

# IN VITRO FERTILIZATION AND ACUPUNCTURE: CLINICAL EFFICACY AND MECHANISTIC BASIS

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**Objective** • To provide an overview of the use of acupuncture as an adjunct therapy for in vitro fertilization (IVF), including an evidence-based evaluation of its efficacy and safety and an examination of possible mechanisms of action.

**Design** • Literature review using PubMed, the Science Citation Index®, The Cochrane Library (Database of Systematic Reviews and Central Register of Controlled Trials), the New England School of Acupuncture library databases, and a cross-referencing of published data, personal libraries, and Chinese medicine textbooks.

**Results** • Limited but supportive evidence from clinical trials and case series suggests that acupuncture may improve the success rate of IVF and the quality of life of patients undergoing IVF and that it is a safe adjunct therapy. However, this conclusion

should be interpreted with caution because most studies reviewed had design limitations, and the acupuncture interventions employed often were not consistent with traditional Chinese medical principles. The reviewed literature suggests 4 possible mechanisms by which acupuncture could improve the outcome of IVF: modulating neuroendocrinological factors; increasing blood flow to the uterus and ovaries; modulating cytokines; and reducing stress, anxiety, and depression.

**Conclusions** • More high-quality randomized, controlled trials incorporating placebo acupuncture controls, authentic acupuncture interventions, and a range of outcome measures representative of both clinical outcomes and putative mechanistic processes are required to better assess the efficacy of acupuncture as an adjunct for IVF. (*Altern Ther Health Med.* 2007;13(3):38-48.)

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**I**nfertility is a significant public health issue with high medical and social costs. In the most recent survey by the Centers for Disease Control and Prevention (CDC) investigating impaired fecundity and infertility in the United States, 1.2 million participants (2% of those surveyed) had an infertility-related medical appointment during the past year.<sup>1</sup> An additional 13% received infertility services at some point in their lives, and 7% of married couples in which the woman was of reproductive age reported they had not used contraception for 12

months but had not conceived. More recent estimates suggest that 10%-15% of couples experience infertility, with a higher prevalence in women over age 34.<sup>2</sup>

In vitro fertilization (IVF) is the most successful of the infertility treatments, and for many people is the last possibility for achieving pregnancy. In 2001 (the most recent year for which national data were published), there were 29,344 deliveries from IVF, which resulted in the birth of 40,687 infants. This represents 1% of all US births in that year.<sup>2</sup>

IVF is the only infertility therapy that can successfully bypass severe pelvic adhesions and male-factor infertility and simultaneously elucidate causes of infertility for which no other tests exist, such as poor oocyte maturation or failure of embryo cleavage. As a result of recent improvements in ovulation induction protocols and adjustments in treatment regimens, 3-6 cycles of standard IVF can result in more than 65% of patients ultimately delivering a baby.<sup>3,4</sup> The average delivery rate resulting from IVF per single initiated cycle using fresh, non-donor oocyte, however, was still only 33%.<sup>5</sup> Therefore, the majority of IVF cycles do not result in pregnancy, and there is generally a need for multiple IVF cycles for pregnancy to be achieved.

For many, the cost of IVF is so high that it is difficult to undergo even a single attempt. Estimates of the direct cost to the patient of a single cycle of IVF range from \$7,000 to \$11,000.<sup>6,7</sup> This figure excludes the cost of medications, which averages over \$1,500 per cycle. Only 4 states in the United States mandate full

insurance coverage for IVF, and 8 mandate partial coverage.<sup>8</sup>

Stress, anxiety, and depression are common among patients undergoing IVF treatment. Potential reasons for this include the invasive nature of the therapy itself, the knowledge that IVF is often the last hope for a biological child, and the high cost of treatment.<sup>9,10</sup> A significant body of literature supports the contention that stress, anxiety, and depression contribute to lower pregnancy rates among women undergoing IVF.<sup>11,12</sup>

Due to the relatively low success rate of IVF per cycle, as well as the high emotional and financial costs associated with IVF, many patients have turned to complementary and alternative medicine (CAM) to enhance the success of IVF treatment.<sup>13</sup> Among CAM treatments, acupuncture is a frequently used adjunctive therapy. However, whether acupuncture is safe and effective for IVF has not yet been established. This paper evaluates the evidence regarding the efficacy and safety of acupuncture for improving the success rate of IVF. We briefly review the biomedical and traditional Chinese medicine (TCM) explanations for infertility and then critically summarize and evaluate the studies conducted to date that include data on the efficacy and safety of acupuncture for improving the success rate of IVF. Finally, we summarize published research exploring the mechanisms that may underlie acupuncture's impact on IVF success and propose 4 possible (interrelated) mechanisms for how acupuncture could improve IVF success rates.

#### **INFERTILITY FROM A WESTERN BIOMEDICAL PERSPECTIVE**

A growing body of research has begun to identify a number of physiological and psychological mechanisms that may underlie female infertility and explain the limited success of IVF treatments. The causes of female infertility can be grouped into 4 major categories:<sup>14</sup> (1) abnormalities in oocyte production; (2) anatomic abnormalities leading to obstruction of transport of the sperm, oocyte, and/or embryo through the reproductive tract (eg, tubal, uterine, cervical, peritoneal factors); (3) abnormalities in the implantation process, including early defects in embryo development, and embryo-endometrial interaction; and (4) numerous other factors that are probably most important in women with unexplained infertility (eg, age, body weight, cigarette smoking, alcohol and caffeine intake, psychological and emotional factors, immunological abnormalities, borderline hormonal imbalances).

The IVF procedure can overcome many of the conditions that cause infertility by artificially modifying oocyte production, fertilizing oocytes in vitro, and ensuring delivery of 1 or more embryos into a hormonally-stimulated endometrium. For these reasons, combined with the superior success of IVF compared to other assisted reproductive technologies, IVF is widely used for the treatment of infertility of known and unexplained etiology.

#### **INFERTILITY FROM A TRADITIONAL CHINESE MEDICINE PERSPECTIVE**

The application of Chinese medicine to women's health has been practiced for thousands of years, and some of the earliest

written records contain rich and detailed descriptions of gynecological and reproductive disorders and their treatment.<sup>15</sup> The most commonly practiced form of Chinese medicine today, both in the West and in China, is TCM.<sup>16</sup> TCM developed at the turn of the last century and represents a systemization of various Chinese medicine practices into a unified medical system that could best be integrated with Western medicine.

