Methodological Problems in the Clinical Research

Assessing Acupuncture as an Adjunct to IVF

By

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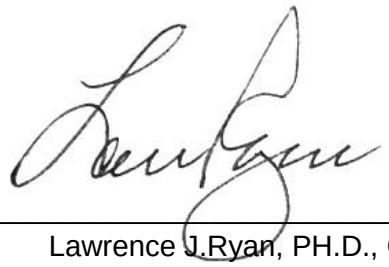

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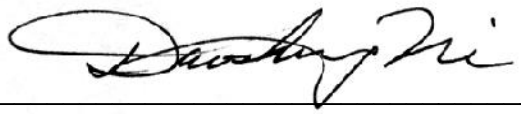

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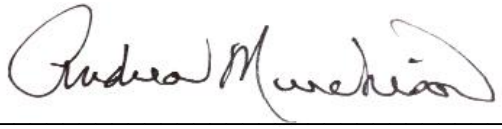

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Abstract

Since 2002 there has been a significant amount of research looking at whether or not acupuncture can be used as an adjunct to IVF treatment as a means to increase IVF success rates. While most of the results of the research have been positive, some of the research results are unclear, and there has been significant controversy concerning the quality, design, and correct interpretation, of the existing literature. The objective of this study was to look at the methodological problems in the literature concerning acupuncture as an adjunct to IVF, to clarify exactly what those problems are, and to provide suggestions for remedying or ameliorating those problems in future. Twenty seven pieces of clinical research and eight research syntheses/meta-analyses were analyzed using a data abstraction form created by the present author to record and measure many of the variables that had already been pointed out as areas of concern by previous authors. The present author found that the interventions in nearly all of the studies were not recorded in enough detail to be reproducible, and that it could not be confirmed that any of the studies used the same acupuncture intervention. Most studies did not note whether the persons employed to perform the acupuncture had had any previous training in acupuncture. The existing literature was also found to suggest that the placebo controls that have been used to date are physiologically active and thus hinder clear interpretation of the effects of acupuncture on IVF cycles.

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Chapter 1: Introduction

Overview

In-vitro fertilization (IVF) has greatly increased the odds of infertile couples being able to conceive. However, most couples will need several expensive, stressful and potentially dangerous IVF cycles to conceive, and so there is great interest in finding ways to improve the success rates of the procedure. The first study showing acupuncture could be used as an adjunct therapy to increase IVF success rates was published in 2002 (Paulus, Zhang, Strehler, El-Danasouri & Sterzak, 2002), where acupuncture was administered for 25 minutes before and after embryo transfer. Much research has been done since then in apparent attempts to verify the Paulus et al.'s findings. The results of these further studies have proven somewhat confusing. Most show that acupuncture improves IVF outcomes, while others show that it does not. One study even found that acupuncture reduced pregnancy rates when combined with IVF (Craig, Criniti, Hansen, Marshall & Soules, 2007).

This increase in research regarding acupuncture and IVF has been concurrent with a similar explosion of acupuncture research generally. This growth in the literature has lead to a secondary body of literature that seeks to identify methodological challenges in acupuncture research design.

Among the issues cited as problems in acupuncture literature is the heterogeneity of outcome measures used. Different studies regarding acupuncture as an adjunct to IVF record different outcome measures, such as implantation rate, clinical pregnancy, ongoing pregnancy, or live birth rate. The patient populations and the acupuncture interventions being assessed often differ significantly. These issues,

however, are common in research regarding reproduction and infertility and are not specific to research assessing acupuncture as an adjunct to IVF.

A second issue that becomes evident from a cursory reading of the literature that assesses the combination of acupuncture and IVF is that many different acupuncture interventions are used. They differ in such ways as to whether or not electrical stimulation was added to the needles, which acupuncture points were used, whether or not specific needling reactions were sought, how long the treatment sessions were, and how many treatment sessions were considered a course of treatment.

A third area of contention is that there is still no consensus about how to perform blinding in RCTs involving acupuncture, and to what extent blinding is necessary. Blinding of patients is problematic in that while it is possible to design controlled studies where the patients are effectively blinded to their allocation, this must be done in combination with a sham or placebo acupuncture treatment, and no sham or placebo acupuncture treatment to date has been proven to be physiologically inactive. As sham interventions are not generally recommended in trials of biomedical interventions for infertility, the rationale for using them in acupuncture interventions for infertility seems unclear.

As for the blinding of practitioners, it seems unlikely that a sham or control acupuncture intervention can be administered by a trained acupuncturist while being unaware that it is a sham treatment. For example, a common forms of sham or placebo acupuncture is inserting acupuncture needles into locations that are not traditionally used as acupuncture points. Another form of sham or placebo is using a specially developed device, the Streitberger needle, which acts in a way similar to a stage knife.

When the acupuncturist appears to insert the ‘needle’ into the skin, the ‘needle’ collapses into the handle in a way that appears to puncture the skin, but in reality does not. It seems unlikely that any acupuncturist could perform these sham procedures without being aware that they were doing so.

There is also inconsistency of use in the terms ‘blind’ and ‘double-blind’, with different sets of authors using them differently to refer to different levels of blinding of patients, practitioners, and assessors. This is however true of research generally, and not specific to the field of acupuncture research (de Hoyos, de Leon, Martin, Morilla & Moreno, 2003).

As noted above, placebo is also a major stumbling block in acupuncture and IVF research, with many studies showing acupuncture to be effective when compared to patients who do not receive acupuncture, but not in comparison to placebo. It is unclear at this point whether a valid, physiologically inactive placebo can be found for acupuncture (Langevin et al., 2011).

Another problem in the literature is that much of it does not specify the training of the persons performing the acupuncture interventions. Some studies use professional acupuncturists, while others use nurses or other support staff to provide acupuncture, and many do not record any description of the persons performing the acupuncture interventions at all (MacPherson et al., 2010).

The question of ecological validity is also a significant area of confusion. Much research into acupuncture does not evaluate acupuncture as it is practiced in a normal clinical setting. Most studies pair a static treatment protocol with a western diagnosis or scientific parameter. In clinical practice, traditional acupuncture regimens are generally

altered during a course of treatment based on evolving clinical signs and symptoms as interpreted by traditional East Asian medical diagnosis, not biomedical parameters (Hammerschlag & Zwickey, 2006). While these studies using static acupuncture intervention protocols against western biomedical parameters are extremely interesting, and perhaps essential, they do not begin to address the issue of how to assess the efficacy of traditional East Asian medicines as practiced in the clinical setting.

And lastly, a common problem in acupuncture research is that the acupuncture intervention is not described in enough detail to allow for the study to be reproduced. Variables such as acupuncture points used, methods of needle stimulation, lengths and numbers of treatment sessions are often not recorded. All of these variables must be recorded for the acupuncture intervention to be reproducible. Recording all of these variables will also allow later studies to evaluate the different parameters of any given protocol and how alteration of these individual parameters may alter effectiveness.

Research Goals

This research synthesis aims to systematically evaluate the research surrounding acupuncture as an adjunct to IVF with an aim to be able to make suggestions for the design of future acupuncture research in this field. While there is a significant body of literature regarding methodological problems in acupuncture research generally, there has been relatively little written about methodological problems in this particular branch of acupuncture research beyond some recommendations embedded within the primary research, and a 2008 piece in the Journal of Chinese medicine by Balk & Horn. While Balk & Horn's work was groundbreaking in this regard, a significant number of studies have been published since then, and so it seemed appropriate to look at all of the

literature to date and to do it in a level of detail and length that was perhaps not possible in a paper journal.

