

Acupuncture as Adjunct Therapy for *In Vitro* Fertilization

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Abstract

Objective: To review the mechanisms and published clinical trials supporting the use of acupuncture as an adjunct therapy for *in vitro* fertilization (IVF)

Design: A search of MEDLINE, PubMed, and publicly available research data was performed to select articles for inclusion. Search results were cross-referenced with acupuncture textbooks to identify relevant articles.

Result(s): An increasing number of published scientific studies have shown that acupuncture positively impacts fertility and IVF success rates. Possible mechanisms influencing the impacts could be: (1) changes in the menstrual cycle (through the secretion of β -endorphins, which affect gonadotropin secretion by their action on the gonadotropin-releasing hormone [GnRH]); (2) alteration of uterine and ovarian blood flow; (3) secreting cytokines; and (4) relief of depression, anxiety, and stress. Various retrospective and randomized controlled trials have found that acupuncture has a statistically significant positive impact on IVF success rates, including implantation, pregnancy, and live birth rates, while reducing the number of miscarriages and ectopic pregnancies.

Conclusions: With the increasing body of evidence-based literature demonstrating mechanistic processes and clinical results, acupuncture should be considered as a viable adjunct therapy for IVF.

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Keywords: acupuncture, infertility, *in vitro* fertilization, IVF

The use of acupuncture for infertility as an adjunct therapy to conventional treatment in assisted reproductive technology (ART) has continued to increase in popularity through evidence-based publications demonstrating clinical efficacy. According to the Centers for Disease Control and Prevention, IVF accounts for 99% of all ART cycles.¹ Considering the increased use of complementary and alternative medicine (CAM) in the United States² along with patients' turning to CAM to enhance their IVF success rates,³ it is important to review current literature and the rationale for acupuncture as an effective complementary adjunct therapy for IVF.

Background

Acupuncture is an integral component of traditional Chinese medicine (TCM). Although TCM is based on empirical evidence from 3000–5000 years ago, extensive scientific research over the last two decades has continued to establish acupuncture in Western medicine. PubMed searches identified almost 20,000 citations with the term “acupuncture” and almost 1,500 randomized controlled trials with “acupuncture” in the title.⁴

Acupuncture is the stimulation of specific points on the body by inserting very fine sterile metallic needles. According to TCM, these points are based on thousands of years of clinical experience. Current research shows that many acupuncture points are located at transition points or boundaries between different body domains or muscles, coinciding with connective tissue planes. These gap junctions have a high electric conductance and density.⁵

The National Institutes of Health and the World Health Organization have recognized the use of acupuncture in the treatment of a wide range of common illnesses, including musculoskeletal, mental and emotional, gastrointestinal, reproductive, neurological, and respiratory disorders and disorders of the eyes, ears, and mouth.⁶

Acupuncture Mechanisms That Potentially Impact IVF Success Rates

The potential mechanisms of acupuncture that have been suggested to impact fertility and IVF success rates are the influence of acupuncture on the hypothalamus-pituitary-gonadal (HPG) and adrenal (HPA) axes; uterine and ovarian blood flow; immune factors, especially cytokines; and stress, anxiety, and depression.⁷ These potential mechanisms help explain how they may impact IVF success rates, including the rates of pregnancies, births, miscarriages, and ectopic pregnancies.

HPG and HPA Axes

One of the most important functions of the HPG axis is to regulate reproduction by controlling the uterine and ovarian cycles,⁸ which may be the most important key to acupuncture and fertility. Although the mechanism of acupuncture in the treatment of female infertility is not yet known, it is believed to involve the central stimulation of endogenous opioid peptides, particularly the secretion of β -endorphins.⁹ This secretion influences the GnRH pulse generator and thereby influences gonadotropin and steroid secretion.^{10,11} Because these neuropeptides influence gonadotropin

secretion through their action on GnRH, Chang et al. concluded it is logical to hypothesize that acupuncture may impact the menstrual cycle through these neuropeptides.¹²

