

Review:

Use of electroacupuncture and transcutaneous electrical acupoint stimulation in reproductive medicine: a group consensus*

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Abstract: With the rapid development of assisted reproductive technology, various reproductive disorders have been effectively addressed. Acupuncture-like therapies, including electroacupuncture (EA) and transcutaneous electrical acupoint stimulation (TEAS), become more popular world-wide. Increasing evidence has demonstrated that EA and TEAS are effective in treating gynecological disorders, especially infertility. This present paper describes how to select acupoints for the treatment of infertility from the view of theories of traditional Chinese medicine and how to determine critical parameters of electric pulses of EA/TEAS based on results from animal and clinical studies. It summarizes the principles of clinical application of EA/TEAS in treating various kinds of reproductive disorders, such as polycystic ovary syndrome (PCOS), pain induced by oocyte retrieval, diminished ovarian reserve, embryo transfer, and oligospermia/asthenospermia. The possible underlying mechanisms mediating the therapeutic effects of EA/TEAS in reproductive medicine are also examined.

Key words: Electroacupuncture (EA); Transcutaneous electrical acupoint stimulation (TEAS); Reproductive medicine; Group consensus

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1 Introduction

Infertility, as a key reproductive disorder, is listed by the World Health Organization (WHO) as one of the top three diseases, affecting 10%–15% married couples worldwide (Boivin *et al.*, 2007). Although some reproductive disorders have been effectively addressed with the development of assisted reproductive technology (ART) (Bjelica and Nikolic, 2015), the pregnancy rate is still unsatisfactory. Acupuncture has been used in treating gynecological and reproductive disorders for thousands of years (Zhou and Qu, 2009). Electroacupuncture (EA) and transcutaneous electrical acupoint stimulation (TEAS), the modern therapies derived from traditional acupuncture, have received increasing attention in recent years (Han and Ho, 2011; Johansson *et al.*, 2013). The present group consensus is intended to provide guidelines for physicians and practitioners using EA or TEAS in the treatment of reproductive disorders (Li *et al.*, 2016). Twenty experts were involved in this study for the group consensus with Delphi methods, which took nine weeks to reach consensus.

EA adds an electrical stimulation pulse to traditional acupuncture needles. The sensory input can be enhanced through the pulsatile current applied to the acupoints. TEAS uses self-adhesive electrodes placed on the surface of acupoints, instead of needles for electrical stimulation. Acupuncture, EA, and TEAS can activate nerve endings or fibers and generate action potentials (Han, 2003; Kagitani *et al.*, 2005; Michikami *et al.*, 2006; Zhao, 2008). The resulting stimulation signals, which are transmitted to the spinal cord and brain, stimulate the central nervous system to generate specific chemical mediators to induce relevant physiological effects. Acupuncture, EA, and TEAS are all attributed to the “peripheral neuromodulation” approach (Han and Terenius, 1982; Wang *et al.*, 2008; Zhao, 2008), by which nerve endings can be activated and action potentials can be generated. The underlying mechanisms of EA or TEAS are not completely understood. It is likely that a wide variety of biological actions of EA and TEAS are mediated by multiple and different mechanisms (Zhao, 2008). The EA-induced analgesia has been studied extensively in the last decades and served as an example how this ancient technique can be interpreted and

employed by modern biomedical science. It is generally accepted that the activation of sensory nerve terminals by either mechanical and/or electrical stimulation is transmitted to various critical pain regulatory centers in the spinal cord and brain to generate specific chemical mediators including endorphins. The descending pain modulator pathways are then activated, to induce an analgesic effect. While there are many data collected from research in acupuncture analgesia, increasing attention has also been paid to other areas such as its application in ART (Cui *et al.*, 2011; Rashidi *et al.*, 2013). This article is intended to summarize the existing data and develop a consensus in application of TEAS in ART. The pulsatile current can be characterized by at least three important parameters: frequency, pulse width, and intensity (Han, 2003). Effective frequency ranges from 2 to 100 Hz for EA and TEAS. It has been reported that stimulation with different frequencies may sometimes generate totally different biological effects. For example, low-frequency (2 Hz) electrical stimulation promotes the production and release of enkephalin in the central nervous system, while high-frequency (100 Hz) electrical stimulation promotes the production and release of dynorphins in the spinal cord (Han *et al.*, 1991). The pulse width, which should range from 0.2 to 0.6 ms, significantly affects the feelings generated by the EA stimulation (Chen and Han, 1992; Han, 2011). The intensity of the current ranges from 0.5 to 5.0 mA for EA, and 5 to 30 mA for TEAS (5–10 mA for upper limbs, 10–30 mA for lower limbs and trunk). For the duration of each treatment, a 30-min program is commonly used in most treatment regimen according to the clinical experience and the relevant scientific evidence (Research Group of Acupuncture Anesthesia, Peking Medical College, 1973; Wang *et al.*, 1992; Cheing *et al.*, 2003). The interval between two treatments is also a matter of consideration. Acute pain may need just one or two sessions of treatment (Liu *et al.*, 2007), while chronic disorders of the endocrine system may need more sessions, for example, 1–3 times per week for several weeks or even months (Zhan and Wang, 2008), depending on the severity of the symptoms.