This research synthesis will to contribute to remedying that situation and answer the question: What are the methodological challenges in research combining acupuncture with IVF? And secondly: How might research into the combination of acupuncture and IVF be more effectively designed in the future?

Glossary of Terms

The following terms are discerned to be relevant to the current study and are listed and defined below in order to provide a common understanding:

- **Alfentanil.** A strong opioid analgesic usually used during surgery (“PubMed Health,” 2012”).
- **Acupuncture.** For the purpose of this study, acupuncture will be defined as the practice of inserting filiform needles through the skin and into strategic points on the body to affect health and well-being, and to influence the course of disease (Cheng & Deng, 1999). Issues of other, broader, and specific contextual definitions, will not be addressed here.
- **Chemical Pregnancy.** A pregnancy indicated by a positive beta hCG test (Fritz and Speroff, 2011).
- **Clinical Pregnancy.** A pregnancy that is confirmed by ultrasound imaging of a fetal sac (Fritz and Speroff, 2011).
- **CONSORT (Consolidated Standards of Reporting Trials).** A set of standards developed by an international body of researchers aimed at alleviating the

problems associated with inadequate recording of randomized controlled trials (RCTs) (Schulz, Altman, & Moher, 2010).

- **Deqi.** A Chinese term that refers to sensations that are often produced during acupuncture. These feelings are often described as tingling, distension, or numbness (Cheng & Deng, 1999). Many schools of acupuncture consider these signs essential for performing clinically effective acupuncture.
- **Electroacupuncture.** Acupuncture that adds electrical stimulation to the needles inserted during an acupuncture treatment (Cheng & Deng, 1999).
- **ICSI (intracytoplasmic sperm injection).** The procedure by which a single sperm is injected into an oocyte that has been removed from a woman's ovary during the process of IVF (Fritz and Speroff, 2011).
- **Implantation rate.** A measure of success used in ART defined by the number of fetal heartbeats detected by ultrasound per embryos transferred (Fritz and Speroff, 2011).
- **IVF (in vitro fertilization).** A surgical process whereby eggs are extracted from a woman's ovaries, fertilized outside her body, and then some or all of the resulting embryos are transferred to her uterus (Fritz and Speroff, 2011).
- **Ongoing Pregnancy.** This study could not find a standardized definition of this term. The most common definitions were pregnancy that was confirmed via ultrasound to have lasted to 16 or 18 weeks (Fritz and Speroff, 2011).
- **Oocyte retrieval.** The surgical procedure through which oocytes, or eggs, are retrieved from a woman's ovaries during an IVF cycle. Often also referred to as oocyte aspiration (Fritz and Speroff, 2011).

- **Oriental/East Asian Medicine.** The traditional medicines of East Asia, including China, Japan, and Korea. Acupuncture is a component of these traditional medicines (Scheid, 2008).
- **Randomized Controlled Trial (RCT).** A trial in which subjects are randomly allocated to either an intervention group or a control group before the intervention to be studied begins (Schulz, Altman, & Moher, 2010).
- **Streitberger Needle.** A placebo device which looks like an acupuncture needle but which does not puncture the skin. When the needle is tapped, the tip disappears into the handle in the manner of a stage knife, and the patient feels a pricking sensation (Streitberger and Kleinhenz, 1998).
- **STRICTA (STandards for Reporting Interventions in Clinical Trials of Acupuncture).** An official extension of the CONSORT statement. It is a set of standards aimed at increasing the methodological quality of acupuncture research through improved reporting of interventions used (MacPherson, White, Cummings, Jobst, Rose & Niemtzow, 2002).
- **TCM (Traditional Chinese Medicine).** For the purpose of this study TCM or traditional Chinese medicine will refer to all traditional Chinese medicinal practices generally. This includes acupuncture, materia medica, traditional dietary therapy, therapeutic massage and bone setting, therapeutic exercise, and the theoretical frameworks underpinning these various practices (Cheng & Deng, 1999).

Chapter 2: Literature Review

Antecedents

The first research into the possibility of increasing IVF success rates by adding acupuncture treatment was published in 1996 when Stener-Victorin et al. demonstrated the positive effects of acupuncture on infertile women with high uterine artery impedance (Stener-Victorin, Waldenström, Andersen & Wikland, 1996). The study involved giving ten women with high uterine artery impedance eight acupuncture treatments over the course of four weeks and then comparing pre- and post-treatment pulsatility indices both immediately after the eighth treatment and then again 10-14 days later. The authors hypothesized that since poor uterine blood flow had been shown to be a predictor of IVF failure (Steer, Campbell, Tan, Crayford, Mills, Mason & Collins, 1991), perhaps acupuncture could be used to enhance effectiveness of IVF transfer in women with high uterine artery impedance.

Acupuncture Combined with IVF

It was not until 2002 however when there was any literature directly measuring the effects of acupuncture on IVF success rates (Paulus, Zhang, Strehler, El-Danasouri & Sterzak, 2002). The study by Paulus et al. was a prospective randomized trial performed at the University of Ulm in Germany. In it, 160 healthy women undergoing IVF (some with, some without, ICSI) were randomly assigned to either IVF alone or IVF plus acupuncture. There was no placebo intervention group, and the group receiving IVF plus acupuncture was compared against a group receiving only IVF. The

acupuncture group received treatment 25 minutes before and after embryo transfer, and the attending physician was blinded as to the patients grouping.

It was also in 2002 that the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) were originally published (MacPherson, White, Cummings, Jobst, Rose & Niemtzow, 2002). The STRICTA guidelines were developed by an international group of acupuncturists and researchers who hoped to improve the quality of acupuncture research by providing clear parameters for recording acupuncture interventions in clinical trials. The original set of guidelines was revised with the input of several journal editors and their advisors before being published in 2002.

In 2003, 2004, and 2005, one RCT on the effects of combining acupuncture and IVF was published each year. The first was a follow-up study by Stener-Victorin evaluating adjunctive acupuncture in 286 patients undergoing IVF (Stener-Victorin, Waldenström, Wikland, Nilsson, Hägglund & Lundeberg, 2003). This study differed from previous work on the subject by administering the acupuncture intervention around the time of oocyte aspiration. This was found not to increase implantation rates, but to be a useful adjunct for pain relief during egg retrieval.

In the following year a pilot study (Quintero, 2004) was published as an abstract in Fertility & Sterility which showed acupuncture benefiting pregnancy rates when using a placebo needling device as control. Only 17 women were enrolled however, and only 7 finished the study. It is notable in that it was the first published study in the literature regarding IVF and acupuncture to mention traditional theories of Qi and Meridians. It stated that ‘Acupuncture is based on patterns of energy flow (Qi) through a network of

meridians. Maintenance of Qi is essential for health, while blockage may provoke disease. Acupuncture works by unblocking the various types of stagnation that can occur along these channels.'

In 2005 another work was published by *Fertility & Sterility* from the Pacific Fertility Center in Los Angeles (Khorram, Horton & Sahakian, 2005). This retrospective study analysed 238 women undergoing IVF and found no significant differences in pregnancy or implantation rates between patients who did or did not receive acupuncture. It was noted that first trimester miscarriage rates were lower in the acupuncture group, but no mention was made of overall miscarriage rates or live birth rates in the two arms of the study.