Cho et al. demonstrated a correlation between brain activation and specific acupuncture point stimulation.¹³ This supports the possibility that acupuncture first stimulates or activates the corresponding brain cortex via the central nervous system (CNS), thereby controlling the chemical or hormone release by the way of the CNS to the diseased or disordered organs for treatment using functional magnetic resonance imaging (fMRI). fMRI is an MRI procedure that measures brain activity by detecting associated changes in blood flow. This demonstrates increased blood flow to a region when an area of the brain is in use. Zhang et al. suggested that the functional activity of certain brain areas may be correlated with the effect of acupuncture.¹⁴

Chen¹⁵ and Chen and Yu¹⁶ demonstrated the potential impact of acupuncture on the hypothalamic-pituitary-ovarian axis and on the uterus, attributing an inhibition of hyperactivity in the sympathetic nervous system. In addition, Stener-Victorin et al. studied the neuroendocrine and endocrine parameters indicative of polycystic ovary syndrome.¹⁷ This study found significant reduction in luteinizing hormone (LH) / follicle-stimulating hormone (FSH) ratios, mean testosterone concentrations, and β -endorphin concentrations with electroacupuncture (EA). However, Stener-Victorin¹⁸ explained that the mechanisms behind the beneficial effect of acupuncture on humans are difficult to study because tissue samples from the ovaries and the CNS are, for obvious reasons, unobtainable. Furthermore, neuropeptides in the gonads and the CNS could be studied in an animal model, provided that such a model exists.

A direct response from the stimulation of points such as SP-6 (*sanyinjiao*) and lower abdominal points may influence ovarian and uterine function¹⁹ as well as the hypothalamic-pituitary-ovarian axis function, normalizing the secretion of hormones, notably of GnRH and LH.¹⁵ Westergaard et al.²⁰ suggested that acupuncture could impact local humoral factors, such as hormones and peptide growth factors, involved in the regulation of implantation based on experiments by She.²¹ These experiments, which administered acupuncture during the preovulatory phase, increased the amount of LH and progesterone in the circulation after needling.

Stener-Victorin and Wu²² created a hypothetical model of the effects of low-frequency EA on the hypothalamus-pituitary-ovarian axis and sympathetic nervous system. They explained this model as follows: "Needle insertion into the skin and muscle excites ergo-receptors and causes afferent activity in A δ - and C-fibers. Needles placed and stimulated in the same somatic innervation area as the ovary decreases sympathetic nerve activity, which leads to decreased secretion and release of ovarian androgens. In parallel, the activity of higher control systems is modulated either directly or by the release of opioids, in particular β -endorphin, that induce functional changes in different organ systems."

Uterine and Ovarian Blood Flow

Arterial uterine blood flow impedance is a method of assessing endometrial receptivity. Optimal endometrial receptivity at the time of implantation is required for successful embryo transfer and IVF. According to Stener-Victorin et al.,²³ optimal endometrial receptivity occurs when the uterine artery vascular impedance is less than three on the pulsation index (an impedance unit). This study showed that acupuncture is extremely effective in lowering

the pulsation index and increasing blood flow to the ovarian and uterine arteries, thus thickening the endometrium and making it more receptive to the transferred embryo. This appears to be a response to a reduction in sympathetic nervous tone induced by acupuncture.²⁴

Another potential role of acupuncture in the enhancement of uterine receptivity is through uterine quiescence and motility. Ayoubi et al.²⁵ concluded that high uterine contraction frequency in IVF at the time of embryo transfer results from the delayed establishment of uteroquiescence after ovulation in IVF as compared with the menstrual cycle. In IVF, low uterine contraction frequency six days after the injection of human chorionic gonadotropin may contribute to the higher pregnancy rates observed with blastocyst transfers. Kim et al. found significantly reduced uterine motility in pregnant rats by stimulating LI-4 (*hegu*) by inhibiting the expression of the COX-2 enzyme in the endometria and myometria.²⁶

Cytokines

The role of T-helper cytokines in human reproduction has been and continues to be studied and reviewed. These studies primarily focus on the expression of T-helper-1 (TH-1) and T-helper-2 (TH-2) cytokines in relation to implantation failure and recurrent miscarriage.