There are several fundamental theoretical constructs that form the foundation of the TCM view of the body and its dysfunctions. Used together, these underlie a complex system of diagnosis. In this system, signs and symptoms are analyzed to allow the choice of one or more TCM patterns that characterize a person's illness. A treatment strategy is tailored around the TCM pattern diagnoses. Acupuncture, exercise, diet, massage, and the use of herbs comprise the fundamental TCM treatment modalities. Acupuncture is based on the notion that there are pathways (meridians) within the body where qi (Chi) flows. Along these meridians are specific regions (acupuncture points, acupoints) that are used to treat specific conditions. Fundamental to the Chinese medicine understanding of the mechanism of acupuncture is the idea that stimulation of these points alters the flow of qi in the meridian system. Scientific studies have shown that acupuncture points and meridians have unique electrical properties and connective tissue characteristics.<sup>17,18</sup>

The most common way that the effect of an inserted acupuncture needle is enhanced is through either manual manipulation or electrical stimulation. Simple manual insertion of acupuncture needles with brief manipulation was the most common form of practice until the middle of the 20th century, when mild electrical stimulation (10-100 Hz) of inserted needles, electro-acupuncture (EA), was developed. The majority of research investigating the efficacy and mechanistic basis of acupuncture (especially when used for pain suppression) has focused on EA, but the most common clinically practiced form of acupuncture in the United States is manual acupuncture.<sup>16</sup> Thus far, there has been only limited investigation into the clinical and mechanistic similarities and differences between EA and manual acupuncture.

When considered from a TCM perspective, infertility is almost always associated with some type of Kidney deficiency, although additional secondary imbalances are often also present.<sup>19,20</sup> The *Kidney* in TCM does not refer to the organ and associated functions from a biomedical perspective (and the "K" is capitalized). Rather, the TCM concept of Kidney encompasses the organ and a range of functions and physiological processes, some of which bear no relationship to kidney function in a biomedical sense. In TCM, the Kidney underlies the fundamental constitution of a person and in women directly relates to a 7-year cycle corresponding with developmental changes from birth through childhood, puberty, the reproductive years, and old age. Within this framework, infertility often reflects an earlier-than-normal decline of Kidney-related functions that results from either constitutional factors (eg, genetic) or lifestyle and dietary issues.<sup>19</sup> Common causes of infertility within the TCM framework are qi imbalances and deficiencies, blood-level imbalances (insufficiency

and blocked circulation), blockages due to the buildup of fluids, and inflammatory processes.<sup>19,21</sup>

Treatment of infertility in TCM begins with the diagnosis of primary and secondary patterns, based on the grouping of signs and symptoms assessed using standard examination techniques (eg, pulse and tongue analysis, interview).<sup>19</sup> According to Liang, the various western medical infertility diagnoses can be viewed within the context of the various TCM patterns.<sup>21</sup> TCM pattern diagnoses of Kidney yin deficiency, Kidney yang deficiency, blood deficiency, and qi deficiency include the Western medical diagnoses of anovulation, small or misshapen uterus, poor follicle and/or egg quality, low estradiol, low progesterone, and high follicle-stimulating hormone (FSH). TCM pattern diagnoses of qi stagnation, blood stasis, and phlegm damp obstruction include the Western medical diagnoses of blocked fallopian tubes, uterine fibroids, ovarian cysts, endometriosis, adhesions, and stress. The TCM pattern diagnosis of damp heat includes the Western medical diagnoses of infections of the cervix, vagina, pelvis, urinary tract, and fallopian tubes.

Based on the patterns diagnosed, a specific acupuncture protocol (treatment strategy) is developed to address imbalances. The treatment strategy dictates the number and location of acupuncture points (eg, specific body and ear acupoints), type of needle stimulation (eg, manual or electrical), and number and frequency of treatments.<sup>19</sup> Though the tailoring of treatment strategies to individual primary and secondary diagnostic patterns is standard in clinical practice and increasingly appreciated in acupuncture research,<sup>22</sup> this approach is not reflected in the research on the use of acupuncture in conjunction with IVF that is summarized below.

## EVALUATING THE EFFICACY OF ACUPUNCTURE AS AN ADJUNCT THERAPY FOR IN VITRO FERTILIZATION

### Methods

To review the existing research regarding acupuncture as an adjunct therapy for IVF, we conducted a literature search using PubMed, the Science Citation Index, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and the New England School of Acupuncture library databases. Additional manual searches of retrieved articles, personal libraries, and TCM textbooks were conducted. Search terms included *acupuncture or electroacupuncture and in vitro fertilization or IVF or fertility or embryo transfer or ovulation*. Only full-length studies (studies reported as abstracts were excluded) that used either acupuncture and/or electroacupuncture (acupressure was excluded) in conjunction with IVF were included in this review. Studies using Chinese herbs in conjunction with acupuncture also were included.

### Results

The table summarizes the 11 studies that resulted from the literature searches in conjunction with the exclusion and inclusion criteria. The table separates the studies according to study aims and experimental design. The first 4 studies were prospec-

tive randomized controlled trials (RCTs)<sup>23-26</sup> specifically designed to address the hypothesis that acupuncture improves the outcome of IVF. The fifth and sixth studies were prospective RCTs primarily investigating the use of electroacupuncture as an alternative to conventional analgesic methods for oocyte retrieval and also collected data on IVF outcome.<sup>27,28</sup> The seventh study was prospective with no randomization,<sup>29</sup> and the eighth through eleventh studies were case series<sup>30,31</sup> and narrative descriptions of case studies in TCM texts.<sup>20,21</sup>

### *Randomized, Controlled Trials to Determine Whether Acupuncture Improves In Vitro Fertilization Outcomes*

Of the 4 RCTs specifically addressing the hypothesis that acupuncture could increase the success rate of IVF, 2 had sham acupuncture controls.<sup>24,25</sup> Of these 4 studies, 3 present evidence suggesting acupuncture can significantly improve the success of IVF. The first study, by Paulus et al, included 160 women (average age 32.5 years) undergoing IVF with or without intracytoplasmic sperm injection (ICSI).<sup>23</sup> Two groups were compared (n=80 each). One group received EA 25 minutes before and 25 minutes after embryo transfer (ET), and the other underwent a standard IVF procedure without acupuncture. The clinical pregnancy rate in the non-acupuncture group was 21/80 (26%) compared to 34/80 (42.5%) in the EA group.

