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Management of Acupuncture as Adjuvant Therapy for *In Vitro* Fertilization

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ABSTRACT

One treatment option for couples with infertility that enables the highest success rate is *in vitro* fertilization (IVF). With this technique, various causes of infertility can be overcome, whether they are caused by anatomical abnormalities in women or abnormalities of sexual dysfunction in men. Acupuncture, a nonpharmacologic therapy with minimal side-effects, according to various studies is be beneficial for increasing the success of IVF. There are several mechanisms of acupuncture related to this, such as: (1) modulating neuroendocrine factors; (2) increasing blood flow to the uterus and ovaries; (3) modulating immune factors; and (4) reducing stress, anxiety, and depression. Because acupuncture does not have bad side-effects, it is an adjuvant therapy that can be performed at each stage of the IVF procedure to increase the chances of successful IVF.

Keywords: acupuncture, *in vitro* fertilization, infertility

INTRODUCTION

Infertility is defined as failure to achieve pregnancy after 12 months of regular and unprotected sexual intercourse. The condition is caused by the inability to reproduce, both individually and as a couple.[1] The prevalence of infertility ranges from 9% to 18% in the general population.[2] According to a recent study, ~12.5% of women are not able to become pregnant after 12 months of unprotected sexual intercourse.[3]

One of the therapeutic options with the highest success rate for couples with infertility is *in vitro* fertilization (IVF). IVF can be used to overcome various causes of infertility such as anatomical abnormalities in women and sexual dysfunctions in men. The weaknesses of IVF are that it is quite expensive and the preparation time is quite long; therefore, both doctors and patients spend a lot of time preparing as much as possible to make the IVF attempt successful and result in a baby who is born alive.

Acupuncture, a nonpharmacologic therapeutic modality, involves using fine needles at acupuncture points to address medical conditions. This modality can activate nerve fibers and peripheral afferent receptors, produce sensory interactions at various levels of the central nervous system, and release various transmitters and modulators, thus producing anti-inflammatory signals as well as neuroendocrine and neuroimmune signals.[4] Many studies have examined the effects of acupuncture as an adjuvant therapy in IVF, but systematic reviews and meta-analyses still yield controversial results.[3,5–7] The purpose of this review is to describe acupuncture as an adjuvant therapy for IVF based on relatively recent studies.

INFERTILITY

Factors that influence infertility include age; time of coitus; duration of pregnancy attempts; and other factors, such as history of contraception, food, lifestyle habits (smoking, caffeine and alcohol consumption), stress, and anxiety.[8]

Many infertility problems are related to hypothalamic and pituitary dysfunction. This can be caused by structural abnormalities, such as tumors, genetic mutations (whether

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acquired or congenital), lifestyle factors (such as poor nutrition, excessive exercise, smoking, obesity, and chronic stress), and psychologic factors (such as eating disorders and depression).[9]

In female infertility, the etiology of infertility is classified into 4 groups, namely: (1) abnormalities in oocyte production; (2) anatomical abnormalities of the reproductive system that can cause obstructions of the reproductive tract; (3) abnormalities in the implantation process; and (4) other factors that might be important in unexplained infertility (e.g., age, body weight, smoking habits, alcohol and caffeine consumption, emotional and psychologic factors, immunologic abnormalities, and hormonal imbalances).[9]

IN VITRO FERTILIZATION

IVF has been used to manage infertility for ~3 decades. With IVF, various procedures can be performed to help overcome the causes of infertility, including by artificially modifying oocyte production, fertilizing oocytes *in vitro*, and using stimulating hormones to ensure the delivery of 1 or more embryos into the endometrium.