Ng et al.²⁷ found that women with implantation failures exhibited dominant TH-1 immune response, concluding that significantly increased TH-1 cytokine expression may be the underlying immune etiology for reproductive failures. A similar study by Lim et al.²⁸ found that women with recurrent miscarriage exhibit primarily TH-1 cytokines, whereas healthy women exhibit decreased TH-1 cytokines and increased TH-2 cytokines. Kalu et al.²⁹ concluded that women with a history of unexplained recurrent failed IVF treatment have

a TH-1 bias and this polarization is more enhanced following hormonal manipulations during IVF treatment. Kwak et al.³⁰ supported this by finding that the prevalence of dominant TH-1 immune responses in peripheral blood lymphocytes may reflect the systemic contribution of TH-1 cytokines to multiple miscarriages or implantation failures in IVF cycles.

Considering these studies, multiple miscarriages or implantation failures may be due to T-helper modulation. Acupuncture may modulate cytokine levels in the brain because of its ability to increase the release of β -endorphins.^{31,32} Gui et al.³³ stated that acupuncture may improve the poor receptive state of the endometrium due to mifepristone by promoting TH-2 cytokine secretion and inhibiting TH-1 cytokines to improve blastocyst implantation. Other studies³⁴⁻³⁶ have demonstrated the normalization of TH-1 and TH-2 cytokines with rats. Finally, Belinda et al.³⁷ summarized extensively various studies demonstrating the influence of acupuncture on cytokine secretions associated with TH-1 and TH-2 responses, including the secretion of interleukin (IL)-1 β , IL-2, IL-6, IL-8, and IL-10.

Depression, Anxiety, and Stress

Because infertility can cause stress, which leads to a release of stress hormones, stress reduction might improve fertility.³⁷ Demyttenaere et al. found that the subgroup with a female indication for IVF demonstrated increased depressive symptomatology.³⁸ This was correlated with increased expression of negative emotions and was associated with lower pregnancy rates. Significantly lower success rates for IVF have also been found in depressed women (versus non-depressed women).³⁹ Smeenk et al. concluded that pre-existing psychological factors are independently related to the treatment outcomes of IVF /

intracytoplasmic sperm injection (ICSI) and should therefore be taken into account in inpatient counseling.⁴⁰ Furthermore, state anxiety was found to have a slightly stronger correlation with treatment outcomes than depression. This data was also in agreement with that of a previous study,⁴¹ which found that state anxiety, not trait anxiety, affects ART outcomes. Demyttenaere et al. also found the negative influence of state anxiety on IVF outcomes but did not publish any data on trait anxiety.⁴² Furthermore, Eugster et al. found that women with episodic anxiety, but not those with high levels of trait or acute anxiety, were less likely to become pregnant after the second IVF/ICSI.⁴³

Psychiatric and counseling interventions significantly decrease anxiety and depression and increase the chances of pregnancy.⁴⁴⁻⁴⁶ This demonstrates a correlation between emotional states and IVF pregnancy rates. Domar et al., Dong, and MacPherson et al. demonstrated the perceived reduction of stress and anxiety in patients with acupuncture, possibly through its sympathoinhibitory property and impact on β -endorphin levels.^{37,47,48} Middlekauff found that sympathetic activation during acute mental stress is eliminated after acupuncture.⁴⁹ Various studies, including Gallagher et al. and Han et al., have shown that acupuncture for the treatment of depression is comparable to validated medical treatments, such as medication.^{50,51}

Verhaak et al.⁵² reported that differences in emotional status between pregnant and nonpregnant women are present before treatment and become more apparent after the first IVF and ICSI cycle. Women who become pregnant show lower levels of depression than those who do not. In a case series study by Johnson, patients who had experienced previous IVF cycles commented on how much more relaxed they were in the acupuncture-supported cycle.⁵³ Similarly, Smith et al.⁵⁴ reported that the most frequently reported side effects of acupuncture treatments are relaxation, feeling calm and peaceful, and feeling energized.