The May 2006 issue of *Fertility & Sterility* published three randomized, prospective clinical trials. Two of the trials (Dieterle, Ying, Hatzmann & Neuer, 2006; Westergaard, Mao, Krogslund, Sandrini, Lenz & Grinsted, 2006) showed benefit to IVF rates from acupuncture, and one (Smith, Coyle & Norman, 2006) showed a statistically insignificant improvement in IVF outcomes. After these papers were published research on the subject began to appear at a much faster rate, and systematic reviews began to appear.

The first systematic review and meta-analysis of the literature was published in BMJ in March of 2008 (Mannheimer, Zhang, Udoff, Harmati, Langenberg, Berman & Bouter, 2008). This analysis included seven trials involving 1366 women undergoing IVF. It concluded that acupuncture around the time of embryo transfer increased both clinical pregnancy rates (CPR) and live birth rates (LBR), and was a useful and cost-effective addition to IVF. The authors noted that there were problems in the published

literature arising from inadequate reporting and suggested that in future, the guidelines developed by the CONSORT group to standardize reporting of RCTs be followed.

The second analysis was published by El-Toukhy (El-Toukhy, Sunkara, Khairy, Dyer, Khalaf & Coomarasamy, 2008) later that year. It involved thirteen trials and 2,500 patients, and found that acupuncture did not raise CPR or LBR in IVF cycles. The authors justified the need for a second meta-analysis by taking issue with the Mannheimer (Mannheimer, Zhang, Udoff, Harmati, Langenberg, Berman & Bouter, 2008) report for not including studies that involved administering acupuncture around the time of oocyte aspiration, and by pointing out that Craig et al's study (Craig, Criniti, Hansen, Marshall & Soules, 2007) showing that acupuncture at the time of embryo transfer decreased pregnancy rates had been published since the Mannheimer report was written. These two facts, they wrote, cast 'uncertainty on the conclusions of the [Mannheimer] review.'

The third analysis (Ng, So, Gao, Wong & Ho, 2008) was more ambitious in intent and attempted to evaluate acupuncture's use in sub-fertility generally, and included the categories of male factor infertility, PCOS, pain relief during egg retrieval, and IVF. The analysis of the literature regarding IVF and acupuncture included ten studies and found that acupuncture on the day of embryo transfer improved pregnancy rates, but that acupuncture around the time of egg retrieval did not.

The *Cochrane Collaboration* published a review in January of 2009 with similar results by analyzing 13 trials involving 2,300 participants (Cheong, Ng & Ledger, 2009). It found that acupuncture at the time of embryo transfer increased live birth rates, while that at the time of oocyte aspiration did not. Later that year, El-Toukhy and another

author from his previous study produced a new systematic review (El-Toukhy & Khalaf, 2009). This new analysis involving 14 trials and 2,870 women found that there was still no evidence to suggest acupuncture as a useful adjunct to IVF. The authors also stated that since the numbers of women that would need to be included in a single study for the study to be definitive are so high, it seemed doubtful to them that acupuncture's benefit to IVF would ever be proven.

The sixth review (Cheong, Nardo, Rutherford & Ledger, 2010) was published in the March 2010 issue of *Human Fertility*. It analyzed 14 trials involving 2,670 subjects and found that there was no evidence to suggest that acupuncture improved IVF success rates when compared to placebo acupuncture. The authors wrote in their concluding remarks however of the inherent difficulties of finding an inert placebo for acupuncture, the great heterogeneity of the studies, the lack of consensus about what constitutes adequate training for acupuncturists, and lack of consensus regarding what is a 'reasonable variation' for acupuncture protocols. The researchers recommended more RCTs and more discussion of these important methodological problems.

The seventh review was published in May 2011 (Huang, Huang, Lu, Dieterle, Neuer & Greb, 2011). In it, the authors reviewed the relevant literature and decided that it suggested a positive result of acupuncture on IVF. The main authors of this study were from the Institute of Integrated Traditional Chinese and Western Medicine from Huazhong University of Science and technology in Wuhan, China. They noted that most of the literature was produced outside of China and did not reflect standard TCM practice, including the use of pattern differentiation and individualized treatment protocols, and that this may have hampered the effectiveness of the treatments.

The most recent systematic review and meta-analysis (Zheng, Huang, Zhang & Wang, 2012) was also produced with researchers from the Huazhong University of Science and Technology. Published in the March 2012 edition of *Fertility & Sterility*, the study included 24 trials involving 5,807 participants. It found that CPR and LBR are improved with acupuncture in studies not involving the Streitberger control, which is a device designed to look like an acupuncture needle and appear to the patient to be piercing the skin even though it is not. The authors posit that the Streitberger control 'may not be inactive', and that 'more positive effects' may be found if an appropriate placebo is found and treatment protocols are individualized to fit traditional pattern differentiation.

Summary

In the 10 years since Paulus' work was published, there has been a huge increase in research regarding acupuncture and IVF. Over 40 clinical trials evaluating acupuncture with IVF (Zheng, Huang, Zhang & Wang, 2012), and eight systematic reviews and meta-analyses have been published to date. The results of these studies have proven somewhat confusing. Some show that acupuncture improves IVF outcomes, while others show that it does not. As a result the current research project is justified and necessary as a means for further clarifying the methodological factors that surround IVF research studies.

There are still many challenges and questions to be answered, but it is encouraging that more recent reviews have started to consider the methodological problems regarding acupuncture research, and how we may produce literature that is

both scientifically sound and intellectually honest. The current study will continue that path of research regarding methodology in IVF.

Chapter 3: Method

Introduction

This chapter will outline the methodology used in conducting my research synthesis. The subjects covered include the research design, sample and sampling procedures, instrumentation, data collection procedures, data analysis, and limitations of the study. The study will look at methodological issues in the literature on acupuncture used in combination with in vitro fertilization. It will seek to clarify the challenges in designing and interpreting studies in IVF and acupuncture by looking at controversies and other issues in acupuncture research generally and how they apply to this branch of medicine specifically.

Research Design

This study will utilize a qualitative research synthesis methodology. The rationale for choosing this method was that it would allow for systematic assessment of the existing literature, identification and descriptive assessment of patterns and themes that could not as effectively be done with other, more quantitative methods. This method is very well suited to the research question, as the question at hand revolves around research methodologies and the existing literature, how the literature is thought about, how it is analyzed, and how it is discussed, not the effectiveness of acupuncture as an intervention per se.

Sample and Sampling Procedures

The data sources reviewed for this project include studies published in peer-reviewed medical journals regarding the use of acupuncture as adjunct to IVF and its effect on IVF outcomes. The online databases PubMed, EBSCOhost, and Google

Scholar were used to search for articles relevant to this capstone project. The terms searched included various combinations of the following terms: acupuncture, electro-acupuncture, IVF, in vitro fertilization, in vitro “fertilisation,” infertility, clinical pregnancy, CPR, live birth rate, and LBR. The bibliographies of systematic reviews/meta-analyses pertaining to the subject were also searched by hand. The research was done primarily in the principal investigator’s home office, and also at the Yo San University library. This search yielded 33 studies, of which 27 clinical trials published as full articles or as abstracts were included in this analysis. Eight systematic reviews and meta-analyses were found, and all eight of these were included. The inclusion criteria for clinical research were that the studies must try to evaluate the effectiveness of acupuncture as an adjunct to IVF. The exclusion criteria was simply if the research did not attempt to evaluate the effects of acupuncture as an adjunct to IVF. The inclusion criteria for research syntheses/meta-analyses were that they synthesize literature regarding the effectiveness of acupuncture as an adjunct to IVF. Any research syntheses that did not meet these criteria were excluded.