The Paulus et al study<sup>23</sup> published in 2002 provided the impetus for further studies, 3 of which were published in 2006.<sup>24-26</sup> In a study involving 225 women (average age 34.9 years), Dieterle et al investigated the effect of real (n=116) and sham (n=109) acupuncture on the outcome of IVF with and without ICSI.<sup>24</sup> Sham acupuncture was undertaken by the use of points that were not appropriate for fertility-related conditions. Two manual acupuncture treatments were given 30 minutes and 3 days after ET. The group that received real acupuncture compared with the sham group had significantly higher implantation rates (14.2% vs 5.9%, respectively), clinical pregnancy rates (33.6% vs 15.6%), biochemical pregnancy rates (35.3% vs 16.5%), and ongoing pregnancy rates (28.4% vs 13.8%).

Smith et al compared real acupuncture to sham acupuncture.<sup>25</sup> The sham intervention involved the use of non-acupuncture points and the non-insertive Streitberger needle (the shaft of the needle collapses into the needle handle) in women undergoing IVF with and without ICSI. All subjects (average age 36 years, randomized into 2 groups) received 3 acupuncture treatments on day 9 of stimulating injections and immediately before and after ET (similar to Paulus et al's methods). Subjects in the real acupuncture group (n=110) as compared with the sham group (n=118) exhibited statistically non-significant trends toward higher pregnancy rates (31% vs 23%, respectively) and ongoing pregnancy rates at 18 weeks (28% vs 18%).

In a study of women (average age 37 years) undergoing IVF with and without ICSI, Westergaard et al compared subjects who had not received acupuncture (n=87) with those who had received acupuncture immediately before and after ET (ACU 1 group, n=95), and with an additional acupuncture treatment 2

TABLE Summary of Studies Evaluating Acupuncture as an Adjunct Therapy for IVF

Author, Year (Reference)	Study Design	Study Population	Intervention (Sample Size)	Acupuncture Treatment	Relevant Outcomes Measured	Results
1. Paulus et al, 2002 (23)	RCT	<ul style="list-style-type: none"> <li>• 160 women</li> <li>• Age 32.5 y; range 28.5-36.5 y</li> </ul>	<ul style="list-style-type: none"> <li>• Acu (n=80)</li> <li>• Control: No Acu (n=80)</li> </ul>	<ul style="list-style-type: none"> <li>• MA</li> <li>• 25 min before and after ET</li> <li>• Fixed protocol</li> </ul>	<ul style="list-style-type: none"> <li>• Clinical pregnancy—presence of a fetal sac (by ultrasound) 6 wks post ET</li> <li>• Uterine artery pulsatility index</li> </ul>	<ul style="list-style-type: none"> <li>• Women receiving Acu had a higher clinical pregnancy rate (42.5% vs 26.3%)*</li> <li>• No difference between the Acu and no-Acu groups in the uterine artery pulsatility index</li> </ul>
2. Dieterle et al, 2006 (24)	RCT	<ul style="list-style-type: none"> <li>• 225 women</li> <li>• Avg age 34.9 y; range 31.3-38.9 y</li> </ul>	<ul style="list-style-type: none"> <li>• Acu (n=116)</li> <li>• Control: placebo Acu (sham pts) (n=109)</li> </ul>	<ul style="list-style-type: none"> <li>• MA</li> <li>• Two txs 30 min and 3 days after ET</li> <li>• Fixed protocol</li> </ul>	<ul style="list-style-type: none"> <li>• Clinical pregnancy rate</li> <li>• Biochemical pregnancy rate</li> <li>• Implantation rate</li> <li>• Ongoing pregnancy rate</li> <li>• Miscarriages</li> </ul>	<ul style="list-style-type: none"> <li>• Acu group compared to the placebo group had significantly higher clinical pregnancy rate (33.6% vs 15.6%)*, biochemical pregnancy rate (35.3% vs 16.5%)*, implantation rate (14.2% vs 5.9%)*, and ongoing pregnancy rate (28.4% vs 13.8%)*</li> <li>• No difference in miscarriages</li> </ul>
3. Smith et al, 2006 (25)	RCT	<ul style="list-style-type: none"> <li>• 128 women</li> <li>• Avg age 36 y; range 31.2-40.9 y</li> </ul>	<ul style="list-style-type: none"> <li>• Acu (n=110)</li> <li>• Control: Placebo (sham pts, Streitberger) (n=118)</li> </ul>	<ul style="list-style-type: none"> <li>• MA</li> <li>• 3 txs: Day 9 of stimulating injections, before and after ET</li> <li>• Used Paulus and TCM to determine pt selection (pts not specified)</li> </ul>	<ul style="list-style-type: none"> <li>• Clinical pregnancy rate</li> <li>• Implantation</li> <li>• Ongoing pregnancy</li> <li>• Adverse events</li> <li>• Health status</li> </ul>	<ul style="list-style-type: none"> <li>• No significant differences in any outcomes</li> <li>• Clinical pregnancy rate: Acupuncture vs placebo – 34% vs 27%</li> </ul>
4. Westergaard et al, 2006 (26)	RCT	<ul style="list-style-type: none"> <li>• 273 women</li> <li>• Avg age 37 y; range 24-45 y</li> </ul>	<ul style="list-style-type: none"> <li>• Acu-1 tx (n=95)</li> <li>• Acu-2 tx (n=91)</li> <li>• Control: no Acu (n=87)</li> </ul>	<ul style="list-style-type: none"> <li>• MA</li> <li>• 25 min before and after ET (Acu-1); plus 2 days post ET (Acu-2)</li> </ul>	<ul style="list-style-type: none"> <li>• Clinical pregnancy</li> <li>• Ongoing pregnancy</li> </ul>	<ul style="list-style-type: none"> <li>• Acu-1 group compared to control had significantly higher clinical and ongoing pregnancy rates (39% vs 26% and 36% vs 22%)*</li> <li>• Acu-2 group not significantly different from control</li> <li>• Acu-2 had a higher, but not significantly, early pregnancy loss compared to Acu-1 and control (33% vs 15% vs 21)</li> </ul>
5. Stener-Victorin et al, 1999 (27)	RCT	<ul style="list-style-type: none"> <li>• 150 women</li> <li>• Avg age 34.4 y; range 25-46 y</li> </ul>	<ul style="list-style-type: none"> <li>• Acu + PCB (n=75)</li> <li>• Control: alfentanil + PCB (n=75)</li> </ul>	<ul style="list-style-type: none"> <li>• EA and MA</li> <li>• One tx, 30 min before and until the end of OA</li> <li>• Fixed protocol</li> </ul>	<ul style="list-style-type: none"> <li>• Pain before/after OA</li> <li>• No. of ICSI cycles</li> <li>• No. of standard IVF cycles</li> <li>• No. of oocytes retrieved</li> <li>• Fertilization rate</li> <li>• No. of ET</li> <li>• No. of pregnancy, and miscarriages before 16th wk</li> <li>• Implantation rate</li> <li>• Take-home baby per ET</li> </ul>	<ul style="list-style-type: none"> <li>• Acu equal to alfentanil in pain management</li> <li>• Acu had significantly higher implantation rate (27.2% vs 16.3%)*, pregnancy rate (45.9% vs 28.3%)*, and take-home baby rate (41% vs 19.4%)* per ET</li> <li>• Acu greater stress before OA and longer period of discomfort</li> </ul>
6. Stener-Victorin et al, 2003 (28)	RCT	<ul style="list-style-type: none"> <li>• 286 women</li> <li>• Avg age 32.9 y; range 22-38 y</li> </ul>	<ul style="list-style-type: none"> <li>• Acu + PCB (n=141)</li> <li>• Control: alfentanil + PCB (n=145)</li> </ul>	<ul style="list-style-type: none"> <li>• EA and MA</li> <li>• One tx, 30 min before and until the end of OA</li> <li>• Fixed protocol</li> </ul>	<ul style="list-style-type: none"> <li>• Pain before/after OA</li> <li>• No. of oocytes retrieved</li> <li>• Fertilization rate</li> <li>• No. of ET procedures</li> <li>• No. of ET</li> <li>• No. of pregnancy, and miscarriages before 16th wk</li> </ul>	<ul style="list-style-type: none"> <li>• Acu equal to alfentanil in pain management</li> <li>• No significant differences between Acu and alfentanil groups in any IVF outcome measures</li> <li>• Neuropeptide Y in FF were significantly higher in the Acu group</li> </ul>

