systematic search of Medline and the MeSH database (1996 to February 2011).

Selection criteria

Prospective, randomized controlled trials comparing acupuncture treatment versus no treatment, placebo acupuncture, sham acupuncture at non-acupoints, and sham acupuncture at non-fertility-related acupoints during IVF treatment with or without intracytoplasmic sperm injection (ICSI).

Inclusion criteria:

- primary or secondary subfertility
- undergoing IVF with or without ICSI
- timing of acupuncture for before and after embryo transfer

Exclusion criteria:

- frozen embryo transfer
- acupuncture used as adjunct to analgesia
- electroacupuncture
- donor oocytes
- non-randomized trials, case-controls, case studies
- studies included in the 2009 Cochrane review

Data collection and analysis

Thirteen randomized controlled trials were identified that involved acupuncture and in vitro fertilization with embryo transfer. Trials were analyzed for the following methodological details and quality criteria: study characteristics (randomization, blinding, power analysis, intention-to-treat analysis), patient characteristics (demographics, inclusion and exclusion criteria), interventions (IVF stimulation

protocols, timing of acupuncture or control, acupoints chosen), and outcomes (ongoing pregnancy rates, live birth rates).

Main results

Only one of the trials demonstrated a result that achieved statistical significance. So 2009 showed that placebo acupuncture resulted in significantly higher overall birth rate when compared to true acupuncture. Even with adequate power, none of the other trials showed a difference that achieved statistical significance in pregnancy rate or live birth rates between acupuncture and control groups.

Conclusions

Acupuncture does not improve IVF outcomes and should not be offered routinely as an adjunct to fertility treatment. The evidence from the current literature suggests a positive effect of sham and placebo acupuncture on IVF outcomes, and therefore merits further study with adequately powered RCTs.

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Background

Infertility, or impaired fecundity, is medically defined as the inability to achieve pregnancy after twelve months of unprotected intercourse. Because rates of fertilization and implantation undergo a natural decline with age, in a woman under the age of 35, the time period of unprotected intercourse is six months. Approximately one-third of infertility issues are due to female factor (occluded Fallopian tubes, impaired tubal motility, poor oocyte quality), one-third are due to male factor (azoospermia, poor sperm quality, poor sperm motility), and one-third are due to a combination of male and female factors.

Infertility may be termed “primary” or “secondary”. Primary infertility occurs in a woman who has never been pregnant, while secondary infertility occurs in women who have already had at least one pregnancy. According to the Centers for Disease Control and Prevention’s 2002 National Survey of Family Growth, 11.8% of women between the ages of 15 and 44 have impaired fecundity, which translates to 7.3 million women. The use of assisted reproductive techniques has doubled over the past decade, with 148,055 cycles performed during 2008 resulting in 46,326 live births and the delivery of 61,426 infants (CDC 2008 ART Success Rates Report). Over 1% of all infants born in the United States every year are conceived using ART.

Assisted reproductive technology includes the use of fertility-enhancing medications such as aromatase inhibitors, selective estrogen receptor modulators (SERMs), and gonadotropins to enhance ovarian follicle formation or sperm production. It also includes more invasive techniques such as intrauterine insemination (IUI), in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), trans-scrotal sperm retrieval, oocyte donation, and gestational carriers.

Patient-perceived stress has been frequently blamed by patients, practitioners, and researchers as a contributor for the failure of assisted reproductive techniques to produce a “take-home” baby. Infertility can be a significant source of stress for patients and their families, with many reporting feelings of anger, hopelessness, guilt, and depression. Furthermore, the high financial and emotional costs of fertility treatments

frequently exacerbate these feelings. Many leading researchers have made public statements about personal stress causing everything from changes in the production of neurotransmitters to alterations in uterine blood flow, with no high-quality studies to back up the assertions. In dealing with these beliefs, patients are often told simply to relax, or that being stressed will result in treatment failure. Since the average success rate per IVF cycle has hovered around 35% for many years, patients who fail to get pregnant immediately may start to blame themselves, creating more stress and reinforcing the myth that stress causes infertility.

Acupuncture is presumed to alleviate stress, with its rituals of lying down quietly on a soft surface, of the time spent in stillness, and of the near-meditative aspects of the practice. Yet a new meta-analysis of fourteen studies and 3,583 women, published in the British Medical Journal this year by Boivin and colleagues, concluded that despite the presence of moderate publication bias, pre-treatment anxiety and depression did not affect the overall likelihood of pregnancy. The objective measurements of stress (serum cortisol level) and the subjective measurements (patient report of stress and anxiety levels) may be changed by sham or real acupuncture; however, the Boivin meta-analysis suggests that in spite of these changes, stress does not have an effect on treatment outcomes anyway.

Acupuncture has been used in China to treat numerous and disparate medical conditions for thousands of years. But what exactly does acupuncture do? Many anecdotal reports and non-randomized studies have claimed that acupuncture improves fertility, but the number of high-quality randomized clinical trials and cohorts is much thinner. Traditional Chinese Medicine (TCM) theory holds that the crossing acupoint of the kidney, spleen, and liver channels, SP6, plays a central role in female infertility. By needling SP6, SP8, SP10, ST29, and ST36, it is assumed that the essence of kidney and liver is “strengthened”, and that Qi and blood perfusion to the uterus is adjusted (So et al., 2009). In what direction the perfusion to the uterus is adjusted, it is not made clear. Other important acupoints are LR3 and L1, the “four gates points”, which ease the stagnation of liver Qi and calms the mind, as well as PC6 and GV20, which are purported

to relieve stress and anxiety. In the So 2009 study, the most common TCM diagnoses were spleen and kidney deficiency, liver Qi stagnation, and blood stasis, making the selection of their acupoints appropriate to the diagnoses that the majority of patients received.