Instrumentation and Data Collection Procedures

In May of 2012 data abstraction forms were created in order to summarize, organize, and highlight important methodological issues in the literature involved. Major themes that were identified as variables of interest prior to conducting the analysis included the heterogeneity of the studies, differing populations of participants, various sorts of interventions, differing study designs, and the various outcome variables that were recorded and assessed. Forms were created to abstract this information and these

were revised as the investigator conducted the literature review and became more familiar with the existing research.

Data Analysis

This section will explain the ways in which data were collected and analyzed, as well as the types of data collected. Data collection was performed through data abstraction forms and the analysis done using thematic/content analysis through various tables, with separate tables for analyzing clinical research and research syntheses/meta-analyses. The use of tables was the most appropriate method of data analysis for this literature review, as it allows the most convenient form of quantifying and assessing the data involved through analysis of frequency counts, range, mode of themes, etc.

Data Abstraction Form

The following groups of information were extracted from the published literature using a data abstraction form for later analysis in table format:

Historical overview of articles.

The first part of the data analysis process included simply recording when the various studies were performed, how many participants or studies (for research syntheses and meta-analyses) were included, and in what country they were carried out. This was intended to give a general overview of the literature, how the amount of research done on the subject has changed, and the geographical distribution of research.

Objectives and outcome measures.

The various outcomes measures used in the research were recorded. These outcome measures included implantation rate, chemical pregnancy rate, clinical pregnancy rate, ongoing pregnancy rate, and live birth rate.

Research design.

The various designs used in the published research were recorded. These included clinical trials that prospective and retrospective, randomized and nonrandomized, research syntheses and meta-analyses. Whether or not the studies were blinded or double-blinded, prospective or retrospective, single-center or multi-center, and controlled non-controlled, was also recorded.

Age & number of participants.

The age of participants of each study, whether stated as an average, mean, or not stated at all, was recorded, as was the number of participants in each study. The number of studies included in each of the published research syntheses/meta-analyses was also recorded.

Interventions.

The variables regarding the acupuncture intervention were largely verbatim from the 2010 STRICTA white paper and sought to reproduce the checklist provided in that paper with slight modifications. They included:

1 Acupuncture rationale. This included three different variables. The first was the ‘style of acupuncture,’ e.g., traditional Chinese acupuncture, traditional Japanese acupuncture, or traditional Korean acupuncture, etc. The second variable was the ‘reasoning for the treatment provided,’ e.g., why specific points or techniques were chosen over others a particular study. The third variable in this group was

the ‘extent to which treatment was varied.’ This recorded whether all patients received the same acupuncture protocol, or whether there was any variation between patients and/or office visits and in what ways or within what parameters those treatments varied.

2 Details of needling. This section of the abstraction form recorded seven different variables regarding the acupuncture needling. These included the ‘number of needle insertions per subject per session (mean and range where relevant).’ The next variable recorded in this section was the names of the points used. The third variable regarding needling was ‘depth of insertion.’ This was followed by ‘response sought.’ This recorded if the acupuncturists sought to obtain responses such as particular subjective sensations felt by the patient, muscle twitches, or other responses from the needling. The fourth variable regarding needling was ‘method of needle stimulation,’ which recorded whether the needles were stimulated after insertion. Common forms of needle stimulation include various manual techniques and the application of electrical stimulation units. The fifth variable regarding needling was the ‘needle retention time,’ or how long the needles were left in the subjects after they had been inserted. The last variable regarding needling was ‘needle type’ which included diameter, length, and manufacturer or material).’

3 Treatment regimen. ‘Number of treatment sessions’ was recorded here. The second variable recorded was ‘frequency and duration of treatment sessions,’ i.e., how many treatments were given in what span of time.

Practitioner qualifications.

This part of the data analysis summarizes the qualifications of the practitioners performing the acupuncture, whether these were professional acupuncturists, medical doctors, nurses, other technicians, or if the study did not state the qualifications of the persons performing the acupuncture.

Controls and comparators.

As per STRICTA standards, the ‘rationale[s] for the control or comparator in the context of the research question, with sources that justify the choice(s)’ were recorded. The ‘precise description of the control or comparator’ was also recorded.

Chapter 4: Results

Data Overview

As discussed in chapter 1, there is a significant body of literature regarding the use of acupuncture as an adjunct in assisted reproductive technology to increase the success rates of IVF transfers. The literature, while generally positive, remains controversial both for the methodologies that have been used and the results achieved. This paper analyzes the existing body of literature using a data abstraction form in order to summarize, organize, and highlight important methodological issues and major themes in the literature involved. This paper aims not to evaluate the effectiveness of acupuncture as an adjuvant to IVF protocols, but to examine areas of controversy in general acupuncture research and how these controversies relate to this specific subset of acupuncture research.

Dates and Geographical Sources of Research

Of the 35 pieces of research examined in this paper, the first was produced in 1996 and the most recent in 2012. The 27 clinical trials were performed in eight different countries: Sweden, Germany, USA, Australia, Denmark, the People's Republic of China (PRC), Brazil, and Italy. The country producing the most literature by far was the US, with 13 studies, followed by the PRC with 5. Sweden, Germany, and Denmark each produced two studies, while Australia, Italy and Brazil produced one each. Table 1 shows this geographic distribution of clinical research combining acupuncture and IVF.

Table 1

Geographic Sources of Clinical Research

Country of Origin	Number of Studies Produced
United States	13
PRC	5
Sweden	2
Germany	2
Denmark	2
Australia	1
Italy	1
Brazil	1

The eight research syntheses and meta-analyses reviewed were published from 2008 to 2012 and were produced primarily from four countries. Four were produced in the UK, two in the PRC, one in the US, and another was a joint venture between Chinese and German researchers. Table 2 shows the geographic sources of the 8 research syntheses/meta-analyses.

Table 2

Geographic Sources of Research Syntheses/Meta-analyses

Country of Origin	Research Syntheses/Meta-analyses produced
UK	4
PRC	2
United States	1
Germany & PRC	1

Outcome Measures Used

When measuring the effects of acupuncture upon IVF, different studies used different outcome variables. Of the clinical research surveyed here, the most common outcome variable was ‘clinical pregnancy rate,’ which was reported in 23 studies. ‘Implantation rate’ was the next most commonly listed outcome measure, as it was reported in 11 studies. ‘Ongoing pregnancy’ rate was observed in nine studies, ‘live birth rate’ and ‘chemical pregnancy’ were both recorded in six pieces of literature, and the term ‘pregnancy’ was used without further elaboration or definition in six studies. Only one study, Stener-Victorin et al., 1996, used the pulsatility index of the uterine arteries as an outcome measure.