TABLE Summary of Studies Evaluating Acupuncture as an Adjunct Therapy for IVF (continued)

Author, Year (Reference)	Study Design	Study Population	Intervention (Sample Size)	Acupuncture Treatment	Relevant Outcomes Measured	Results
					<ul style="list-style-type: none"> <li>• No. gestational sacs</li> <li>• Pregnancy and implantation rates</li> <li>• No. of on-going pregnancy</li> <li>• Neuropeptide Y in FF</li> <li>• Amount of additional analgesic</li> </ul>	<ul style="list-style-type: none"> <li>• Acu group reported significantly lower amounts of additional alfentanil</li> <li>• 2 hr after OA Acu group reported significantly less abdominal pain, other pain, nausea and stress and were significantly more calm</li> </ul>
7. Balk et al, 2003 (31)	CT	<ul style="list-style-type: none"> <li>• 10 women</li> <li>• Avg age 36 y, range 31-41 y</li> </ul>	<ul style="list-style-type: none"> <li>• Acu (n=10)</li> <li>• Control: No-Acu group were other women at the clinic</li> </ul>	<ul style="list-style-type: none"> <li>• EA</li> <li>• 2 tx/wk for 4 wk prior to ET</li> <li>• Fixed protocol</li> </ul>	<ul style="list-style-type: none"> <li>• Uterine artery pulsatility index</li> <li>• Endometrial lining</li> <li>• Eggs retrieved</li> <li>• Eggs fertilized</li> <li>• Embryos transferred</li> </ul>	<ul style="list-style-type: none"> <li>• No significant differences between Acu and no-Acu group in any outcome measures</li> </ul>
8. Emmons and Patton, 2000 (32)	Case series	<ul style="list-style-type: none"> <li>• 6 women</li> <li>• Avg age 35.8 y; range 29-41 y</li> </ul>	<ul style="list-style-type: none"> <li>• Acu (n=6)</li> </ul>	<ul style="list-style-type: none"> <li>• MA</li> <li>• 3-4 twice weekly tx on days 1-3, 4-6, 7-9, and 9-11 + tx on day of or prior to egg retrieval</li> <li>• Fixed protocol + individual points</li> </ul>	<ul style="list-style-type: none"> <li>• No of follicles retrieved</li> <li>• Pregnancy rate</li> <li>• Pregnancy rate past first trimester</li> </ul>	<ul style="list-style-type: none"> <li>• No pregnancy in non-Acu cycles</li> <li>• 3 women produced more follicles following Acu tx (11.3 vs 3.9), all 3 women conceived, but only 1 pregnancy lasted past the first trimester</li> </ul>
9. Johnson 2006 (33)	Case series	<ul style="list-style-type: none"> <li>• 22 women</li> <li>• Avg age 36.2 y; range 31.5-43.2</li> </ul>	<ul style="list-style-type: none"> <li>• Acu (n=22)</li> <li>• Control: No acu group were women at the clinic during 2003</li> </ul>	<ul style="list-style-type: none"> <li>• MA</li> <li>• Introductory and 3 full tx prior to ET, 2 tx 25 min before and after ET</li> </ul>	<ul style="list-style-type: none"> <li>• Fetal heart beat 4 weeks after ET</li> </ul>	<ul style="list-style-type: none"> <li>• Acu group had greater pregnancy rate than control (57.7% vs 45.3%), but not statistically significant</li> </ul>
10. Liang 2003 (21)	Case study	<ul style="list-style-type: none"> <li>• 11 women</li> <li>• Ages 32-48 y</li> </ul>	<ul style="list-style-type: none"> <li>• Acu and Chinese herbs (n=10)</li> <li>• Acu only (n=1)</li> </ul>	<ul style="list-style-type: none"> <li>• MA</li> <li>• Individual protocol</li> </ul>	<ul style="list-style-type: none"> <li>• Take-home baby</li> </ul>	<ul style="list-style-type: none"> <li>• Tx resulted in take-home baby for all subjects</li> </ul>
11. Lyttleton 2004 (20)	Case study	<ul style="list-style-type: none"> <li>• 2 women</li> <li>• Ages 39 and 40 y</li> </ul>	<ul style="list-style-type: none"> <li>• Acu and Chinese herbs (n=2)</li> </ul>	<ul style="list-style-type: none"> <li>• MA</li> <li>• Individual protocol</li> </ul>	<ul style="list-style-type: none"> <li>• Take-home baby</li> </ul>	<ul style="list-style-type: none"> <li>• Tx resulted in take-home baby for both subjects</li> </ul>