Objectives

To determine whether the use of acupuncture results in higher pregnancy rates in patients undergoing in vitro fertilization compared with placebo acupuncture or no treatment. To avoid duplicating results, this systematic review excludes the studies included in the 2009 Cochrane Review by Cheong and colleagues.

Methods

Criteria for considering studies for the review

Types of studies

Prospective, randomized controlled trials comparing acupuncture treatment versus no treatment, placebo acupuncture, sham acupuncture at non-acupoints, and sham acupuncture at non-fertility-related acupoints during IVF treatment with or without intracytoplasmic sperm injection (ICSI).

Types of participants

Reproductive-age infertile women undergoing IVF. Causes of infertility included female factor (e.g. tubal abnormalities, poor ovarian reserve), male factor (e.g. poor sperm motility, low sperm quality), and mixed factor (male and female factors combined).

Inclusion criteria:

- primary or secondary subfertility
- undergoing IVF with or without ICSI
- timing of acupuncture for before and after embryo transfer

Exclusion criteria:

- frozen embryo transfer

- acupuncture used as adjunct to analgesia
- electroacupuncture
- donor oocytes
- non-randomized trials, case-controls, case studies
- studies included in the 2009 Cochrane review

Types of interventions

Trials included in the review compared acupuncture with placebo, sham acupuncture, and no treatment. Sham acupuncture involves needling at non-acupuncture points. Placebo acupuncture involves the use of validated non-penetrating Streitberger needles from the Asia-Med company (Suhl, Germany; Streitberger and Kleinhenz, 1998). Streitberger needles are blunt-tipped, and the needle is not fixed inside the copper handle. Similar to a stage-knife, when the Streitberger needle touches the skin, it retracts into the handle and appears shortened. The patient experiences a pricking sensation without the skin being punctured.

Selection of acupoints

Acupuncture points were selected either according to the traditional Chinese medicine practitioner performing the acupuncture, or according to previously published protocols by Paulus et al., 2002, and Westergaard et al., 2006.

Types of outcome measures

Primary outcomes

- ongoing pregnancy rate
- live birth rate

Secondary outcomes

- implantation rate
- chemical pregnancy rate

- Perceive Stress Scale scores
- Trait-State Anxiety scores
- Clinical discomfort/pain per McGill Pain Questionnaire response
- Endometrial and subendometrial vascularity
- Serum cortisol level

Search method for identification of studies

Medline was searched for randomized controlled trials and prospective cohorts of acupuncture and in vitro fertilization using the following search query:

Systematic[sb] AND ((“acupuncture”[MeSH Terms] OR “acupuncture”[All Fields] OR “acupuncture therapy”[MeSH Terms] OR (“acupuncture”[All Fields] AND “therapy”[All Fields]) OR “acupuncture therapy”[All Fields]) AND (fertilization”[All Fields] OR “fertilization”[MeSH Terms] OR “fertilization”[All Fields]))

acupuncture and in vitro fertilization Limits: Complementary Medicine

Data collection and analysis

Trials were analyzed for the following methodological details and quality criteria:

Study characteristics:

- Presence, method, and quality of randomization
- Presence, method, and quality of blinding to treatment arm
- Performance of power calculation
- Number of patients enrolled, excluded, randomized, and lost to follow-up
- Performance of intention-to-treat analysis

Participant characteristics:

- Demographics of women in the study
- Inclusion and exclusion criteria

Interventions:

- acupoints used for “true” acupuncture arm

- timing of acupuncture, sham, or placebo acupuncture
- type of needle used for placebo acupuncture
- IVF stimulation protocol

Outcomes:

- ongoing pregnancy rate -- acupuncture
- live birth rate -- acupuncture
- ongoing pregnancy rate – control
- live birth rate – control

Results

Description of studies

Thirteen randomized controlled trials were identified that involved acupuncture and in vitro fertilization with embryo transfer. Four trials were included and nine trials were excluded.

Trials excluded from the review

Chen 2009 conducted a study using electroacupuncture in patients with poor ovarian response. No power analysis was performed, and the method of blinding was not described. While the observation group had better fertility markers (superior levels of estradiol, higher fertilization rates, higher rates of good quality embryos, higher fertilization rates, and improved pregnancy rates), none of the differences between the observation and the control group achieved significance. Ho 2009 was excluded because of its description of inadequate randomization technique, because no power analysis was performed, and because the study involved electroacupuncture on the days leading up to oocyte retrieval but did not include acupuncture performed around the time of embryo transfer. The Meng 2008 and 2009 trials were excluded because pregnancy rates were not reported, and the trials were focused instead on the use of acupuncture as an analgesia adjunct during oocyte retrieval. Humaidan 2006 was excluded because although it was not powered to discover differences in pregnancy

rates, and the focus of the study was instead on acupuncture as analgesia and as an anesthesia adjunct. Stener-Victorin 2003 was rejected because it focused on electroacupuncture as a perioperative analgesic method compared to standard alfentanil, and though it did report pregnancy rates, it was not powered to investigate differences in this outcome. It was also excluded in a group along with Dieterle 2006, Paulus 2002, and Stener-Victorin 1999 because these studies have already been discussed in the Cochrane Collaboration's 2009 review.