Finally, Magarelli, Cridennda, and Cohen⁵⁵ investigated whether changes in stress hormones serum cortisol (CORT) and prolactin (PRL) influence reproductive outcomes (i.e., pregnancy rates) in IVF patients treated with acupuncture. Results showed that the CORT levels in the acupuncture group were significantly higher on IVF medication days 7, 8, 9, 11, 12, and 13 than those of the controls. PRL levels in the acupuncture group were significantly higher on IVF medication days 5, 6, 7, and 8 than those of the controls. They concluded that there appeared to be a beneficial regulation of CORT and PRL in the acupuncture group during the medication phase of the IVF treatment, with a trend toward more normal fertile cycle dynamics.

Acupuncture as Adjunct Therapy for IVF

A growing body of available published literature continues to demonstrate the positive influence of acupuncture on IVF success rates, including the rates of pregnancies, births, miscarriages, and ectopic pregnancies. Table 1 summarizes seven retrospective, randomized, and/or controlled studies that demonstrate the improvement of IVF success rates with acupuncture.

Table 1: Summary of retrospective, randomized and/or controlled studies demonstrating acupuncture as an adjunct therapy for IVF

Author, Year	Design	Patients	Intervention	Treatment	Results
Kong et al, 2009 (56)	RT	<ul style="list-style-type: none"> • 52 women • Avg age 38. range 29-45 y 	<ul style="list-style-type: none"> • TCA + EA (n=22) • First control: TCA only (n=14) • Second control: EA only (n=16) 	<ul style="list-style-type: none"> • TCA and EA • Minimum 12 txs, 2 tx/week prior to ET • Pt selection based on TCM pattern and diagnosis 	<ul style="list-style-type: none"> • TCA+EA group compared to US IVF avg had significantly higher PR (P<.01) (81.8% vs 40.2%)* • TCA+EA demonstrated higher PR than TCA or EA alone (81.8% vs 64.3% vs 62.5%)
Cridennda and Magarelli, 2007 (57)	RS	<ul style="list-style-type: none"> • 131 women • Poor prognosis 	<ul style="list-style-type: none"> • Poor prognosis given choice of Acu • Control: declined Acu (n=83) • Accepted Acu (n=48) 	<ul style="list-style-type: none"> • EA and MA • 9 txs during ovarian stimulation: Stener-Victorin EA protocol (1996) • 2 tx- Paulus protocol (2002) 24 hours prior to ET and 1 hour after ET • Fixed protocol 	<ul style="list-style-type: none"> • No significant difference in PR between Acu group and control (50% vs 45%) • Statistical significance in SAB (8% vs 14%), ectopic pregnancies (0% vs 9%), and BR (21% vs 16%)
Magarelli, Cridennda, and Cohen, 2004 (58)	RS	<ul style="list-style-type: none"> • 114 women • Good prognosis 	<ul style="list-style-type: none"> • Acu (n=53) • Control: No Acu (n=61) 	<ul style="list-style-type: none"> • EA and MA • Pre/Post ET protocols • Fixed Protocol 	<ul style="list-style-type: none"> • PR significantly improved Acu to Non-Acu group (51% vs 36%)* • SAB significantly improved (8% vs 20%)* • Ectopic pregnancies (0% vs 9%), p < 0.008. • BR for Acu group significantly higher, with 23% more*
Dieterle et al, 2006 (59)	RCT	<ul style="list-style-type: none"> • 225 women • Avg age 34.9 y; range 31.3-38.9 y 	<ul style="list-style-type: none"> • Acu (n=116) • Control: placebo Acu (sham pts) (n=109) 	<ul style="list-style-type: none"> • MA • Two txs 30 min and 3 days after ET • Fixed protocol 	<ul style="list-style-type: none"> • Significantly higher clinical PR (33.6% vs 15.6%)*, biochemical PR (35.3% vs 16.5%)*, implantation rate (14.2% vs 5.9%)*, and ongoing PR (28.4% vs 13.8%)* in Acu vs placebo
Paulus et al, 2002 (60)	RCT	<ul style="list-style-type: none"> • 160 women • Age 32.5 y; range 28.5-36.5 y 	<ul style="list-style-type: none"> • Acu (n=80) • Control: No Acu (n=80) 	<ul style="list-style-type: none"> • MA • 25 min before and after ET • Fixed protocol 	<ul style="list-style-type: none"> • Higher clinical PR (42.5% vs 26.3%)* in Acu group vs control
Stener-Victorin et al, 1999 (61)	RCT	<ul style="list-style-type: none"> • 150 women • Avg age 34.4 y; range 25-46 y 	<ul style="list-style-type: none"> • Acu + PCB (n=75) • Control: alfentanil + PCB (n=75) 	<ul style="list-style-type: none"> • EA and MA • One tx, 30 min before and until the end of OA • Fixed protocol 	<ul style="list-style-type: none"> • Significantly higher implantation rate (27.2% vs 16.3%)*, PR (45.9% vs 28.3%)*, and take-home baby rate (41% vs 19.4%)* per ET in Acu group vs control
Westergaard et al, 2006 (20)	RCT	<ul style="list-style-type: none"> • 273 women • Avg age 37 y; range 24-45 y 	<ul style="list-style-type: none"> • Acu-1 tx (n=95) • Acu -2 tx (n=91) • Control: no Acu (n=87) 	<ul style="list-style-type: none"> • MA • 25 min before and after ET (Acu-1); plus 2 days post ET (Acu-2) • Fixed Protocol 	<ul style="list-style-type: none"> • Significantly higher clinical and ongoing PR (39% vs 26% and 36% vs 22%)* in Acu-1 group vs control • Acu-2 group demonstrated no significant difference vs control • Early pregnancy loss in Acu-2 was higher, but not significantly, vs Acu-1 and control (33% vs 15% vs 21%)