Acu=acupuncture; Avg=average; CT=controlled trial; EA=electroacupuncture; ET=embryo transfer; FF=follicular fluid; ICSI=intracytoplasmic sperm injection; IVF=in vitro fertilization; MA>manual acupuncture; OA=oocyte aspiration; PCB=paracervical block; Preg=pregnancy; Pts=points; RCT=randomized controlled trial; Y=years; STAI=State Trait Anxiety Inventory; TCM=traditional Chinese medicine; Tx=treatment

\*Significant to at least  $P < .05$

days after ET (ACU 2 group, n=91).<sup>26</sup> Clinical and ongoing pregnancy rates were significantly higher in the ACU 1 group compared with controls (39% vs 26% and 36% vs 22%, respectively). The ACU 2 group, compared with the control group, exhibited statistically non-significant trends toward higher clinical and ongoing pregnancy rates (36% vs 26%, respectively).

#### *Trials Investigating the Use of Acupuncture as an Alternative to Conventional Analgesic Methods for Oocyte Retrieval*

Two prospective, randomized studies were aimed primarily

at investigating the efficacy of acupuncture as an alternative to pharmacological analgesia for oocyte aspiration.<sup>27,28</sup> These studies also assessed differences in pregnancy rates between those receiving acupuncture and those receiving conventional analgesia. Each of these studies used a single acupuncture treatment (consisting of EA and manual acupuncture) performed 30 minutes before oocyte aspiration and lasting until just after aspiration was completed. The first study showed that women who received acupuncture had significantly higher implantation rates (27.2% vs 16.3%), pregnancy rates (45.9% vs 28.3%), and take-home baby rates (41%

vs 19.4%) per embryo transfer.<sup>27</sup> The similarly designed subsequent study<sup>28</sup> and others<sup>29,30</sup> failed to confirm these results.

#### **Prospective Non-randomized Study, Case Series, and Narrative Descriptions of Case Studies in Traditional Chinese Medicine Texts**

In a study by Balk et al, 10 women (average age 36 years) were given EA twice a week for 4 weeks prior to embryo transfer and compared with an unknown number of women in the same clinic who did not receive EA.<sup>31</sup> No significant difference was seen between the women who received EA and those who did not in any of the outcome measures.

Emmons and Patton undertook a case series involving 6 women (average age 35.8 years) who had previously responded poorly to gonadotropin therapy and who were undergoing IVF with ICSI.<sup>32</sup> These women received twice-weekly manual acupuncture for 3 or 4 weeks. There were no pregnancies in non-acupuncture cycles. Of the 6 women, 3 produced more follicles after acupuncture treatment and all 3 conceived; only 1 woman's pregnancy lasted past the first trimester. Johnson undertook a case series of 22 women (average age 36.2 years) who received an introductory treatment followed by 3 full treatments prior to ET and 2 treatments 25 minutes before and after ET.<sup>33</sup> These women were compared to other women in the clinic who had not received acupuncture and exhibited statistically non-significant trends toward higher pregnancy rates (57.7% in the acupuncture group vs 45.3% in the no-acupuncture group). A couple of narrative case studies involving 13 women who were treated with acupuncture and Chinese herbs reported that all women gave birth to healthy babies.<sup>20,21</sup>

Collectively, the studies summarized in the table suggest the following.

**Acupuncture may improve the success rate of IVF.** Four of 6 RCTs (including 3 of the 4 specifically designed to test improved pregnancy rates),<sup>23-27</sup> 1 case series,<sup>32</sup> and 13 narrative case studies<sup>20,21</sup> suggest that acupuncture may improve IVF outcome.

**Acupuncture may improve the quality of life (QOL) of patients undergoing IVF.** Two RCTs demonstrated that acupuncture was equivalent to conventional analgesia for managing pain associated with oocyte aspiration.<sup>27,28</sup> Stener-Victorin et al also reported that women receiving acupuncture reported significantly less abdominal pain, other pain, nausea, and stress 2 hours after oocyte aspiration compared to women receiving conventional analgesia.<sup>28</sup> Another RCT reported that women who had received acupuncture for pain management associated with oocyte aspiration had less postoperative tiredness and confusion when compared with women receiving conventional analgesia.<sup>29</sup> In 2 of these studies, however, patients who had received acupuncture were reported to have experienced greater stress, discomfort, and/or pain.<sup>27,29</sup> Smith et al reported that the most frequently reported side effects of the acupuncture treatments were relaxation, feeling calm and peaceful, and feeling energized.<sup>25</sup>

**Acupuncture may be a safe adjunct therapy for IVF patients.** No adverse events were reported in any of the studies presented in the table. This coincides with the excellent general

safety profile of acupuncture.<sup>34,35</sup>

Although the studies summarized in the table suggest acupuncture may improve pregnancy rates and QOL among patients undergoing IVF, these results must be considered inconclusive and interpreted with caution for the following reasons.