Trials included in this review:

Four randomized controlled trials were included in this review. All four trials had a similar design.

Two of the studies were performed in the United States (Moy 2011, Domar 2009), one was performed in Denmark (Andersen 2010), and one was performed in Hong Kong (So 2009). The Moy trial was conducted at Northwestern University in Illinois at an academic fertility clinic and the Domar study was performed in Boston, Massachusetts at a private but academically affiliated fertility clinic. The Andersen trial was a multi-center study conducted at four public Danish fertility clinics, and the So trial was conducted in Hong Kong at an academically affiliated fertility clinic associated with the University of Hong Kong. All studies had pregnancy rates as a primary outcome measure. Two studies reported on subjective, patient-centered outcomes such as anxiety (Domar 2009, So 2009), optimism (Domar 2009), and subjective, affective, and total pain symptoms during embryo transfer (Moy 2011). Two studies were able to report live birth rates (Andersen 2010, So 2009). So 2009 reported endometrial and subendometrial vascularity as well as cortisol levels.

Participants

So 2009 conducted a study randomizing 370 patients into two study groups: real acupuncture (n=185) and placebo acupuncture using non-penetrating Streitberger placebo needles (n=185). Both groups received treatments for 25 minutes before and

after embryo transfer. Endometrial vascularity, subendometrial vascularity, and plasma cortisol levels were evaluated before and after the real and placebo acupuncture. The mean age (range) of the patients was 36 years (33-38) for the acupuncture group and 36 years (34-38) for the placebo group. The mean duration (range) of infertility was 4 years (2.0-6.0) for the acupuncture group and 4 years (2.5-7.0) for the placebo group. There were no significant differences in demographic characteristics between the two groups in terms of BMI, prior acupuncture exposure, cause of infertility, number of cycles, antral follicle count, number of oocytes retrieved, and number of embryos transferred.

Domar 2009 conducted a study randomizing patients to either the acupuncture group (n=78) or control group (n=68), which consisted of lying quietly. Both groups underwent their treatments for 25 minutes before and after embryo transfer. The average age of the patients was 36.1 years in both groups, and there were no significant differences in number of prior IVF cycles, number of oocytes retrieved, number of embryos transferred, baseline Life Orientation Test scores, or Spielberger Trait Anxiety Inventory scores. The causes of subfertility, BMI, and prior exposure to acupuncture were not described in this study.

Moy 2011 conducted a study randomizing 161 patients into true acupuncture (n=87) or sham acupuncture (n=74), in which penetrating needles were inserted into non-qi points. Both groups underwent 25 minutes of treatment before and after embryo transfer. One patient in the true acupuncture group discontinued intervention. No patients were lost to follow-up, however, one patient in the sham acupuncture group did not complete a post-treatment questionnaire. The mean age of patients was 33.30 ± 0.307 years in the acupuncture group and 33.16 ± 0.334 years in the sham group, which is not significantly different. There were no statistically significant differences in any of the other demographic characteristics, including parity, number of cycles, BMI, cause of subfertility, estradiol level, number of oocytes retrieved, and number of embryos transferred. The most common cause of subfertility was male factor, followed by unexplained, ovarian dysfunction, and tubal factor.

Andersen 2010 conducted a study in which 635 patients were randomized to receive true acupuncture (n=314) or placebo acupuncture (n=321) with non-penetrating Streitberger needles.

Due to postponement or cancellation of embryo transfer, patient discontinuation of true or placebo acupuncture, and realization that the inclusion criteria had not actually been met, the protocol was followed in 305 patients in the acupuncture needle group and 313 patients in the placebo needle group. The average age of the patients was 31 in both groups, BMI was 22.5 in both groups, and average duration of infertility was 2.5 years in both groups. The groups were also comparable in terms of type of subfertility, number of previous IVF cycles, and number of oocytes retrieved. Most women were diagnosed with male factor subfertility, followed by tubal factor, unexplained, and combined male/female factor subfertility. Prior exposure to acupuncture was not reported on, although concomitant acupuncture use at an outside facility was an exclusion criterion.

Interventions

Timing of acupuncture

The Domar 2009, So 2009, and Moy 2011 trials were designed so that patients would receive 25 minutes of acupuncture (or control treatment) before and after embryo transfer. In the Andersen 2010 trial, patients received 30 minutes of pre- and post-ET acupuncture or placebo treatment.

Acupuncture points

A summary of the acupuncture points used is provided in table 2. Domar 2009 chose to use the same 22-needle protocol as the Paulus 2002 study. These acupoints were chosen for their sedative effect as well as to increase uterine blood flow. The pre-transfer acupoints were as follows: Cx6, Sp8, Liv3, Gv20, St29; the post-transfer acupoints were as follows: St36, Sp6, Sp10, Li4. In keeping with Paulus 2002, Domar 2009 also chose to use one-sided auricular acupuncture at ear points 55, 58, 22, 34, changing sides post-transfer. So 2009 used the same acupoints as Domar 2009, but did not perform the auricular acupuncture. Moy 2011 used the same acupoints, including auricular acupoints, as Domar 2009 with the exception of Cx6 (Neiguan) pre-embryo

transfer. Andersen 2010 describes using the same points as Paulus et al., 2002 and Westergaard et al., 2006, with the exception of needling Gv20 both pre- and post-ET, whereas Paulus and Westergaard only needled Gv20 pre-ET.