It should be noted that many of the studies did not clearly define the terms they used when referring to outcome measures, and that it was common for terms to be used differently by different authors. As an example, Smith et al., 2006 measured ‘ongoing pregnancy rate’ at 18 weeks, while Stener-Victorin et al., 2003 defined ‘on-going pregnancies’ as the ‘number of pregnancies per embryo transfer after the 16th week of gestation.’ Most studies did not define what they meant by ‘ongoing pregnancy’

at all. Table 3 summarizes the measurement outcomes used in the literature and the number of studies that observed these particular outcomes.

Table 3

Outcome Measurements

Outcome measurements	Frequency of Use
Clinical pregnancy rate	23
Implantation rate	11
Ongoing pregnancy rate	9
Live birth rate	6
Chemical pregnancy	6
‘pregnancy’	6
Uterine artery pulsatility index	1

Details of Acupuncture Interventions

The acupuncture interventions used in the clinical research differed considerably. In fact, it could not be confirmed that any of the studies used the same acupuncture intervention. Though several authors wrote that they had aimed to reproduce the protocol used in Paulus et al., 2002, none of the published works described their interventions in ways that did not differ significantly from that used in the 2002 work. It should be noted however that an inherent problem exists with reproducing the Paulus protocol in that the report of the intervention first used was published in such a way as to make the name of one of the acupuncture points used unclear, i.e., one of the points

used was listed as ‘Cx6 (Neiguan),’ but the name ‘Cx6’ and ‘Neiguan’ are not names for the same point. It is unclear from the originally published account if the abbreviation ‘Cx6’ was simply a mistake for the more commonly used ‘Pc6’, or if ‘Cx6’ refers to the sixth point on the ‘Conception’ vessel. This point is occasionally named ‘Cv6’ or ‘Co6**’** in older English textbooks, and older English textbooks tended to be less standardized in English language abbreviations and point names. Thus, we cannot be certain without more input from the authors exactly which points were used.

Number of Needles Used

Fourteen studies listed the numbers of needles inserted during their treatments either in exact number or by giving ranges, e.g., 6-10 needles. Eight pieces of literature did not list the numbers of points used, and five authors published information that was confusing and/or contradictory and thus made it impossible to know how many points had been used. The most common confusion was literature stating that it had reproduced the Paulus protocol, but then going on to list details of the intervention that did not match the Paulus protocol. Table 4 lists the extent to which each study recorded the number of needles that they used.

Table 4

Number of Needles Used

Number of Needles Used	Number of Studies
Recorded	14
Not recorded	8
Recorded in unclear manner	5

Acupuncture Points Used

Twelve studies listed the exact points used, eight studies did not list what points were used, and seven listed the points used in ways confusing and/or contradictory enough to make the intervention un-reproducible from the published account. Table 5 lists to what extent each study clearly recorded the points used in their interventions.

Table 5

Points Used

Points Used	Number of Studies
Recorded	13
Not recorded	9
Recorded in unclear manner	6

Depth of Needle Insertions

Eight studies listed the depth to which the acupuncture needles were inserted. Eighteen studies did not, and one (Smith et al., 2006) described inserting the needles

‘to tissue level’ with no further explanation. Table 6 lists the extent to which needle depth was recorded in the literature.

Table 6

Depth of Needle Insertions

Depth of Needle Insertion	Number of Studies
Recorded	8
Not recorded	18
Recorded in unclear manner	1

Needling Responses Sought

Ten authors listed the response sought from needling, e.g., a sensation of soreness or numbness, or muscle contraction. Seventeen studies did not report the response sought. Table 7 lists in graphic form how many studies recorded the needling response that they sought.

Table 7

Needling Responses Sought

Needling Response Sought	Number of Studies
Recorded	10
Not recorded	17

Method(s) of Needle Stimulation

Fifteen studies described their methods of needle stimulation, i.e., whether the needles were manually stimulated to produce needle sensation, whether needles were stimulated electrically, or whether no stimulation was used after needle insertion.

Descriptions of needle stimulation were not reported in 12 of the published accounts. No studies reported that they did not stimulate the needles after insertion. Table 8 shows how many studies reported their methods of needle stimulation.

Table 8

Method(s) of Needle Stimulation

Method(s) of Needle Stimulation	Number of Studies
Recorded	15
Not recorded	12

Needle Retention Time

Needle retention time, i.e., how long needles were left in the subjects after insertion, was listed in 16 accounts. Length of needle retention was not discussed in 11 cases. Table 9 presents whether or not needle retention was reported.

Table 9

Needle Retention Time

Needle Retention Time	Number of Studies
Recorded	16
Not recorded	11

Needles Used

Seventeen studies provided no information about the needles used during acupuncture. Five provided information including length and gauge of the needles. Five studies provided some information about the needles e.g., manufacturer, but not both the length and gauge of all needles used.

Table 10

Needles Used

Needles Used	Number of Studies
Length & gauge recorded	5
Insufficient information recorded	5
No information recorded	17

Treatment Regimen

Six studies did not list how many treatment sessions were included in their treatment regimens. Twelve used two treatment sessions in the intervention. Two studies measure the effects of a single acupuncture treatment, while single authors chose to investigate the effects of three treatment sessions (Smith et al., 2006), eight acupuncture sessions (Stener-Victorin et al., 1996), and 11 sessions (Magarelli et al., 2009). Khorram et al., 2005, administered a ‘minimum of two sessions;’ Westergaard et al., 2006, used two acupuncture treatments in one arm and three in another; Kong & Hughes, 2009, used a minimum of 12 treatments; and Udoff et al., 2006, used a minimum of four acupuncture treatments. Table 11 lists the number of treatment sessions used in each study.

Table 11

Number of Treatment Sessions

Number of Treatment Sessions	Number of Studies
2	12
Not recorded	6
1	2
3	1
8	1
11	1
≥2	1
2 compared to 3	1
≥12	1
≥4	1

Blinding in the Clinical Trials

Blinding was attempted in various ways throughout the literature. Patient blinding was used in ten of the 27 clinical studies. Blinding of acupuncturists was not attempted in any of the studies, and blinding of other staff such as MDs and nurses performing the IVF, and assessors of data was noted in eight cases. Nine studies did not record any attempt at blinding. Table 12 shows the information available concerning blinding in the literature.

Table 12

Blinding in Clinical Research

Blinding	Number of Studies
Patient blinding recorded	10
Blinding of acupuncturists recorded	0
Blinding of other staff recorded	8
Blinding not recorded	9

Controls Used

Acupuncture treatment was compared to 13 different controls throughout the literature. The most common control was standard IVF, with 14 studies using this as comparison to acupuncture intervention. The second most common control was the sham, or Streitberger needle, which was observed in five trials. Three studies used the sham needle on the same points used in the treatment group, one used the sham needle in places not associated with traditional acupuncture points, and one study (Quintero, 2004) did not state where or how the sham needle was used. Four studies compared acupuncture with relaxation or lying quietly. Two studies used lasers pointed at traditional acupuncture points as well as lasers that were not turned on, i.e., ‘sham lasers’ as controls. One study compared acupuncture given at the time of oocyte aspiration with the pain reliever alfentanil given around the same time. One study used standard needling of points which the researcher deemed to have no influence on fertility. Another used shallow needling of non-acupuncture points. One compared three different acupuncture protocols, and one used needling of non-acupuncture points on the trunk and limbs with traditional points on the ear not deemed to be relevant to

reproduction. One study also used no control group at all. Table 13 lists the different forms of blinding that were used.