It should be noted that although the selection of acupoints is mainly determined by the meridian and collateral theory in traditional Chinese medicine (TCM), the outcome measures as well as the parameter

design of EA and TEAS are based on modern biomedical research.

2 Principles of selecting acupoints

The “kidney-Tian Gui-Chong Ren-uterus” theory of TCM resembles the “hypothalamic-pituitary axis” theory in modern medicine. The selection of acupoints is based on the mechanisms of infertility as follows.

2.1 Ovarian hypofunction

The deficiency of kidney, disharmony of Chong and Ren, disorder of Qi and blood are the basic pathological situation. Thus invigorating the kidney, promoting Qi and blood, and regulating Chong and Ren are the principles for selecting acupoints.

1. Acupoints for invigorating the spleen and stomach, tonifying Qi and activating blood: Guanyuan (CV 4), Tianshu (ST 5), and Zhongji (CV 3).

2. Acupoints for nourishing the heart and activating blood, soothing the liver and regulating Qi: Zigong (EX-CA1) and Sanyinjiao (SP 6).

3. Acupoints for warming or nourishing the kidney to strengthen kidney essence: Mingmen (GV 4), Shenshu (BL 23), and Yaoyangguan (GV 3).

2.2 Promoting embryo implantation

Acupoint selection is according to the principle of invigorating the kidney and nourishing blood.

1. Acupoints for activating blood and smoothing the collaterals prior to embryo transfer (ET): Guilai (ST 29), Zigong (EX-CA1), Xuehai (SP 10), and Diji (SP 8).

2. Acupoints for invigorating the spleen and kidney, tonifying Qi and soothing mind after ET: Zhongwan (CV 12), Guanyuan (CV 4), Zusanli (ST 36), Taixi (KI 4), and Shenshu (BL 23).

2.3 Ovulation induction

Based on the principle of “to treat deficiency with tonification, fullness with relief, and prolonged stagnation with elimination”, acupoint selection should be in accordance with the effect of invigorating the kidney, soothing the liver, invigorating blood, and regulating Chong and Ren: Tianshu (ST 25), Guanyuan (CV 4), Zhongji (CV 3), Zigong (EX-CA1), and Sanyinjiao (SP 6).

2.4 Asthenospermia and oligospermia

TCM believes that asthenospermia and oligospermia are caused by kidney deficiency, spleen and stomach weakness. Based on the theory of “to treat deficiency with tonification”, acupoint selection depends on the effect of invigorating the kidney: Shenshu (BL 23), Guanyuan (CV 4), Huiyin (CV 1), and Zusanli (ST 36).

3 Mechanism mediating the effects of acupuncture, EA, and TEAS

In terms of modern medicine, the therapeutic benefits of acupuncture on a variety of clinical diseases seem to be mainly attributed to the regulation of the neuroendocrine system and the blood flow to reproductive organs. For example, in the condition of low sex hormone like ovarian dysfunction or menopausal syndrome, acupuncture can activate aromatase, promote the generation of neuropeptide Y (NPY), and improve the local blood flow of the ovary, enhancing the utilization efficiency of estrogens, and the apparent improvement of the reproductive systems is manifested as inhibition of the elevations of follicle stimulating hormone (FSH) and luteinizing hormone (LH) (Stener-Victorin *et al.*, 2003; Zhao *et al.*, 2005). The effect of acupuncture on polycystic ovary syndrome (PCOS), a state of high sex hormone function, is likely to be achieved by promoting the release of β -endorphin and inhibiting the generation of gonadotropin-releasing hormone (GnRH) in the hypothalamus (Stener-Victorin and Lindholm, 2004), thereby reducing the blood level of FSH and LH (Wildt *et al.*, 1993). Acupuncture also plays a role in increasing the release of β -endorphin, endomorphins, enkephalins, serotonin, and other neurochemical substances to relieve pain and mental stress and reduce anxiety and/or depression of patients (Han and Terenius, 1982; Han *et al.*, 1991; Han, 2003). Therefore, acupuncture can improve the function of the reproductive system and induce a positive feedback effect on the hypothalamic-pituitary-gonad (HPG) axis due to the effect on central and peripheral neurobiological key points. The selection of the electrical stimulation time, location, and stimulation parameters (frequency and intensity) varies for different diseases.