IVF is mostly done in cases of infertility, whether this is caused by female factors or male factors. Indications for female factors include damage to the uterine tube, moderate-to-severe endometriosis, diminished ovarian reserve, uterine cervical disorders, antibodies, and antiphospholipid syndrome. Meanwhile, male factors include hormonal disorders, oligoastenoazoospermia, leukospermia, varicoceles, antisperm antibodies, azoospermia due to obstruction, idiopathic causes, and coitus disorders.[9]

The commonly performed IVF protocol consists of several sequential stages, namely: (1) controlled ovarian stimulation (COS); (2) ovum pick-up (OPU); (3) and embryo transfer (ET).[10] The basis of COS for IVF is administration of exogenous gonadotropins (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]), with or without prior oral hormone therapy. Gonadotropin-releasing hormone (GnRH) agonists or antagonists are given together with FSH to stimulate the ovaries and prevent an increase in premature endogenous LH, which will cause early ovulation. In COS with FSH, factors need to be considered, such as a patient being a poor responder, the individual dosage according to patient characteristics, a natural cycle or mild stimulation, prevention of ovarian hyperstimulation syndrome (OHSS), and cycle monitoring. It is important to identify women who tend to have an excessive response to COS, because it is a major risk factor for OHSS, which can cause morbidity. Final oocyte maturation is triggered by administration of human chorionic gonadotropin, GnRH agonists, or both.[11,12] After COS, OPU is carried out to be fertilized with sperm cells *in vitro*.

Fertilization results in an embryo, which is then transferred into the uterus for implantation onto the endometrium that will enable a positive pregnancy result. During the ET period, when the uterus is in the luteal phase, supplementation with the hormone progesterone is done to improve the pregnancy outcome.[11]

IVF success is assessed by measuring several outcomes, such as clinical pregnancy rate (CPR), ongoing pregnancy rate (OPR), and live-birth rate (LBR).[5,13,14] CPR is defined as a pregnancy diagnosed by ultrasound visualization of one or more gestational sacs or definite clinical signs of pregnancy. LBR is defined as the birth of a baby resulting from fertilization after 20 weeks of gestation, which, after birth shows signs of life, such as heart rate and pulsation of the umbilical cord or muscle movement, regardless of whether the umbilical cord has been broken or the placenta is still attached.[3]

MECHANISMS OF ACUPUNCTURE IN IVF

Understanding the mechanism of acupuncture in increasing IVF success is important, so that evaluation of results can be carried out on clinical trials that assess the effect of acupuncture in IVF.

According to several studies, the success of IVF is better when acupuncture is done not only during ET, but also from the follicular phase to the implantation phase.[14,15] This can be related to the mechanism of acupuncture for improving female infertility through modulation of the hypothalamic–pituitary–ovarian (HPO) axis, estrogen regulation, and increased ß-endorphins to correct the imbalance of the endocrine system. Acupuncture can stimulate ovulation through modulation of the HPO axis in women with anovulatory infertility.

In addition to increasing blood flow to the uterus and ovaries, acupuncture increases endometrial and follicular receptivity, which, in turn, improves the quality of oocytes produced by the follicles, and also helps repair the endometrial lining, which is needed for implantation.[3,6,7] Increasing blood flow is influenced by vascular endothelial growth factor (VEGF), which promotes angiogenesis.[9] It has been reported that acupuncture can reduce uterine contractility to prevent embryo expulsion after ET.[3,6,7] Increasing the quality of oocytes might be related to tumor-necrosis factor–α (TNF-α) levels, wherein acupuncture could reduce TNF-α levels in follicular fluid, reduce apoptosis of granulosa cells, and improve oocyte quality, thereby, increasing pregnancy rates in patients undergoing IVF.[16]

The effect of acupuncture on increasing IVF success is influenced by immune-system modulation. Physiologically, a woman's pregnancy is influenced by the ability to modulate T-helper cell responses properly, and the T-helper cell response is influenced strongly by pregnancy hormones. If there is a dysregulation of T-helper cells, both systemically and at the endometrial or follicular level, pregnancy failure will occur. Acupuncture has been reported to increase Th2 cells both locally and systemically, thus, increasing pregnancy rates.[9]

Furthermore, acupuncture is very useful for reducing stress and anxiety caused by changes in the cortisol hormone and the psychologic effects of IVF itself.[3,9] This mechanism can occur through acupuncture modulating neuropeptide-Y (NPY) levels in the amygdala, increasing ß-endorphin production, suppressing the system's sympathetic nerves, increasing vagus-nerve activity, and increasing levels of neurotropic factors in the hippocampus. In addition, acupuncture affects the hypothalamic–pituitary–adrenal axis so to change the physiologic response to stress. In an IVF program, especially in a patient with long a history of infertility, a woman's psychologic condition influences the IVF success rate greatly.