Table 13

Controls Used

Controls Used	Number of Studies
Standard IVF	14
Relaxation/lying quietly	4
Sham needle on same points as intervention	3
Sham needle on unknown points	1
Sham needle on nontraditional points	1
Laser directed at acupuncture points	2
Sham laser on acupuncture points	2
Acupuncture on points not intended to affect fertility	2
Acupuncture on nontraditional points	1
Shallow needling of nontraditional points	1
Different acupuncture treatments	1
Alfentanil	1
No control group	1

Qualifications of Persons Performing Acupuncture Interventions

The persons performing the acupuncture interventions used in the literature had varying qualifications and training. It was most common for authors not to list the training or titles of persons performing the acupuncture interventions at all. Eleven studies did not publish this information. Seven studies noted that professional acupuncturists performed the interventions, and the current researcher corroborated these claims with internet searches regarding the individuals involved. Five studies had the interventions performed by technicians of unclear training or by persons with credentials that could not be verified by internet search. One of these studies listed the technician simply as a ‘well-trained examiner.’ Another notes that its interventions were performed by ‘the same professional,’ but a brief internet search showed this person to be an embryologist, and no information could be found to suggest any acupuncture training. Another study described the two persons who performed the acupuncture as ‘licensed acupuncturists,’ though one of the centers participating in the study was located in Oklahoma, which appears not to have been licensing acupuncturists at the time. The names of the acupuncturists in this study could not be obtained from the published account, and so the training of the individuals involved could not be confirmed. Another study merely described the interventionist as an ‘acupuncturist,’ so it was unclear if this was a professional title or simply conferred de facto by the act of performing acupuncture during the course of the study. Acupuncture was performed by an MD in one study. Three studies listed the interventionists as nurses, and one listed them as midwives, but it was unclear if these midwives were also nurses. Table 14 lists

the various qualifications of persons performing acupuncture interventions in the studies examined here.

Table 14

Interventionist Qualifications

Interventionist Qualifications	Number of Studies
Not recorded	11
Professional acupuncturists	7
Other technicians/unclear	5
Nurses	3
MD	1
Midwives	1

Style of Acupuncture

Of the 27 clinical studies surveyed, only one (Kong & Hughes, 2009) noted the style of acupuncture used in the intervention in a meaningful way, describing the needling style as ‘traditional Chinese acupuncture.’ One study (Benson et al., 2006) described the intervention as ‘traditional,’ while another (Quintero, 2004) described the acupuncture as ‘standard.’ The other 24 studies made no mention of acupuncture style. Table 15 lists how the various authors reported the style of acupuncture used in their interventions.

Table 15

Style of Acupuncture

Style of Acupuncture	Number of Studies
Not recorded	24
Traditional Chinese acupuncture	1
Unclear description	2

Rationale for Acupuncture Protocols

Thirteen of the studies gave reasons why they chose their particular acupuncture protocols and 14 did not list any rationale for why they chose their particular intervention(s) over any other acupuncture intervention. Table 16 displays this recording of acupuncture rationales in graphic form.

Table 16

Acupuncture Rationale

Acupuncture Rationale	Number of Studies
Recorded	13
Not recorded	14

Variation of Interventions

Seventeen of the studies did not vary the acupuncture intervention, i.e., all patients received the same treatment within that particular trial. One study (Smith et al., 2006) was unclear about to what extent the acupuncture treatment was varied among their subjects, and another (Kong & Hughes, 2009) implied that treatment varied, from

patient to patient and from visit to visit, according to clinical TCM standards of care. Eight studies did not report enough information to discern whether treatment interventions were standardized, and if not, to what extent they varied. Table 17 lists the whether or not individual studies varied their treatment protocols during the research.

Table 17

Variation of Interventions

Variation of Interventions	Number of Studies
Not varied	17
Varied according to TCM standards of care	1
Unclear	1
Not recorded	8

Chapter 5: Discussion

Summary of Findings:

This study used research synthesis to analyze methodological problems in the literature evaluating acupuncture as adjunctive therapy to IVF. This qualitative design allowed for systematic assessment of the existing literature, identifying and descriptively assessing patterns and themes that could not as effectively be done with other, more quantitative, methods. The geographical origins of the extant literature and dates of their production were summarized before going on to record and analyze a significant numbers of variables found in the published work. Among the variables recorded and analyzed were the rationale for the interventions used, details of the needling performed, number of treatments administered, the controls used, and the training of persons performing the acupuncture interventions. From the analysis of these variables, and what was or was not reported about them, several salient themes became apparent.

The first theme that became apparent is that, in almost all studies examined, not enough information about the acupuncture intervention was provided for another researcher to reproduce the study. Several studies simply stated that they provided ‘acupuncture’ and gave no further description of the interventions performed. Combined with this lack of information about the interventions, was the heterogeneity of the acupuncture protocols. It was not clear from the published materials that any two studies used the same acupuncture protocols. The need for consensus surrounding what constitutes an appropriate control or comparator group in studies of acupuncture’s effects on IVF was also clearly displayed, as many different methods of control

intervention were found, with the authors publishing different opinions regarding what constitutes an ideal or appropriate control or comparator. Several authors pointed out that placebo acupuncture often statistically improved pregnancy rates when combined with IVF and that this strongly implied that the shams being used were not physiologically inactive. Lastly, most literature did not clearly record the training of the persons performing the acupuncture, with a small minority reporting the use of professional acupuncturists. In nearly 75% of the studies it was unclear if the persons performing the acupuncture were qualified to do so.

Implications for Theory

The explicit implications for theory in this study are relatively modest in that most of the conclusions were more readily applicable to the empirical practice of acupuncture research. This study did not attempt to formally analyze the theory of research design. It must be noted though that this study's findings regarding the implied physiological activity of sham interventions suggests that a more nuanced understanding of what constitutes an appropriate control and what role placebo plays in the therapeutic intervention may be required. This would seem particularly pertinent in areas such as reproductive endocrinology where the importance of the hypothalamus is unquestioned, but the influence of sensory input and the frontal cortex's connection to, and influence upon the hypothalamus is acknowledged, it is still poorly understood.

Implications for Practice

1 Implications for the practice of research: There are multiple implications for the practice of acupuncture research that can be gleaned from this study. The first is that the acupuncture interventions must be recorded in a way that allows for the

interventions to be evaluated and compared, and that allows for the study to be reproduced. This means that STRICTA standards for reporting acupuncture research must be adopted by researchers and publishers in the field of infertility and reproductive medicine. The second implication for the practice of research is that the groups of patients receiving acupuncture should be compared to patients receiving IVF alone, not IVF plus placebo or sham acupuncture. Until a placebo or sham acupuncture procedure can be devised that is proven to be physiologically inactive, using placebo as a control group only serves to make the literature more confusing. And thirdly, professional acupuncturists should be involved in the design and implementation of acupuncture research in order to avoid mistakes, such as the confusion over the point ‘Cx(Neiguan)’ published in Paulus et al., 2002, that would’ve been caught by a working acupuncture clinician. Working acupuncturists should also be employed to perform the acupuncture interventions to be sure that treatments are carried out within the normal standards of care observed in normal practice. Also, by recording the training of the acupuncturists employed, it may become clear whether certain training seems to produce better clinical results or not.