Table 2 – Summary of acupuncture points

Study	Domar 2009	So 2009	Andersen 2010	Moy 2011
Cx6 (Neiguan) aka PC6	Y (pre-ET)	Y (pre-ET)	Y (pre-ET)	
Cv6 (Qi hai)				Y (pre-ET)
Sp8 (Di ji)	Y (pre-ET)	Y (pre-ET)	Y (pre-ET)	Y (pre-ET)
Liv 3 (Tai chong) aka LR3	Y (pre-ET)	Y (pre-ET)	Y (pre-ET)	Y (pre-ET)
Gv20 (Bai hui) aka DU20	Y (pre-ET)	Y (pre-ET)	Y (pre- and post-ET)	Y (pre-ET)
St29 (Gui lai)	Y (pre-ET)	Y (pre-ET)	Y (pre-ET)	Y (pre-ET)
St36 (Zu san li)	Y (post-ET)	Y (post-ET)	Y (post-ET)	Y (post-ET)
Sp6 (San yin jiao)	Y (post-ET)	Y (post-ET)	Y (post-ET)	Y (post-ET)
Sp10 (Xue hai)	Y (post-ET)	Y (post-ET)	Y (post-ET)	Y (post-ET)
Li4 (He gu)	Y (post-ET)	Y (post-ET)	Y (post-ET)	Y (post-ET)
ear point 55 (Shenmen)	Y			Y
ear point 58 (Zhi gong)	Y			Y
ear point 22 (Neifenmi)	Y			Y
ear point 34 (Naodian)	Y			Y

Control groups

With the exception of So 2009 and Andersen 2010, each trial used a different control. Domar 2009 had the control subjects lie quietly for 25 minutes before and after embryo transfer. The control groups in the So 2009 and Andersen 2010 trials underwent placebo acupuncture for 25 minutes before and after embryo transfer, using non-puncturing Streitberger needles in the same acupoints as the true acupuncture group. Moy 2011 used sham acupuncture as a control, in which patients were needled in non-qi lines at “predetermined locations”, “near, but not on, true acupuncture points” (Moy et al., 2011). The patients receiving sham acupuncture also underwent auricular acupuncture at points determined by the acupuncturists to be not related to fertility: knee, heel, allergic area, mouth.

Acupuncturists

Domar 2009 used a single acupuncturist for all of the patients. The training or credentialing of this acupuncturist is not described. The only information given is that

the practitioner performing the acupuncture has “extensive clinical experience”. So 2009 also used a single acupuncturist for all patients, and states that this acupuncturist had completed a degree in Chinese Medicine and had two years of acupuncture experience, and “followed a standard way of communicating with patients whether they were in the real or placebo acupuncture groups” (So et al., 2009). Moy 2011 describes “licensed hospital-employed acupuncturists”, but does not give other details on the specific licensing of the acupuncturists or how many of them participated in the study. Andersen 2010 describes the acupuncture being performed by nurses who were “authorized professional acupuncturists,” as well as nurses who “before initiation of the study had received thorough instruction and training by the four professional acupuncturists” (Andersen et al., 2010). The degrees or certifications of the acupuncturists are not described further, and the total number of personnel providing acupuncture is not reported.

TCM diagnosis pre-treatment

So 2009 describes all patients receiving a pre-treatment diagnostic evaluation by a separate TCM practitioner than the one performing the acupuncture. Using observation, auscultation, interrogation, and palpation, the TCM practitioner classified patients into related syndromes such as kidney/yang deficiency, liver Qi stagnation with blood stasis, spleen Qi deficiency with phlegm, or a combination of these syndromes (So et al., 2009). Domar 2009, Moy 2011, and Andersen 2010 did not have a TCM practitioner diagnose patients before performing acupuncture.

Assisted reproduction protocols

So 2009 used a standard long agonist controlled ovarian stimulation protocol. In brief, ovarian function was suppressed with 150 ug intranasal buserelin (Suprecur, Hoechst, Frankfurt, Germany) four times daily starting in the mid-luteal phase of the cycle preceding the treatment cycle. Ultrasound confirmation of no ovarian cysts and sufficiently low serum E2 concentration (<200 pmol/L) resulted in the commencement

of ovarian stimulation using HMG (Menogon, Ferring GmbH, Kiel, Germany). Ovarian response was monitored using transvaginal scanning. An intramuscular human chorionic gonadotropin trigger was given when the largest follicle reached 18 mm diameter. Transvaginal ultrasound guided oocyte retrieval was performed 48 hours after the trigger was administered. A maximum of two embryos were transferred on day 3. Luteal support involved 1500 IU hCG on the day of embryo transfer and again six days later, in addition to 400 mg vaginal progesterone (Cyclogest, Cox Pharmaceuticals, Barnstaple, UK) twice daily for 14 days after ET. Moy 2011 used a standard long protocol ovarian stimulation scheme. Andersen 2010 used both standard long agonist and short antagonist protocols for ovarian stimulation. In the long protocol (n=439), patients underwent initial ovarian suppression with one of two GnRH agonists (Synerela, Pfizer; or Suprefact, Sanofi-Aventis), followed by stimulation with either recombinant follicle-stimulating hormone (rFSH; Puregon, Organon; or Gonal-F, Merck Serono) or highly purified human menopausal gonadotropin (HMG; Menopur, Ferring). The short protocol (n=179) involved stimulation with rFSH or HMG starting on cycle day 3, followed by a GnRH antagonist when the leading follicle reached 12-14 mm diameter. Both protocols utilized an intramuscular HCG trigger 36 hours before oocyte aspiration. Luteal support was given in the form of 600 mg transvaginal progesterone daily (Progestan; NycoMed, Denmark) for 14 days post-ET. Domar 2009 does not describe the ovarian stimulation protocol that the patients underwent.