RESEARCH ON ACUPUNCTURE THERAPY FOR IVF

In 2019, Gillerman et al. conducted a randomized controlled clinical trial on 157 women ages 23–43, to examine the effect of acupuncture therapy on IVF results based on the latest consensus.[17] Acupuncture therapy is performed based on the Delphi consensus, which consists of 3 sessions, namely: (1) between the 6th to 8th day of COS by using acupuncture points ST 29, CV 4, CV 6, SP 6, SP 10, and a maximum of 5 additional points according to the patient's complaint; (2) before ET by using SP 8, SP 10, LR 3, ST 29, CV 4, HT 7/PC 6/Ex-HN 3, and ear *Zhigong*; and (3) after ET by using GV 20, K I3, ST 36, SP 6, PC 6, and ear *Shenmen*. There was a higher LBR and positive pregnancy rate in the acupuncture group, compared to the control group.[14]

A randomized controlled trial study using the same consensus of acupuncture was conducted in 2018 by Smith et al. on 848 female subjects with the aim of seeing the efficacy of verum acupuncture on IVF compared to sham acupuncture.[15] In women undergoing IVF, verum acupuncture did not induce a different LBR compared to sham acupuncture.

A retrospective study conducted in 2017 by Seto et al. examined the effects of acupuncture therapy on the day of ET on IVF results.[13] The acupuncture intervention was 2 sessions of manual acupuncture, which were before and after ET for 25 minutes. Before ET, the acupuncture points used were PC 6, SP 8, LR 3, GV 20, and ST 29; and after ET, the acupuncture points used were ST 36, SP 6, SP 10, and LI 4. In 596 subjects undergoing acupuncture (370 with fresh embryos and 226 with frozen-thawed embryos), there were higher pregnancy rates and LBRs in the acupuncture group, compared with the placebo group. In addition, there were fewer pregnancy complications (such as gestational hypertension and diabetes) in the acupuncture group, compared with the placebo group.

In 2017, Qu, et al. conducted a randomized controlled clinical trial on 481 infertile patients undergoing IVF.[18] Transcutaneous electrical acupoint stimulation (TEAS) was carried out just before OPU and 2 hours after ET at acupoints SP 10, SP 8, LR 3, ST 36, Ex-CA 1, CV 4, PC 6, and CV 12. The treatment group was divided into 3 groups, namely TEAS at 2 Hz, TEAS at 100 Hz, and TEAS at 2/100-Hz. The assessed outcomes were oocyte quality, pregnancy rate, implantation rate, and LBR. TEAS at 2/100 Hz increased the success of IVF by increasing NPY levels in follicular fluid.

In 2017, Morin et al conducted a randomized controlled clinical trial to examine the effects of laser acupuncture on IVF success.[19] This study involved 4 groups: (1) needle acupuncture; (2) laser acupuncture; (3) laser sham; (4) and control. The points used in both needle and laser acupuncture were: (1) before ET, PC 6, SP 8, LR 3, GV 20, and ST 29; and (2) after ET, ST 36, SP 6, SP 10, and LI 4. In addition, ear acupuncture was performed at the ear points 55 (*Shenmen*), 58 (*Zhigong*), 22 (*Neifenmi*), and 34 (*Naodian*). The laser acupuncture group had the highest implantation rate, compared to the other 3 groups, while the pregnancy rates and LBRs were not significantly different.

A systematic review and meta-analysis in 2017, by Qian et al., reported the effects of acupuncture on IVF.[7] This study included randomized controlled trials (RCTs) with treatment groups receiving manual acupuncture, electroacupuncture (EA), auricular acupuncture, or other forms of acupuncture, whereas the control groups had no treatment, sham acupuncture, and/or placebo acupuncture. The outcomes assessed in this study were biochemical pregnancy rate (BPR), CPR, LBR, and OPR. After the authors analyzed the results of the 30 RCTs in the review—with a total of 6344 participants—it was concluded that acupuncture could increase CPR in patients undergoing IVF. Meanwhile, if the study was restricted in Asian and non-Asian populations, the EA results were better for increasing IVF success, compared to other methods.