**The majority of available studies have significant design limitations.** Of the 6 RCTs, only 4 were specifically designed to address the hypothesis that acupuncture could increase the success rate of IVF, and only 2 of these included sham acupuncture controls. Though case series and non-randomized studies provide additional support, the absence of randomization and control groups in these studies results in great potential for bias. In studies that did not include a sham acupuncture control, it is difficult to distinguish the effects of acupuncture needling from placebo, non-specific effects associated with treatments.<sup>36,37</sup> In many studies, details of procedures related to eligibility screening, randomization, blinding, and statistical analyses were absent. Other reviews of this literature highlight these and additional limitations of the studies, especially in relation to the choice of the primary outcome measure (pregnancy rate) and a range of issues related to sample size calculation and statistical analysis of outcome data.<sup>38-40</sup>

**The majority of the acupuncture protocols employed in studies to date do not reflect clinical practice.** First, the dosages of acupuncture employed in most of the trials were very low (1-9 treatments). In standard clinical practice, acupuncture treatment protocols occur over a period of weeks or months, especially for conditions such as infertility, which often are associated with long-standing deficiencies and imbalances.<sup>19</sup> Second, TCM diagnoses were assessed in only 1 of the trials presented in the table and even in that study were not used to determine all acupuncture treatments.<sup>25</sup> Consequently, in all other studies, treatment protocols were not tailored to address TCM-specific imbalances and symptoms. Rather, the same treatment protocol was given to all subjects regardless of the basis of their infertility from a TCM perspective. This potentially creates a fixed-protocol bias and reduces the likelihood that the treatment will be appropriate and effective for individual subjects.<sup>41</sup>

Several studies used EA, a form of treatment that is not commonly used in a clinical setting for the treatment of infertility.<sup>27,28,31</sup> The choice of acupuncture points was often difficult to understand and justify and without a high degree of similarity to suggested protocols in Chinese medicine texts.<sup>19-21</sup> Furthermore, some points (Sp6 and LI4) are contraindicated in pregnancy and may therefore be unsuitable after ET. This may explain the outcome reported by Westergaard et al of a greater early pregnancy loss in subjects who were given acupuncture 2 days after ET, as compared with those not receiving acupuncture and those only receiving acupuncture immediately before and after ET (33% vs 21% vs 15% respectively).<sup>26</sup>

Several of the recent study critiques commented on problems associated with the choice of acupuncture points and ear treatments that were used in some of these studies. This touches on a much larger issue of the authentic use of acupuncture in a conventional medical setting within the confines of a clinical trial.

TCM diagnosis and point selection are complex issues based on an in-depth understanding of a large body of theoretical information. Clinical trials need to involve properly trained acupuncturists who are knowledgeable in the discipline, preferably with nationally recognized qualifications, certifications, and appropriate licenses. This would negate the readers' need to try and understand, validate, and justify the acupuncture protocols when the majority of them are not qualified to do so.

**Important details of the experimental protocol are not provided.** The qualifications and experience of the acupuncturists involved in the design and administration of the treatment protocols are poorly described, making it difficult to assess the validity of the intervention. Additionally, many other details of the experimental protocol, as suggested by the standards for reporting interventions in controlled trials of acupuncture (STRICTA),<sup>42</sup> were not reported, making the quality of the these trials' outcomes difficult to evaluate.

In summary, although methodological problems with the existing clinical research limit conclusions, there is some evidence to suggest that acupuncture may be a safe and effective adjunct therapy for women undergoing IVF. There is a definite need for more thorough and carefully designed clinical trials to evaluate the effect of acupuncture on IVF success rates.

#### **POTENTIAL MECHANISMS UNDERLYING ACUPUNCTURE'S IMPACT ON FERTILITY AND IN VITRO FERTILIZATION SUCCESS RATES**

Understanding the mechanism by which acupuncture improves IVF success rates is important because it defines appropriate outcome measures that should be evaluated in future clinical trials assessing the use of acupuncture with IVF. It also furthers our understanding of how acupuncture modulates specific physiological processes, which could lead to a more targeted approach to identifying women who would specifically benefit from acupuncture while undergoing IVF.

Drawing on a broad body of literature evaluating the mechanistic basis of acupuncture as well as our understanding of the physiological basis of female fertility, we propose 4 interrelated mechanisms by which acupuncture could improve the outcome of IVF: (1) modulating neuroendocrinological factors; (2) increasing blood flow to the uterus and ovaries; (3) modulating immune factors, especially cytokines; and (4) reducing stress, anxiety, and depression.

#### **Acupuncture and the Hypothalamus-Pituitary-Gonadal and -Adrenal Axes**

The hypothalamus releases a range of hypophysiotrophic hormones, several of which are directly or indirectly important for fertility: gonadotropin-releasing hormone (GnRH), corticotrophin-releasing hormone (CRH), growth hormone-releasing hormone (GHRH), and thyroid-releasing hormone (TRH). These hormones act on the pituitary gland to regulate its own hormone production.<sup>14</sup> GnRH regulates the production of FSH and luteinizing hormone (LH), which in turn regulates the activity of the

ovaries and their production of estrogen and progesterone. The ovarian steroid hormones then provide a feedback mechanism to regulate the hypothalamus. The connection of the hypothalamus-pituitary-gonads is called the HPG axis. Likewise, CRH regulates the production of adrenocorticotrophic hormone (ACTH), which in turn regulates the secretion of cortisol by the adrenal gland. Cortisol can then negatively feed back on the hypothalamus and pituitary gland to control the further production of both ACTH and CRH. The connection of the hypothalamus-pituitary-adrenal gland is called the HPA axis. Both of these axes play important roles in reproductive function.<sup>14</sup> The production of GHRH and TRH and the physiological functions that they regulate also can play an important role in fertility.<sup>14</sup>

Many reproductive problems are related to abnormalities in hypothalamic and pituitary function. These can be caused by structural abnormalities such as tumors; genetic mutations (either acquired or congenital); lifestyle factors (such as poor nutrition, excessive exercise, smoking, obesity, and chronic stress); and psychological factors (such as eating disorders and depression). The HPA axis is intimately involved in the negative effects that stress has upon fertility. Stress elevates cortisol levels. Cortisol enhances vascular reactivity, activates the catabolism of protein and fat to provide energy, and inhibits insulin activity. Chronic exposure to stress and elevated cortisol levels inhibit nonessential processes such as reproduction.

Precisely how acupuncture can affect neuroendocrinological factors is not known. It is well established, however, that EA inhibits pain perception by elevating several classes of neurochemicals,<sup>43</sup> including  $\beta$ -endorphin.<sup>44</sup> The ability of acupuncture to affect a range of cellular and physiological functions is attributed to this modulation of neurochemicals. These substances then influence a range of hypothalamic functions and affect reproduction, autonomic function, and even the immune system.<sup>14,45,46</sup> It has been suggested that acupuncture acts to modulate both the HPG<sup>28,47,48</sup> and HPA<sup>49,50</sup> axes.