Acu=acupuncture; Avg=average; BR=birth rates; EA=electroacupuncture; ET=embryo transfer; IVF=in vitro fertilization; MA>manual acupuncture; OA=oocyte aspiration; PCB=paracervical block; PR=pregnancy rate; Pt(s)=point(s); RCT=randomized controlled trial; RS=retrospective trial; RT=randomized trial; SAB=miscarriage rates; Y=years; TCA=traditional Chinese acupuncture; TCM=traditional Chinese medicine; Tx=treatment

*Significant to at least P<.05

Acupuncture has demonstrated a statistically significant ($p < .05$) increase in implantation and pregnancy rates (PR) among IVF patients. In a study of 52 women with an average age of 38 years, the acupuncture (Acu) group, which was administered traditional and electro-acupuncture ($n=22$), had significantly higher PR ($P < .01$) than the US IVF average (81.8% vs. 40.2%).⁵⁶ In a study of 114 women with good prognosis, the Acu group ($n=53$) had significantly improved PR compared with the non-Acu group ($n=61$) (51% vs. 36%).⁵⁸ Paulus et al.⁶⁰ demonstrated higher clinical PR (42.5% vs. 26.3%) in women receiving Acu ($n=80$) than that in the non-Acu group ($n=80$). Westergaard et al.²⁰ found that the Acu group ($n=95$), compared with the non-Acu group ($n=87$), had significantly higher clinical and ongoing PR (39% vs. 26% and 36% vs. 22%, respectively). In a study by Stener-Victorin,⁶¹ the Acu group ($n=75$) had significantly higher implantation rate (27.2% vs. 16.3%) and PR (45.9% vs. 28.3%) than the non-Acu group ($n=75$). Finally, Dieterle et al.⁵⁹ demonstrated that the Acu group ($n=116$), compared with the placebo group ($n=109$), had significantly higher clinical PR (33.6% vs. 15.6%), biochemical PR (35.3% vs. 16.5%), implantation rate (14.2% vs. 5.9%), and ongoing PR (28.4% vs. 13.8%).