Randomization and allocation concealment

Table 3 provides a comparison of methodological quality across the studies. Domar 2009 used a computer-generated random numbers table and concealed patients behind a curtain so as to prevent nurses and doctors from discovering which group they had been allocated to. In “a few cases”, a nurse came behind the curtain and was able to see if the patient was receiving acupuncture or not, however it is not stated how many times this occurred. So 2009 and Moy 2011 describe computer-generated randomization lists and the use of sealed, opaque, envelopes. Allocations were not

unmasked until the study and statistical analysis were complete. Andersen 2010 used a computer-generated list of random numbers, but offered randomization to the first patients who called in to the office; if patients declined, the next patients to call in were given the same offer.

Blinding

Blinding is a particular problem when studying acupuncture. In the Domar 2009 study, patients were not blinded as to their allocation group, since the control group was lying quietly. The patients were asked to not reveal their allocation to the nurses or the physician performing the embryo transfer. So 2009 had patients, clinical staff, and embryologists blinded. Moy 2011 reports that the physicians and patients were blinded to the allocation group until the study was concluded, but does not detail whether the statistical analysis was complete at the time of the un-blinding. Andersen 2010 reports that patients and the physician performing the embryo transfer were blinded. However, the authors of the study, who were also the acupuncturists, were not blinded to patient allocations, and an independent blinded statistician was not used.

Table 3 – Methodological quality across studies

Study	Adequate sequence generation?	Allocation concealment?	Blinding?	Free from other bias?
Domar 2009	Yes	No	Yes	No
So 2009	Yes	Yes	Yes	Yes
Andersen 2010	No	Yes	Yes	No
Moy 2011	Yes	Yes	Yes	Yes

Intention-to-treat analysis and follow-up

Two trials (So 2009, Andersen 2010) stated that they used intention-to-treat analysis.

Baseline similarity of comparison groups

All trials had comparable baseline demographics and fertility characteristics between intervention and control groups.

Effects of interventions

A summary of the effects of the interventions is provided in Table 1.

- acupuncture vs no acupuncture: Domar 2009
 - o positive β -hCG: 50.0% (Ac) vs. 42.6% (no Ac), p=0.47
 - o ongoing pregnancy rate: 30.8% (Ac) vs. 33.8% (no Ac), p=0.69
 - o live birth rate: not reported
 - o miscarriage rate: not reported
 - o side effects: not reported
- true acupuncture vs sham acupuncture w/ non-penetrating needles: So 2009, Andersen 2010
 - o positive β -hCG:
 - 38.9% (true Ac) vs. 49.2% (sham Ac), p=0.059 [So 2009]
 - 40% (true Ac) vs. 46% (sham Ac), p=NS (not significant) [Andersen 2010]
 - o ongoing pregnancy rate:
 - 31.9% (true Ac) vs. 40.5% (sham Ac), p=0.105 [So 2009]
 - 27% (true Ac) vs. 32% (sham Ac), p=NS [Andersen 2010]
 - o live birth rate:
 - 29.7% (true Ac) vs. 38.4% (sham Ac), p=0.100 [So 2009]
 - 25% (true Ac) vs. 30% (sham Ac), p=NS [Andersen 2010]
 - o miscarriage rate:
 - 32.1% (true Ac) vs. 30.4% (sham Ac), p=0.931 [So 2009]
 - not reported [Andersen 2010]
 - o side effects:
 - reported, no significant differences between groups, no serious side effects [So 2009]

- not reported [Andersen 2010]
- acupuncture vs sham acupuncture w/ penetrating needles at non-acupoints:
 - Moy 2011
 - positive β -hCG: not reported
 - ongoing pregnancy rate: 45.3% (true Ac) vs. 52.7% (sham Ac), p=0.353
 - live birth rate: not reported
 - miscarriage rate: not reported
 - side effects: not reported

Table 1: Comparison of effects of interventions across studies

Study	N	Median age	Control type	Ac PR	Control PR	Ac LBR	Control LBR	Intention-to-treat analysis	Achieved significance?
Domar et al 2009 **	146	36.1	Lying quietly	30.8%	33.8%	Did not report	Did not report	No	No
So et al 2009	370	36	Strietberger placebo needling; same qi points	43.8% (overall PR)	55.1% (overall PR)	29.7%	38.4%	Yes	Yes; p=.038 for overall PR; e.g. control group achieved higher pregnancy rate than intervention group
Andersen et al 2010	635	31	Strietberger placebo needling; same qi points	27%	32%	25%	30%	Yes	No
Moy et al 2011	160	33	Non-qi needling; non-fertility auricular	45.3%	52.7%	Did not report	Did not report	No	No

**replication of the Paulus et al 2002 study

Discussion

The Paulus study published in 2002 was the first randomized controlled trial investigating the impact of acupuncture on pregnancy rates in IVF patients.