2 Implications for publishers: All journals that publish acupuncture research should endorse and adhere to the STRICTA recommendations. Currently only eight journals have adopted these standards, and none of research regarding the combination of acupuncture and IVF was published in journals adhering to these standards. If peer-reviewed journals were to accept these standards, the quality of published acupuncture research would improve significantly.

3 Implications for practice of AOM: The implications for the practice of acupuncture and East Asian medicines is that practitioners of acupuncture and East Asian medicines must become involved in research and contribute to the establishment of a scientific knowledge base regarding acupuncture and East Asian medicines. If practitioners were to become more actively involved in scientific research, the research would be better designed and implemented, and thus would more easily influence the clinical practice of acupuncture. As it stands now, many acupuncturists are aware of the poor quality of much acupuncture research and so are hesitant to make use the implications published therein. Also, having practicing acupuncturists more actively involved in research could help build relationships between the acupuncture and East Asian medical communities and the scientific/western medical communities in a way that might help dispel the mistrust that can prevent western medicine and East Asian medicines from learning from each other and benefiting patients.

4 Implications for practice of western medicine: The implication for western medicine is that they Western medicine journals should be encouraged to adhere to the STRICTA standards. This will encourage the production of research that is more methodologically sound and thus more able to inform their own clinical decision making about when to refer to acupuncture and what to advise their patients who have questions regarding acupuncture.

Limitations of the Current Study

The limitations of this qualitative review include the fact that all of the data was coded and interpreted by a single investigator. Also, the principal investigator was only able to analyze literature published in English. Another limitation is inherent in the method and intention of this study. This study was a research synthesis, which cannot take the place of primary clinical research in proving or disproving the results of acupuncture upon IVF outcome rates.

Recommendations for Future Research

The recommendations for future research are simply to put the findings of this study into practice by producing a large randomized controlled clinical trial that is published according to the STRICTA standards. A natural place to start would be to properly reproduce the seminal 2002 study by Paulus at al. using professional acupuncturists to make sure that the acupuncture intervention does in fact match the one used in the original study and that the confusion over points used in the published version is corrected.

Conclusion

The purpose of this retrospective research synthesis was to explore the methodological problems in the research that assesses acupuncture as an adjunctive therapy to IVF. It found that one of the major problems in the literature was that the acupuncture interventions were recorded in insufficient detail to allow the study's to be reproduced. Most studies also did not record the training of the persons performing acupuncture in their studies, and most did not record the rationale behind choosing the particular interventions studied. The current study recommends widespread adoption of

the STRICTA standards to remedy these problems in future research. Another significant finding was that it could not be confirmed that any author had ever reproduced the acupuncture intervention used in the seminal work published by Paulus et al in 2002. The final problem was that no sham or placebo acupuncture intervention had been proven to be physiologically inactive and that several studies suggest that the most commonly used sham interventions do have statistically significant effects on IVF outcomes. It is therefore recommended that future research should be designed as large randomized trials that compare treatment arms of one group receiving IVF with another group receiving IVF plus acupuncture. These studies should be published according to the latest published STRICTA guidelines.

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Appendix A: Historical Overview of Clinical Trials

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Author(s)	Publication Date	Country of origin	# of participants
1. Stener-Victorin et al	1996	Sweden	10
2. Paulus et al	2002	Germany	160
3. Stener-Victorin et al	2003	Sweden	286
4. Quintero	2004	USA	17 (7?)
5. Khorram et al	2005	USA	238
6. Smith et al	2006	Australia	228
7. Westergaard et al	2006	Denmark	300
8. Dieterle et al	2006	Germany	225
9. Benson et al	2006	USA	258
10. Domar et al	2006	USA	83
11. Udoff et al	2006	USA	13
12. Cui et al	2007	PRC	94
13. Wang et al	2007	USA	32
14. Magarelli et al	2007	USA	232 cycles
15. Craig et al	2007	USA	94
16. So et al	2008	Hong Kong, PRC	370
17. Fratterelli et al	2008	USA	1,000
18. Domar et al	2009	USA	146
19. Kong & Hughes	2009	USA	52
20. Chen et al	2009	PRC	60
21. Magarelli et al	2009	USA	67
22. Madaschi et al	2010	Brazil	416

23. Omodei et al	2010	Italy	168
24. Andersen et al	2010	Denmark	635
25. So et al	2010	Hong Kong, PRC	226
26. Moy et al	2011	USA	160
27. Cui et al	2011	PRC	66

Appendix B: Historical Overview of Research Syntheses/Meta-Analyses

Appendix B: Historical Overview of Research Syntheses/Meta-Analyses

Study #	Publication Date	Country of Origin	# of Studies Analyzed	# of patients
1. Manheimer et al	March 2008	USA (+1)	7	1,366
2. El-Toukhy et al	June 2008	UK	13	2,500
3. Ng et al	July 2008	Hong Kong, PRC	10	-
4. Cheong et al	Jan 2009	UK	13	2,209
5. El-Toukhy & Khalaf	June 2009	UK	14	2,870 (?)
6. Cheong et al	March 2010	UK	14	2,670 (?)
7. Huang et al	May 2011	PRC & Germany	14	-
8. Cui et al	March 2012	PRC	24	5,807

Appendix C: Design of Clinical Trials

Appendix C: Design of Clinical Trials

Study #	Prospective	Randomized	Patient Blinding	L.Ac. blinding	Other blinding	Single Center	Multi-Center	Controlled
1	X					X		
2	X	X				X		X
3	X	X					X	X
4	x	X	X		X	X		X
5						X		X
6	x	X	X			X		X
7	X	X				X		X
8	X	X	X			X		X
9	X	X	X			X		X
10	X	X	X		X	X		X
11	x	X	X					X
12	x	X				X		
13						X		X
14					X		X	X
15	X	X					X	X
16	X	X	X		X	X		X
17	X	X	in one arm	in one arm		X		X
18	X	X			X	X		X
19	X	X				X		
20	X	X				X		X
21	X			X				
22	X	X						X

23	X	X				X		X
24	X	X	X		X		X	X
25	X	X	X		X	X		X
26	X	X	X		X	X		X
27	X	X				X		X
Study #	Prospective	Randomized	Patient Blinding	L.Ac. blinding	Other blinding	Single Center	Multi-Center	Controlled

Appendix D: Outcome Measures in Clinical Trials

Appendix D: Outcome Measures in Clinical Trials

Study #	Uterine artery pulsatility index	Implantation Rate	Clinical Pregnancy Rate	Ongoing Pregnancy Rate	Live Birth Rate	"pregnancy"	chemical pre
1	X						
2			X				
3		X	X	X			
4			X	X			X
5		X				X	
6		X		X		X	
7			X	X			
8			X	X			
9		X	X				X
10						X	
11			X		X		X
12			X				
13			X	X	X		
14						X	
15			X		X		X
16		X	X	X	X		X
17		X					
18			X				
19						X	
20		X					
21		X					
22		X	X				

23			X				X
24		X	X	X	X		
25		X	X	X	X	X	
26			X				
27			X				
	1	11	23	9	6	6	6
Study #	Uterine artery pulsatility index	Implantation Rate	Clinical Pregnancy Rate	Ongoing Pregnancy Rate	Live Birth Rate	“pregnancy”	chemical pregnancy