A systematic review and meta-analysis in 2015 by Shen et al. produced controversial results.[6] These authors evaluated the effect of acupuncture on IVF success RCTs.[6] The analysis included 21 RCTs were included with a total of 5428 participants. Acupuncture did not have significant effects on CPR when performed only during ET, whereas if acupuncture was performed during the follicular phase, 25 minutes before and after ET, and during the implantation phase, acupuncture did increase IVF success.

In 2012, Zheng et al. conducted a systematic review and meta-analysis of RCTs that examined the effects of acupuncture on IVF.[20] The primary outcomes studied were CPR and LBR. The review included 24 RCTs, with a total of 5807 participants. Acupuncture increased CPR and LBR in women undergoing IVF.

An RCT by Moy et al., in 2011, examined the effect of verum acupuncture versus sham acupuncture on pregnancy rates of women undergoing IVF.[21] The trial had 160 subjects undergoing IVF, who were randomized into 2 groups: (1) a verum acupuncture group and (2) a sham acupuncture group. The intervention involved acupuncture 25 minutes before and after ET. The points selected before ET were CV

Table 1. Acupuncture Modalities in Various Studies of Acupuncture on IVF

	Gillerman et al. 2019[14]	Smith et al. 2018[15]	Seto et al. 2017[13]	Qu et al. 2017[18]	Morin et al. 2017[19]	Qian et al 2017[7]	Shen et al. 2015[6]	Zheng et al. 2012[20]	Moy et al. 2011[21]
Manual acupuncture	√	√	√		√	√	√	√	√
Electroacupuncture				√		√	√	√	
Laser acupuncture					√	√	√	√	
Auricular acupuncture	√	√			√	√			√

IVF, *in vitro* fertilization.

6, SP 8, LR 3, ST 29, and GV 20, while the points after ET were ST 36, SP 6, SP 10, and LI 4. Ear acupuncture was also performed at the *Shenmen*, Sympathetic, Uterine, and Endocrine points. There were no significant differences in pregnancy rates in the 2 treatment groups. See Table 1.

ACUPUNCTURE AS AN ADJUVANT THERAPY FOR IVF

The role of acupuncture in increasing the success of IVF can be through several mechanisms in accordance with the basic understanding of female reproductive physiology. First, acupuncture can modulate neuroendocrine factors through the HPO axis, which will correct the imbalance of the endocrine system. Second, acupuncture can increase blood flow to the uterus and ovaries via VEGF, which will improve the quality of oocytes and improve the endometrial lining for preparation of embryo implantation.[3,6,7] Third, acupuncture can modulate the immune system, through regulation of Th2 cells, both locally at the level of the follicles and endometrium, as well as systemically.[9] Fourth, acupuncture is very useful for reducing stress and anxiety caused by changes in cortisol levels and caused by the psychologic effects of IVF.[3,9]

According to what has been reported in the literature about the effects of acupuncture on IVF success, acupuncture can be performed at every stage of IVF. Types of acupuncture used in IVF include manual acupuncture, EA, and laser acupuncture. Meanwhile, according to the latest consensus on acupuncture therapy for IVF, the modality used is manual acupuncture.[14,15] One systematic review comparing various acupuncture modalities (manual acupuncture, EA, laser acupuncture, and ear acupuncture),[7] showed that EA produced a higher IVF success rate than the other forms of acupuncture did.

The choice of acupuncture points chosen in IVF therapy depends on the IVF procedure performed. Acupuncture can be done on day 6–8 of COS by using ST 29 (*Guilai*), CV 4 (*Guanyuan*), CV 6 (*Qihai*), SP 6 (*Sanyinjiao*), SP 10 (*Xuehai*), and a maximum of 5 additional points according to the patient's complaints. Acupuncture is also performed before OPU by using SP 10 (*Xuehai*), SP 8 (*Diji*), LR 3 (*Taichong*), ST 36 (*Zusanli*), Ex-CA 1 (*Zhigong*), CV 4 (*Guanyuan*), PC 6 (*Neiguan*), and CV 12 (*Zhongwan*). On the day of ET, acupuncture can be performed before ET with SP 8 (*Diji*), SP 10 (*Xuehai*), LR 3 (*Taichong*), ST 29 (*Guilai*), CV 4 (*Guanyuan*), HT 7/PC 6/Ex-HN 3, and ear *Zhigong*; and after ET with acupoints GV 20 (*Baihui*), KI 3 (*Taixi*), ST 36 (*Zusanli*), SP 6 (*Sanyinjiao*), PC 6 (*Neiguan*), and ear *Shenmen*. See Figure 1.