Acupuncture has demonstrated a statistically significant ($p < .05$) increase in birth rates (BR) along with a decrease in miscarriage rates (SAB) and ectopic pregnancies among IVF patients. A study of 131 women with poor prognosis found no significant difference in PR between the Acu ($n=48$) and non-Acu groups ($n=83$) (50% vs. 45%).⁵⁷ However, the Acu group demonstrated statistical significance in SAB (8% vs. 14%), ectopic pregnancies (0% vs. 9%), and BR (21% vs. 16%). In a similar study,⁵⁸ this time with good-prognosis patients, the Acu group ($n=53$), compared with the non-Acu group ($n=61$), demonstrated significant improvement in PR (51% vs. 36%), SAB (8% vs. 20%), and ectopic pregnancies (0% vs. 9%) ($p < 0.008$). The Acu group had a 23% increase

in BR. Finally, Stener-Victorin et al.⁶¹ found that the Acu group ($n=75$) had significantly higher implantation rates (27.2% vs. 16.3%) and BR (41% vs. 19.4%) than the non-Acu group ($n=75$).

Discussion

The results of these studies are promising, but it is important to note that acupuncture protocols generally do not reflect TCM clinical practice. In many of the summarized published studies, very few acupuncture treatments, often fewer than three, were performed. Out of the seven summarized studies, only the most recent⁵⁶ did not follow a fixed protocol. The patients were administered acupuncture in which three to five points were chosen depending on TCM clinical symptoms and pattern diagnosis. Furthermore, the patients were required to have a minimum of 12 treatments, almost half of them receiving more than 13 treatments, a stark contrast from those in the majority of the other studies. Kong and Hughes⁵⁶ demonstrated significantly higher IVF success rates than those in the studies with fixed protocols and limited treatments.

According to TCM, one course of treatment for female infertility is three months, with efficacy seen within one to three courses of treatment by focusing on regulating the menses.⁶² Furthermore, a fixed protocol by nature directly ignores TCM principles and clinical practice. Acupuncture treatments are based on TCM-specific symptoms and diagnosis; therefore, each treatment for each patient should be tailored to address individual TCM-specific imbalances. However, protocols provide the same treatment for each patient, regardless of the patient's TCM diagnosis.

In addition, many of these protocols involve a questionable choice of acupuncture points and techniques, and a lack thereof for the sake of controlled clinical trials in a medical setting. For example, Westergaard et al.²⁰ concluded

that repeating acupuncture two days after embryo transfer provides no additional benefit. In fact, the control group (Acu2) that received additional acupuncture two days later had a higher (albeit not significantly) early-pregnancy loss than the acupuncture group (Acu1) and the non-Acu group (33% vs. 15% vs. 21%). However, it is important to note that the protocol administered two days after embryo transfer contained two points, LI-4 (*hegu*) and SP-6 (*sanyinjiao*), which are contraindicated in pregnancy⁶³ and may therefore be unsuitable after embryo transfer.

It is necessary for future clinical trials to be true to TCM principles and clinical practice to evaluate the potential greater impact of acupuncture on infertility and IVF success rates. However, it is promising that following even a fixed protocol produces positive results.

Conclusion

The use of acupuncture for infertility as an adjunct therapy to conventional treatment in ART (mainly as an adjunct to IVF) has continued to increase in popularity through evidence-based publications demonstrating clinical efficacy. Although acupuncture is based on ancient medical theory, an increasing

number of published scientific studies show that acupuncture positively impacts fertility and IVF success rates due to possible mechanisms influencing the menstrual cycle through β -endorphin secretion, affecting gonadotropin secretion through their action on GnRH. These possible mechanisms also impact uterine and ovarian blood flow; cytokines; and depression, anxiety, and stress. Retrospective and randomized controlled trials have found that acupuncture has a statistically significant positive impact on IVF success rates, including implantation, pregnancy, and live birth rates, while reducing the number of miscarriages and ectopic pregnancies.

Current scientific data and clinical trials are promising. They show the value and effectiveness of acupuncture as an adjunct therapy for IVF. However, it is necessary for future clinical trials not only to further examine the mechanistic processes involved but also to follow TCM principles and clinical practice to evaluate the true potential impact on IVF success rates. With the increasing body of evidence-based literature demonstrating mechanistic processes and clinical results, acupuncture should be considered as a viable and recommendable adjunct therapy for IVF.

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