Recent studies have demonstrated that EA can alter several different neuroendocrinological factors that are important determinants of female fertility. Stener-Victorin et al showed that low-frequency (2 Hz) EA treatment induced regular ovulation in one third of women with anovulation associated with polycystic ovary syndrome (PCOS).<sup>51</sup> Using a rat model of steroid-induced PCOS, low-frequency EA has been shown to reduce elevated ovarian nerve growth factor, corticotrophin-releasing factor, and endothelial concentrations<sup>47,50</sup> and to increase concentrations of hypothalamic  $\beta$ -endorphin.<sup>52</sup> This appears to result from a modulation of the sympathetic nerve activity in the ovary<sup>53</sup> and allows EA to normalize most of the steroid-induced changes in ovarian adrenoceptors and to prevent steroid-induced up-regulation of the low-affinity p75 neurotrophin receptor.<sup>54</sup>

#### **Acupuncture and Uterine and Ovarian Blood Flow**

Adequate blood flow to the developing ovarian follicle and decidualized endometrium is essential to the initiation and maintenance of normal human pregnancy. Doppler ultrasound evalua-

tion of uterine and ovarian blood flow has demonstrated that improved blood flow in either vascular system is associated with improved fertility outcomes, although follicular flow measurements are more closely correlated with improved fertility outcomes.<sup>55-57</sup> Blood flow impedance in the uterine arteries expressed as a resistance index, the pulsatility index (PI), is considered valuable in assessing endometrial receptivity. A high uterine artery PI is associated with a decreased pregnancy rate following IVF-embryo transfer.<sup>58,59</sup>

The use of ultrasound guidance for the retrieval of oocytes during IVF cycles has demonstrated that the systolic velocity of blood flow to a particular ovarian follicle was directly associated with the ability to retrieve an oocyte from that follicle.<sup>60</sup> Women who respond poorly to ovarian stimulation for IVF have compromised blood flow to their ovarian follicles (and uteri) when compared to women with normal ovarian responses.<sup>57</sup> The levels of the vasoactive protein vascular endothelial growth factor (VEGF) in the follicular fluid of poor responders is higher than that of normal responders, and levels are inversely related to the subsequent quality of the embryo that is produced by the retrieved egg. VEGF promotes angiogenesis and is produced and secreted in response to hypoxia. High levels of VEGF in the follicular fluid can be used to identify poor follicular development.<sup>61</sup>

Acupuncture has been shown to modulate the circulation of blood in many different parts of the body. Studies have shown that acupuncture can alter cerebral blood flow<sup>62-64</sup> and peripheral blood flow.<sup>65-68</sup> The efficacy of acupuncture in the treatment of several disorders, including migraine headaches,<sup>69</sup> cerebral ischemia,<sup>70,71</sup> and fibromyalgia,<sup>66</sup> has been proposed to be mediated by its effects on blood flow.

In a study by Stener-Victorin et al, repeated EA treatments in 10 infertile women resulted in a significantly decreased PI of the uterine arteries.<sup>72</sup> This decrease was sustained for 10-14 days after the EA treatment period. Latter studies in rats by the same group showed that low-frequency EA increased ovarian blood flow as a reflex response via the ovarian sympathetic nerves.<sup>53,73</sup> In contrast, high-frequency EA decreased ovarian blood flow following systemic circulatory changes in both normal rats and rats with PCOS. Acupuncture also has been shown to modulate the production of several angiogenic factors, such as endothelin-150 and VEGF.<sup>74</sup>

### Acupuncture and Cytokines

A growing body of literature supports a role between certain soluble mediators of immune responses and the achievement and maintenance of pregnancy. A brief description of the classification of these factors is presented, followed by a discussion of their putative role in fertility.

T helper cell phenotypes have been subcategorized based on the cytokine secretory profiles of CD4+ cells. Th1 cells promote inflammation via the secretion of inflammatory cytokines (eg, interferon [IFN] gamma, interleukin [IL]-2, IL-12, IL-18), whereas Th2 cells promote allergic-type responses, including mast cell and eosinophil activation and antibody production. Cytokine secretion associated with Th2 responses involves IL-4, IL-6, IL-10, and IL-13.

Th3 responses are characterized by the secretion of transforming growth factor beta (TGF $\beta$ ). Development of these phenotypes begins with the naïve T helper progenitor (Thp) cell. Cytokines and chemokines in the environment where Thp cells encounter major histocompatibility complex (MHC) class II-presented antigen direct the development of Th1, Th2, or Th3 phenotypes.

With the exception of a brief and immediate pro-inflammatory response at the site of implantation, successful human pregnancy appears to be characterized by a local and systemic Th2 dominance; women with repeated pregnancy failure may be unable to modulate their T helper responses appropriately upon becoming pregnant.<sup>75,76</sup> T helper cytokine profiles and their modulation in pregnancy and upon exposure to pregnancy-related hormones have been studied extensively. This includes their relationship with fertility,<sup>77</sup> repeated implantation failure after IVF,<sup>78</sup> and recurrent clinical pregnancy loss.<sup>79</sup> T helper cell dysregulation that adversely affects pregnancy outcomes could be occurring systemically, at the level of the endometrium/implantation, within the microenvironment of the developing ovarian follicle, or at all sites.

Several studies have demonstrated acupuncture's ability to modulate cytokine production. It has been proposed that in the brain, acupuncture may modulate cytokine levels via its ability to increase the release of  $\beta$ -endorphin.<sup>45,80</sup> Investigators have demonstrated that acupuncture normalizes Th1- and/or Th2-type cytokines in the ventral midbrains of healthy rats,<sup>81</sup> in the hypothalamus of rats with lipopolysaccharide-induced fever,<sup>82</sup> and in the ischemic cortices of rats with middle cerebral artery occlusion.<sup>83</sup> Chen et al showed that EA stimulation significantly up-regulated IL-6 mRNA levels in rat cortex and striatum following cerebral ischemia/reperfusion.<sup>84</sup> This may explain the neuroprotective effect of acupuncture in cerebral ischemic injury. Other investigators have shown similar protective peripheral cytokine modulation when acupuncture was used in rats with induced ulcerative colitis<sup>85</sup> and in rats that had experienced operative trauma.<sup>86</sup> Yu et al showed that rats receiving acupuncture had elevated levels of IL-2 in aqueous spleen extracts.<sup>87</sup>

In humans, Jeong et al investigated the effect of acupuncture on the production of inflammatory cytokines in patients with chronic headaches and found that acupuncture resulted in decreased levels of IL-1 $\beta$  and IL-6.<sup>88</sup> Petti et al showed that acupuncture treatment reduced the plasma levels of IL-2 and IL-10 in subjects with chronic allergic rhinitis when compared to subjects receiving no treatment or those receiving sham acupuncture.<sup>89</sup> Joos et al conducted an RCT to assess the effects of acupuncture in the treatment of allergic asthma and found that there was a significant reduction in the plasma levels of IL-6 and IL-10 in subjects receiving acupuncture.<sup>90</sup> In contrast, IL-8 levels rose significantly. Others have demonstrated similar cytokine normalization in patients with malignant tumors<sup>91</sup> or rheumatoid arthritis<sup>92</sup> who were treated with acupuncture.