Appendix E: Interventions Used in Clinical Trials

Appendix E: Interventions Used in Clinical Trials

Study #	# of Treatments	TCM pattern differentiation	Paulus Protocol	Stener-Victorin Protocol	Deqi Achieved	Electro acup.	Needles	ear seeds
1	8			X	X	X	X	
2	2		X		X		X	
3	1				X	X	X	
4	?						X	
5	≥2						X	
6	3				X		X	
7	2-3				X		X	
8	2				X		X	
9	2			X			X	
10	2						X	
11	?						X	
12	?					X	X	
13	?					X	X	
14	?						X	
15	2						X	
16	2				X		X	
17	2						X	
18	2						X	
19	≥12	in 2 arms		in 2 arms		in 2 arms	3 arms	
20	?	kidney deficiency sx noted				X	X	
21	11			X	X	X	X	
22	2				X		X	

23	2						X	
24	2						X	
25	1	X			X		X	
26	2						X	
27	?					X	X	
Study #	# of Treatments	TCM pattern differentiation	Paulus Protocol	Stener-Victorin Protocol	Deqi Achieved	Electro acup.	Needles	ear seeds

Appendix F: Controls Used in Clinical Trials

Appendix F: Controls Used in Clinical Trials

Study #	No Control	Laser	Sham Needle on unknown points	Standard IVF	sham laser	Relaxation/lying quietly
1	X					
2				X		
3						
4			X			
5				X		
6						
7				X		
8						
9		X		X	X	X
10						X
11						
12				X		
13				X		
14				X		
15				X		
16						
17		X		X	X	X
18						X
19						
20				X		
21				X		
22				X		
23				X		

24						
25						
26						
27				X		
Study #	No Control	Laser	Sham Needle on unknown points	Standard IVF	sham laser	Relaxation/lying quietly
	1	2	1	14	2	4

Appendix G: Controls Used in Clinical Trials (continued)

Appendix G: Controls Used in Clinical Trials (continued)

Study #	Needling Nontraditional Points	'non fertility' acupuncture	shallow needling of nontraditional points	other acupuncture interventions	alfentanil	sham needle on same points	sham needle on non-points
1							
2							
3					X		
4							
5							
6							X
7							
8		X					
9							
10							
11			X				
12							
13							
14							
15							
16						X	
17							
18							
19				X compared 3 different acu tx			
20							
21							

22							
23							
24						X	
25						X	
26	X on body	X in ear					
27							
Study #	Needling Nontraditional Points	‘non fertility’ acupuncture	shallow needling of nontraditional points	other acupuncture interventions	alfentanil	sham needle on same points	sham needle on non-points
	1	2	1	1	1	3	1

Appendix H: Qualifications of Persons Administering Acupuncture

Appendix H: Qualifications of Persons Administering Acupuncture

Study #	Professional Acupuncturist	MD/'physician'	Nurse	Other Technician - unclear	Not Stated	Midwives
1					X	
2				X 'well-trained examiner'		
3			X unclear if midwives are the same as nurses in this country			X see left
4					X	
5				'acupuncturist' probably an L.Ac., but could not be confirmed		
6	X B.Hlth.Sc. (Acup)					
7			X			
8		X				
9					X	
10					X	
11					X	
12					X	
13				'well-trained acupuncturist'		
14					X	
15				X 'licensed acupuncturists' but study center in OK did not have licensing.		
16	X Chinese degree + 2 yrs experience					
17					X	
18	X L.Ac.					

19	X 'OMD' Chinese training + NCCAOM					
20					X	
21	X Diane Cridennda					
22				X 'the same professional' who appears to be an embryologist		
23					X	
24			X			
25	X same as #16					
26	X L.Ac.s					
27					X	
Study #	Professional Acupuncturist	MD/'physician'	Nurse	Other Technician - unclear	Not Stated	Midwife
	7	1	3	5	11	1

Appendix I: Acupuncture Rationale

Appendix I: Acupuncture Rationale

Study #	style of acupuncture	reasoning for treatment provided	extent to which treatment was varied
1		x	not
2		x	not
3		x	not
4	'standard acupuncture'	x	
5			
6		x	
7		x	not
8	X	x	not
9	'traditional'		
10		x	not
11			
12			
13			not
14			
15			not
16		TCM theory	not
17			
18		x	not
19	TCM	TCM diagnosis	some patients received standardized SV protocol, some received TCM individualized care, some received both
20			
21			not
22		x	not
23		x	not
24		x	not

25			not
26			not
27			not
Study #	style of acupuncture	reasoning for treatment provided	extent to which treatment was varied

Appendix J: Details of Needling

Appendix J: Details of Needling

study #	needles per session	points used	depth	response sought	method of needle stimulation	retention time	needle type
1	X	X	x	x	x	x	
2	unclear due to cx/neiguan	x	x	x	x	x	gauge given for body points, not ear points
3	X	x	x	x	x	'at least 30 min'	x
4							
5							
6	X	conflicting data	'tissue level'	x	x	x	x
7	X	x		x	x	x	
8	X	x	x	x	x	x	length and maker given, but no gauge
9							
10	x 22	conflicting report. No of points does not match Paulus				x	
11	6-10				x		
12					x electrical		
13	unclear due to Cx6/neiguan(17 or 18) and 13	x but confusion over P6 or Ren6 from Paulus				x 30 min	gauge
14							
15	unclear - 'Paulus plus Ren6 + Kd3'						
16	8 & 9	x	x	x	x	x	x
17						x	
18	unclear. 'the same 22-needle protocol' as Paulus	unclear - see previous. points not listed				25 min	
19	X	x	x	x	x	x	x

20		unclear: 'Ren4, K3, Sp6, ETC.'			x		
21					x		
22	9 & 8	x	x	x	x	x	x brand, but no gauge
23	unclear. probably 4-9	unclear					
24	9	x				30 min	brand, but no gauge
25	8	x	x	x	x	x	x
26	12	x				x	
27	8	x			x		
study #	needles per session	points used	depth	response sought	method of needle stimulation	retention time	needle type

Appendix K: Treatment Regimen

Appendix K: Treatment Regimen

Study #	number of treatment sessions	frequency and duration of treatment	timing in regards to embryo transfer (ET)
1	8	2/week x 4 wks	
2	2	2 in one day	same day
3	1	NA	before aspiration
4			
5	'minimum of 2 sessions'	6-8 days	'5 to 7 days prior to and on the day of' ET
6	3	x	x complicated
7	2-3	x	x 2 different regimens
8	2	x	x day of ET + 3 days later
9	2	same day	same day
10	2	same day	same day
11	unclear, probably ≥4	unclear	x (too complicated to list here)
12			
13		twice per week from cycle day 5 to 2 wks after oocyte retrieval	see previous
14			
15	2	unclear	unclear 'before and after ET'
16	2	same day	before and after ET on day of ET
17	2	same day	before and after ET on day of transfer
18	2	same day	before and after. not explicitly on same day
19	x at least 12	x	x
20			
21	11		x
22	2	same day	immediately before and after
23	2	same day	25 min before and after
24	2	unclear	Not clear. First treatment was on day of ET, but date of 2nd not specified.
25	1	x	x
26	2	Unclear: 'before and after'	see previous
27			

Study #	number of treatment sessions	frequency and duration of treatment	timing in regards to embryo transfer (ET)