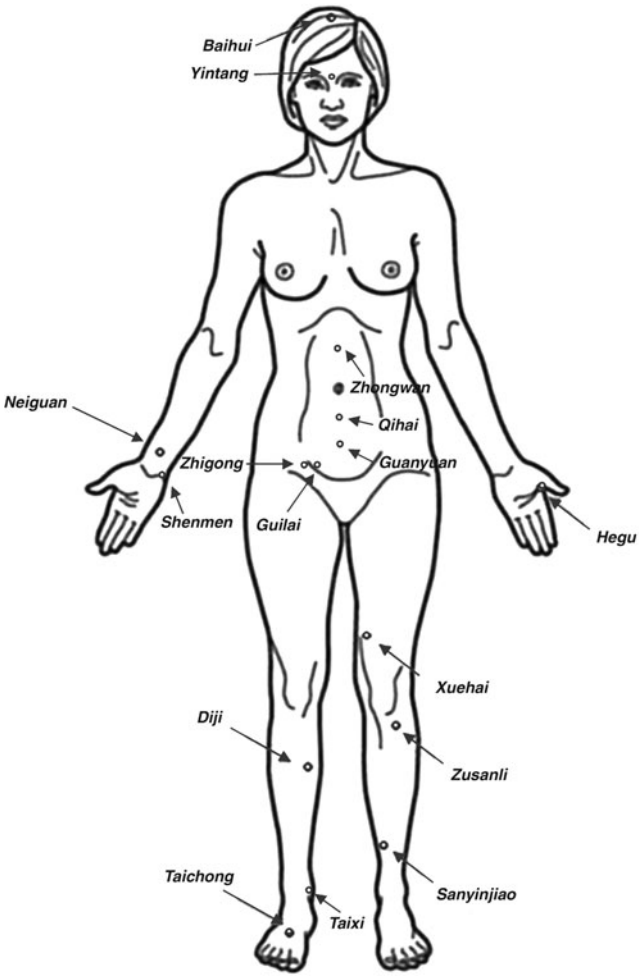

FIG. 1. Acupuncture points used for *in vitro* fertilization.

CONCLUSIONS

Acupuncture can increase the success of IVF through the effects of acupuncture at various stages of IVF procedures. At the stage of controlled ovarian stimulation, acupuncture can help increase blood flow to the ovaries, which improves the quality of oocytes further so that good embryonic quality is obtained. At the stage of OPU, which is treated transvaginally, acupuncture is useful for reducing pain. In the ET stage and the implantation phase, acupuncture can prepare the endometrial lining for embryo implantation, modulate immune factors, and reduce anxiety, which can also result in a positive pregnancy rate and increase IVF success. Because acupuncture is known to have minimal side-effects, it can be used as an adjuvant therapy that can be performed at each stage of IVF to increase IVF success.