Subsequently, it has been used by many researchers as a starting point from which to design new studies. This author would suggest that this should be done with caution, as

the Paulus study surprised many in the IVF community by reporting an astonishing 42.5% pregnancy rate in the placebo group, much higher than the 30-35% pregnancy rate per transfer that is the average at most fertility clinics, and a pregnancy rate of 26.3% in the no-acupuncture IVF-alone control arm, much lower than the average. Pregnancy rates that are so much higher and lower than the norm should be viewed with some skepticism. Subsequently, three meta-analyses examining the effect of acupuncture on IVF outcomes were published in 2008 and 2009. El-Toukhy et al. found no difference in pregnancy rates, while both the Manheimer review and the Cochrane review reported increased pregnancy rates in women who underwent acupuncture on the day of embryo transfer.

This systematic review of the literature shows that acupuncture before and after embryo transfer does not have a statistically significant effect on pregnancy or live birth rates. The only result which achieved significance in the So 2009 study was the “overall pregnancy rate”, which lumps together those patients who had positive urine pregnancy tests with those who had false-negative tests but ended up in fact being pregnant. The analysis showed that patients who received placebo acupuncture with non-puncturing needles had a higher overall pregnancy rate than those who received real acupuncture in the same acupoints (respectively, 55.1% vs. 43.8%, $p=0.038$). While this is an interesting result that begs for further research into the effects of placebo and sham acupuncture, it does not focus on that most important patient-centered outcome: live birth rate. In every other study, including the Domar 2009 trial in which the control group simply lay still in a quiet room, the control group achieved higher pregnancy rates than the acupuncture group. These results, while not achieving statistical significance, are still interesting, and bring up a point that the acupuncture and fertility community have been debating for some time. That is, what is a good control for acupuncture? Sham acupuncture is commonly performed on sites that are not considered acupoints, while placebo acupuncture involves stimulating acupoints (with a fingernail, toothpick, blunt needle, or retractable needle) without actually penetrating the skin. Non-invasive placebo acupuncture using retractable needles is currently considered the gold standard

for acupuncture studies. However, the results of the studies in which placebo groups had a greater response than the acupuncture groups calls into question the status of sham acupuncture as a truly inert placebo.

The Streitberger placebo needle (White et al., 2003) and the Park's device (Park et al., 2002, 2005) have both been independently verified as placebo controls. In the studies that showed a greater effect from the placebo treatment (So et al., 2009), despite having a study population of which 30% had already been exposed to acupuncture treatment, there was no difference in the proportion of correct guessing between the acupuncture group and the placebo group, suggesting that valid blinding was achieved. Despite this, the So 2009 study brings up the interesting point that there were significant differences in serum cortisol concentration, anxiety level, and endometrial and subendometrial vascularity in both the acupuncture and placebo groups, suggesting that even non-penetrating stimulation of acupoints can cause a physiologic change in the subjects that are exposed to it. This "acupressure effect" has been brought up in the past as a criticism of the Streitberger needle system (Cheong et al., 2008). It is possible that the change in endometrial and subendometrial vascularity may have been caused by the simple act of lying down for 25 minutes while the acupuncturist went about his or her business. So and colleagues attempted to address this by using 3D power Doppler to analyze the endometrial and subendometrial vascularity in a small sub-group of 27 patients both before and after 25 minutes of lying down. They were unable to find any significant change in the pre- and post-rest vascularity, after which they concluded that both the sham and real acupuncture must be having an effect. This small subset of data was not published, however, and the small number of subjects makes it difficult to draw conclusions. A double-blinded study with a greater number of subjects might offer some insight into whether or not changing endometrial and subendometrial vascularity might be induced simply by lying flat for a prescribed period of time.

In order to tease out the real effects of acupuncture, or indeed to if there is any effect, it will be necessary to first clarify the effects of sham and placebo acupuncture

on patients. In order to achieve this, it will be necessary to perform trials comparing the effect of needling or placebo-needling standard sets of acupoints. This introduces a fixed protocol bias, which is the central tenet of randomized controlled trials and evidence-based medicine in general; that is, that the same treatment should be compared across different people. Unfortunately, this runs counter to the very principles that TCM and much of complementary and alternative medicine draw a basis from. TCM diagnoses are highly personalized according to each patient, and a common refrain in the CAM community is a rejection of common causes of disease. That is, each condition has its own unique etiology according to the person who has it, requiring its own unique and “personalized” treatment. According to the principles of TCM, the acupoints that were originally chosen by Paulus for the 2002 study were thus: “the kidney system dominates the reproductive system, the liver (LR) regulates *Qi* (vital force and energy), and spleen (SP) and stomach (ST) are sources of *Qi* and blood. Spleen 6 (SP6) is the crossing point of the spleen, kidney, and liver meridians and is considered the key point in treating infertility. Needling SP6, SP8, SP10, ST36, and ST29 aims to provide improved blood perfusion and more energy.” (Westergaard et al., 2006). By these principles, the goal of acupuncture is to improve perfusion to the uterus, shunting more blood to the area. Yet many studies point to a beneficial role for a relative state of hypoxia following fertilization and leading up to implantation (Sharkey et al., 2000). This is corroborated by several studies showing that vascular endothelial growth factor expression is upregulated in the human endometrial stromal cell in hypoxic states (Nasu et al., 2004) as well as the evidence that there is a relatively low concentration of oxygen present around blastocysts at the time of implantation (Graham et al., 2000; Hu et al., 2003).