### Acupuncture and Stress, Anxiety, and Depression

A significant amount of literature supports the contention that women who experience depression while undergoing IVF



have lower pregnancy rates than women who are not depressed.<sup>11,93</sup> Depressive symptoms are common among patients who undergo IVF, and the severity and prevalence of depression increase as the number of IVF treatment failures increases.<sup>93</sup> Anxiety is also correlated with pregnancy rates in IVF. Women with significant concerns about the financial cost associated with IVF were at much higher risk of not achieving a successful delivery.<sup>12</sup> A prospective study of 291 women found that anxiety had a stronger negative correlation with IVF outcome than did depression.<sup>94</sup> Another study found that women with episodic anxiety, but not those with trait or acute anxiety, were less likely to conceive in the second IVF attempt if the first was not successful.<sup>95</sup>

Stress reduction appears to enhance fertility. A randomized, controlled study of 184 women undergoing a combination of infertility treatments evaluated the impact of cognitive behavioral therapy (including relaxation and yoga) on pregnancy rates.<sup>96</sup> Women undergoing cognitive behavioral therapy were compared to those attending a standard support group and routine care controls. Patients with depression were excluded from the study. Pregnancy rates were significantly higher in women undergoing cognitive behavioral therapy and in those attending support groups when compared to the control group; treatment groups did not differ from one another. In a smaller study of couples undergoing IVF,<sup>60</sup> couples were randomized to either counseling or a control group during IVF.<sup>97</sup> The group who underwent counseling experienced significantly lower anxiety and depression scores, higher life satisfaction scores, and significantly higher pregnancy rates than control couples. These data make a strong case for the use of therapies that can reduce stress and negative emotional states in women undergoing IVF.

Studies have shown that acupuncture may be effective in the treatment of depression,<sup>98-100</sup> anxiety,<sup>101,102</sup> and stress.<sup>103-106</sup> Gallagher et al conducted an RCT with 38 participants and concluded that compared to other empirically validated treatments (eg, medication, talk therapy), acupuncture designed specifically to treat major depression produces results that are comparable in terms of rates of response and of relapse or recurrence.<sup>98</sup> In a clinical trial involving 30 subjects receiving acupuncture compared with 31 subjects receiving drug therapy, Han et al concluded that EA can produce the same clinical therapeutic effect as that produced by the tetracyclic antidepressant maprotiline, with fewer side effects and better symptom improvement.<sup>99</sup> Spence et al conducted a clinical trial involving 18 anxious adult subjects who complained of insomnia.<sup>102</sup> Five weeks of acupuncture treatment was associated with a significant nocturnal increase in endogenous melatonin secretion and significant improvements in polysomnographic measures of sleep onset latency, arousal index, total sleep time, and sleep efficiency. Additionally, state and trait anxiety scores were lowered significantly. Middlekauff et al tested the hypothesis that acupuncture is sympathoinhibitory in humans with heart failure.<sup>103</sup> Fifteen advanced heart failure patients underwent acute mental stress testing before and during "real" acupuncture (n=10), non-acupoint acupuncture (n=10), or no-needle acupuncture

(n=10). During the pretreatment mental stress testing, sympathetic nerve activity increased significantly. This increase was eliminated after real acupuncture but not after non-acupoint or no-needle acupuncture control treatments.

With regard to the use of acupuncture during the IVF procedure, Gejervall et al demonstrated that acupuncture significantly reduced postoperative tiredness and confusion in women undergoing oocyte aspiration for IVF.<sup>29</sup> Stener-Victorin et al showed that 2 hours after oocyte aspiration, the group of women receiving acupuncture (at the time of oocyte aspiration) experienced significantly less abdominal pain, other pain, nausea, and stress and were significantly calmer than those in the control group, who had received conventional analgesia.<sup>28</sup>

The mechanistic basis for the effects of acupuncture on depression, anxiety, and stress are not well understood. A number of possibilities have been suggested, however, including modulation of neuropeptide Y levels in the amygdala,<sup>28</sup> increased production of opioid peptides,<sup>44,106</sup> attenuation of the sympathetic nervous system,<sup>103,104</sup> enhanced vagal nervous activity,<sup>104</sup> and restoration of hippocampal brain-derived neurotrophic factor levels.<sup>105</sup> It also has been proposed that acupuncture may influence the HPA axis and thereby alter many of the physiological responses to stress.<sup>49,50</sup>

## CONCLUSION

There is a growing body of literature to support an understanding of how acupuncture may alter several physiological and psychological processes. This literature helps to define the most probable mechanistic pathways that are relevant to understanding the use of acupuncture for IVF. However, many of the mechanistic studies presented here were not designed to directly investigate acupuncture mechanisms as they relate to female infertility or IVF. Therefore, an important next step in understanding the mechanistic basis of acupuncture as an adjunct therapy for IVF is a targeted investigation of the effects of acupuncture therapy during IVF.

Although methodological problems with the existing clinical research significantly limit their conclusions, the studies reviewed in this article suggest that acupuncture may be a safe and effective adjunct therapy for women undergoing IVF. Given that many women use acupuncture during IVF therapy, there is a highly justified need for more definitive clinical trials investigating the use of acupuncture for improving IVF outcomes. A quality clinical trial investigating this issue would have the following characteristics: randomization, blinding, sham acupuncture control, an acupuncture treatment protocol that is consistent with TCM principles, a range of outcome measures representative of both clinical outcomes and putative mechanistic processes, and compliance with rigorous statistical standards and other guidelines specified by STRICTA.

Such studies will provide a greater understanding of the clinical applicability of acupuncture, may allow more specialized usage for specific infertility conditions, and will enhance the credibility and integration of acupuncture in conventional Western medical settings.

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