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REFERENCES

1. Zegers-Hochschild F, Adamson GD, Dyer S, et al. *The International Glossary on Infertility and Fertility Care, 2017. Hum Reprod*. 2017;32(9):1786–1801.
2. Hanson B, Johnstone E, Dorais J, Silver B, Peterson CM, Hotaling J. Female infertility, infertility-associated diagnoses, and comorbidities: A review. *J Assist Reprod Genet*. 2017; 34(2):167–177.
3. Xie ZY, Peng ZH, Yao B, et al. The effects of acupuncture on pregnancy outcomes of *in vitro* fertilization: A systematic review and meta-analysis. *BMC Complement Altern Med*. 2019;19(1):131.
4. Cho ZH, Hwang SC, Wong EK, et al. Neural substrates, experimental evidences *[sic]* and functional hypothesis of acupuncture mechanisms. *Acta Neurol Scand*. 2006;113(6):370–377.
5. Smith CA, Armour M, Shewamene Z, Tan HY, Norman RJ, Johnson NP. Acupuncture performed around the time of embryo transfer: A systematic review and meta-analysis. *Reprod Biomed Online*. 2019;38(3):364–379.
6. Shen C, Wu M, Shu D, Zhao X, Gao Y. The role of acupuncture in *in vitro* fertilization: A systematic review and meta-analysis. *Gynecol Obstet Invest*. 2015;79(1):1–12.
7. Qian Y, Xia XR, Ochin H, et al. Therapeutic effect of acupuncture on the outcomes of *in vitro* fertilization: A systematic review and meta-analysis. *Arch Gynecol Obstet*. 2017;295(3):543–558.
8. Bayer SR, Alper MM. *Boston IVF Handbook of Infertility: A Practical Guide for Practitioners Who Care for Infertile Couples.* London: CRC Press; 2007.
9. Anderson BJ, Haimovici F, Ginsburg ES, Schust DJ, Wayne PM. *In vitro* fertilization and acupuncture: Clinical efficacy and mechanistic basis. *Altern Ther Health Med*. 2007;13(3):38–48.
10. Ikechebelu JI, Eleje GU, Ibadin K, Joe-Ikechebelu NN, Nwaefulu K, Okwelogu SI. Outcome of *in vitro* fertilization procedure at a private fertility center in Nnewi, South-East Nigeria. *Afr J Infertility Assist Conception*. 2016;1(1):2–5.
11. Farquhar C, Marjoribanks J, Brown J, et al. Management of ovarian stimulation for IVF: Narrative review of evidence provided for World Health Organization guidance. *Reprod Biomed Online*. 2017;35(1):3–16.
12. Nargund G, Datta AK, Fauser BC. Mild stimulation for *in vitro* fertilization. *Fertil Steril*. 2017;108(4):558–567.
13. Seto MT, Cheung KW, Lo TK, Ng EH. Pregnancy outcomes of women randomized to receive real versus placebo acupuncture on the day of fresh or frozen-thawed embryo transfer. *Eur J Obstet Bynecol Reprod Biol*. 2017;218:119–122.
14. Gillerman K, Kulkarni A, Shah A, Gudi A, Homburg R. The impact of acupuncture on IVF success rates: A randomised controlled trial. *Fertil Sci Res*. 2019;5(2):48–54.
15. Smith CA, de Lacey S, Chapman M, et al. Effect of acupuncture vs sham acupuncture on live births among women undergoing *in vitro* fertilization: A randomized clinical trial. *JAMA*. 2018;319(19):1990–1998.
16. Jing L, Wei C, Wei S, Ji W. Effect of electroacupuncture on egg quality and tumor necrosis factor-α of patients with polycystic ovarian syndrome. *World J Acupunct Moxibustion*. 2014;24(3):9–15.
17. Smith CA, Grant S, Lyttleton J, Cochrane S. Using a Delphi consensus process to develop an acupuncture treatment protocol by consensus for women undergoing assisted reproductive technology (ART) treatment. *BMC Complement Altern Med*. 2012;12:88.
18. Qu F, Wang FF, Wu Y, et al. Transcutaneous electrical acupoint stimulation improves the outcomes of *in vitro* fertilization: A prospective, randomized and controlled study. *Explore (NY)*. 2017;13(5):306–312.
19. Morin SJ, Frattarelli JL, Franasiak JM, Juneau CR, Scott Jr RT. Laser acupuncture before and after embryo transfer improves *in vitro* fertilization outcomes: A four-armed randomized controlled trial. *Med Acupunct*. 2017;29(2):56–65.
20. Zheng CH, Huang GY, Zhang MM, Wang W. Effects of acupuncture on pregnancy rates in women undergoing *in vitro* fertilization: A systematic review and meta-analysis. *Fertil Steril*. 2012;97(3):599–611.
21. Moy I, Milad MP, Barnes R, Confino E, Kazer RR, Zhang X. Randomized controlled trial: Effects of acupuncture on pregnancy rates in women undergoing *in vitro* fertilization. *Fertil Steril*. 2011;95(2):583–537.

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