Some of the central questions regarding acupuncture for the treatment of health problems are these: how does it work? What does it do? So far, research has not been able to clearly answer either one of these questions. Furthermore, our understanding of the science of implantation is imperfect. The complicated chemical milieu into which a transferred embryo is placed, and the intricate dance of steps it must take to undergo

implantation, remains largely a mystery. As the adage goes, it takes two to tango. In the case of baby-making, it takes many, many more: sperm and egg, embryo and endometrium, vascular growth factors and the maternal antineoplastic response...the list goes on and it has only glimpsed it through a keyhole. Needling the woman applies an unknown and poorly-understood stimulus to a small part of the infertility equation.

Because of the emphasis in the complementary and alternative medical community on individualistic diagnoses and individual causes of similar symptoms, is CAM therefore like Schrodinger's cat? As soon as you attempt to look at it, it's dead, or at least, no longer functioning the way it is supposed to? And should this be a reason to not study it scientifically, according to the scientific method? This author would argue that this is not necessary, but to maximize translatability of results, guidelines should be agreed upon for the study of fertility and acupuncture. Because even established IVF clinics are constantly reviewing and changing their ovarian stimulation and luteal support protocols, large-scale studies with a sufficient number of patients are difficult to bring to fruition. The addition of acupuncture to an ovarian stimulation protocol adds yet another wrinkle and demonstrates the difficulty and complexity of studying CAM methods with EBM. When examining questions related to clinical treatments, the best way to minimize bias is to focus on randomized controlled trials. Meta-analyses may also include observational studies, but these types of studies often include the same biases, which are then combined in the pooled result from all the trials. One thing is certain – any study of fertility treatment should, at a minimum, report live birth rates. The live birth rate is the patient-centered outcome, arguably the single most important outcome that fertility patients care about. To enhance comparability between studies, the following guidelines are offered for RCTs investigating the effect of acupuncture on IVF outcomes:

1. Adequate blinding of patient, nurses, physician performing transfer, and statisticians performing analysis of pregnancy and live birth rates

2. Report on the following: chemical pregnancy rate, ongoing pregnancy rate (e.g. ultrasound confirmation of fetal heart tones at 5-7 weeks of life), live birth rate, miscarriage rate
3. Also report on: premature birth rate, multiple gestation rate, and discussion of any fetal anomalies
4. Adequate power analysis
5. Include four arms:
 - a. standardized acupuncture in which every patient is needled in the same acupoints
 - b. sham acupuncture in which every patient is “needled” in the same acupoints
 - c. placebo acupuncture in which every patient is needled in the same non-acupoints
 - d. no treatment
6. Acupuncture to be performed before and after day 3 fresh embryo transfer

Some weaknesses associated with this systematic review include the exclusion of non-English sources and the lack of follow-up questions put to the researchers whose work was included. These two points were not possible due to a lack of resources and time. However, given the scope of the review, it is an adequate starting point for further investigation of the topic at hand. With more time and resources, a systematic review and meta-analysis that fits the QUOROM checklist set forth in the Lancet in 1999 by Moher and colleagues (Moher et al., 1999) would serve as a more comprehensive review of the evidence.

Acupuncture has the benefit of few adverse effects and thus, a perception exists that it is a fairly harmless adjunct to conventional fertility treatment. However, pooled results from the Cochrane 2009 study showed that for those getting extra, post-embryo transfer acupuncture, any benefit the review found for increased pregnancy rates disappeared when the live birth rate was examined, suggesting that acupuncture may actually be detrimental to a nascent pregnancy in the early luteal period. Additionally,

the patients in the true acupuncture arm of the Moy 2011 trial reported feeling that their sessions were more “tiring” ($p < 0.005$), “fearful” ($p < 0.001$), and reported more “achiness” ($p < 0.018$) than those in the sham arm. These sensations are likely the result of the desired “de Qi” effect, a desired sensation that TCM practitioners use to determine whether or not the acupuncture process is “working”. This is something that individual patients should be counseled on, so that each patient can make a decision about whether or not this is a desirable or tolerable aspect of the IVF process for them.

Further questions of interest include examining whether acupuncture relieves emotional stress, and whether emotional stress is related to fertility. Preliminary evidence from the Boivin review in the British Medical Journal in February 2011 suggests that stress and fertility are not linked; however, the research is ongoing. Other questions of interest include whether acupuncture causes biochemical changes in patients, and an examination of how those possible biochemical or hormonal changes relate in a plausible way to the causes of infertility

Author’s conclusions

Acupuncture does not improve IVF outcomes and should not be offered routinely as an adjunct to fertility treatment. The evidence from the current literature suggests a positive effect of sham and placebo acupuncture on IVF outcomes, and therefore merits further study with adequately powered RCTs.

REFERENCES

References to studies included in this review

Andersen D, Lossl K, Andersen AN, Furbringer J, Bach H, Simonsen J, Larsen E. Acupuncture on the day of embryo transfer: a randomized controlled trial of 635 patients. *Reprod Biomed Online* 2010;21:366-72.

Domar A, Meshay I, Kelliher J, Alper M, Powers RD. The impact of acupuncture on in vitro fertilization outcome. *Fertil Steril* 2009;91:723-6.

Moy I, Milad M, Barnes R, Confino E, Kazer R, Zhang X. Randomized controlled trial: effects of acupuncture on pregnancy rates in women undergoing in vitro fertilization. *Fertil Steril* 2011;95:583-7.

So EW, Ng EH, Wong YY, Lau EY, Yeung WS, Ho PC. A randomized double blind comparison of real and placebo acupuncture in IVF treatment. *Hum Reprod* 2009;24:341-8.

References to studies excluded from this review

Chen J, Liu LL, Cui W, Sun W. Effects of electroacupuncture on in vitro fertilization-embryo transfer (IVF-ET) of patients with poor ovarian response. *Zhongguo Zhen Jiu* 2009;29:775-9.

Dieterle S, Ying G, Hatzmann W, Neuer A. 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.

Ho M, Huang LC, Chang YY, Chen HY, Chang WC, Yang TC, Tsai HD. Electroacupuncture reduces uterine artery blood flow impedance in infertile women. *Taiwan J Obstet Gynecol* 2009;48:148-51.

Humaidan P, Brock K, Bungum L, Stener-Victorin E. Pain relief during oocyte retrieval—exploring the role of different frequencies of electro-acupuncture. *Reprod Biomed Online* 2006;13:120-5.

Meng P, Wang LL. Analgesic effect of acupuncture compound anesthesia for patients of different pain thresholds. *Zhongguo Zhen Jiu* 2009;29:29-31.

Paulus WE, Zhang M, Strehler E, El-Danasouri I, Sterzik K. Influence of acupuncture on the pregnancy rate in patients who undergo assisted reproduction therapy. *Fertil Steril* 2002;77:721-4.

Stener-Victorin E, Waldenstrom U, Nilsson L, Wikland M, Janson PO. A prospective randomized study of electro-acupuncture versus alfentanil as anaesthesia during oocyte aspiration in in vitro fertilization. *Hum Reprod* 1999;14:2480-4.

General references

- Boivin J, Griffiths E, Venetis CA. Emotional distress in infertile women and failure of assisted reproductive technologies: meta-analysis of prospective psychosocial studies. *BMJ*. 2011 Feb 23;342:d223.
- Cheong YC, Hung Yu Ng E, Ledger WL. Acupuncture and assisted conception. *Cochrane Database of Systematic Reviews* 2008, Issue 4.
- El-Toukhy T, Sunkara SK, Khairy M, Dyer R, Khalaf Y, Coomarasamy A. A systematic review and meta analysis of acupuncture in in-vitro fertilization. *Br J Obstet Gynecol* 2008;115:1203-13.
- Fertility, Family Planning, and Reproductive Health of U.S. Women: Data from the 2002 National Survey of Family Growth, tables 67, 69, 97.
- Graham CH, Postovit LM, Park H, Canning MT, Fitzpatrick TE, Adriana and Luisa Castellucci award lecture 1999: role of oxygen in the regulation of trophoblast gene expression and invasion. *Placenta*. 2000;21:443-450.
- Hu CJ, Pan Y, Simon MC. Oxygen and angiogenesis. In: Hoying JB (ed). *Genetics of Angiogenesis*. Oxford, UK: BIOS Scientific, 2003.
- Manheimer E, Zhang G, Udoff L, Haramati A, Langenberg P, Berman BM, et al. Effects of acupuncture on rates of pregnancy and live birth among women undergoing in vitro fertilization: systematic review and meta-analysis. *BMJ*. 2008;336:545-49.
- Moher D, Cook D, Eastwood S, Olkin I, Rennie D, Stroup D. *Lancet* 1999;354:1896–900.
- Nasu K, Nishida M, Fukuda J, Kawano Y, Nishida Y, Miyakawa I. Hypoxia simultaneously inhibits endostatin production and stimulates vascular endothelial growth factor production by cultured human endometrial stromal cells. *Fertil Steril*. 2004;82:756-59.
- Park J, White A, Stevinson C, Ernst E, James M. Validating a new non-penetrating sham acupuncture device: two randomized controlled trials. *Acupunct Med* 2002;20:168-174.
- Park J, White AR, James MA, Hemsley AG, Johnson P, Chambers J, Ernst E. Acupuncture for subacute stroke rehabilitation: a sham-controlled, subject- and assessor-blind, randomized trials. *Arch Intern Med*. 2005;165:2026-2031.
- Paulus WE, Zhang M, Strehler E, Seybold B, Sterzik K. Placebo-controlled trial of acupuncture effects in assisted reproduction therapy. *Hum Repro* 2002;18:18-19.
- Sharkey AM, Day K, McPherson A, Malik S, Licence D, Smith SK, Charnock-Jones DS. Vascular endothelial growth factor expression in human endometrium is regulated by hypoxia. *J Clin Endocrinol Metab*. 2000;85:402-9.

Standard acupuncture nomenclature: a brief explanation of 361 classical acupuncture point names and their multilingual comparative list. 2nd ed. Manila, Phillipines: Office for the Western Pacific, World Health Organization, 1993.

<http://www.wpro.who.int/NR/rdonlyres/8DDB198B B00B-47AB-9BA1 9337CF49C5A5/0/Standard_Acupuncture_Nomenclature_2nd_ed.pdf>

Streitberger K, Kleinhenz J. Introducing a placebo needle into acupuncture research. *Lancet*. 1998;352:364-365.

Westergaard LG, Mao QH, Kroglund M, Sandrini S, Lenz S, Grindsted J. 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.

White P, Lewith G, Hopwood V, Prescott P. The placebo needle, is it a valid and convincing placebo for use in acupuncture trials? A randomized, single-blind, cross-over pilot trial. *Pain*. 2003;106:401-9.