4 Outcome measures in clinical trials for EA and TEAS

Many different aspects could be taken into consideration in evaluation of the ovarian function. The changes in serum hormone levels are widely used to assess the ovarian reserve function. The most frequently used biomarkers include FSH, LH, basal FSH/LH, estradiol (E_2), inhibin B, anti-mullerian hormone (AMH). The ovarian size and antral follicle count (AFC) also provide valuable information (Erdem *et al.*, 2003; Mutlu and Erdem, 2012).

Many values and indexes help to estimate the perfusion of the ovary, including peak systolic velocity (PSV), end diastolic velocity (EDV), PSV/EDV of ovarian interstitial blood flow, resistance index (RI), pulsatility index (PI), vascular index (VI), blood flow index (FI), and vascular blood flow index (VFI) of ovarian stromal blood flow (Schild *et al.*, 2000; Polisca *et al.*, 2013; Hançerlioğullaria *et al.*, 2015). The perfusion state of the ovary correlated closely to the ovarian reserve function. In addition, dynamic tests including the clomiphene stimulation test and the GnRH stimulation test are also commonly used to reflect ovarian functions (Griesinger *et al.*, 2016).

Proper perfusion of the endometrial membrane has been considered as an important permitting factor allowing embryo implantation to occur. Various methods have been developed to determine uterine blood flows and various formulae have been used to calculate the resistance of the blood vessels. Endometrial receptivity is usually evaluated by thickness and type of endometrium and PSV, EDV, PSV/EDV and RI of the endometrial spiral artery under transvaginal ultrasound assessment (Zhang *et al.*, 2016). The expressions of pinopodes, estrogen receptor, progesterone receptor, cytokines related to embryo implantation integrin family, such as homeobox A10 (HOXA10), heparin binding epidermal growth factor, and leukemia inhibitory factor, are also useful markers (Achache and Revel, 2006).

Sperm quality is commonly evaluated by a semen routine (sperm quantity, motility, and morphology), seminal plasma biochemistry (seminal plasma fructose and α -glucosidase), and DNA fragmentation (Esteves and Chan, 2015).

ART outcomes include ovulation rate (OR), metaphase II oocytes rate, fertilization rate, good-

quality embryo rate, implantation rate, biochemical pregnancy rate, clinical pregnancy rate, miscarriage rate, and live birth rate (Neyens *et al.*, 2016).

5 Application of EA/TEAS in treating PCOS

Based on the basic theory of TCM, acupoints mostly belong to the meridians of Du and Ren, and stomach and spleen in the treatment of PCOS. The vital acupoints include Guanyuan (CV 4), Zhongwan (CV 12), Tianshu (ST 25), Zusanli (ST 36), and Sanyinjiao (SP 6). In addition, acupoints in other meridians, such as Zigong (EX-CA1) and Taichong (LR 3), are also commonly used in clinical practice (Cui *et al.*, 2011; Johansson *et al.*, 2013; Lei and Feng, 2014).

In the treatment of PCOS, the EA/TEAS with low frequency (2 and 20 Hz) is more prevalent; the range for intensity is determined by patient tolerance; and the course of treatment ranges from 1 to 6 months according to the patient's condition (Jedel *et al.*, 2011). Too many therapeutic indexes, as menstrual cycles, body mass index (BMI), LH/FSH, OR, and pregnancy rate, are used to evaluate the curative effect of acupuncture on PCOS, which may lead to confused therapeutic assessments (Wu *et al.*, 2016).

6 Application of EA/TEAS during oocyte retrieval for analgesia

Up to now, the biggest highlight of the application of EA/TEAS is linked to analgesia. Acupuncture is acknowledged as one of the analgesic methods in the field of pathological pain, including inflammatory pain and neuropathic pain. Abundant laboratory findings revealed that acupuncture can mobilize opioid peptides. Further, EA with different frequencies can specifically activate different kinds of opioid peptides as mentioned above to relieve pain. The time period needed for the full expression of the analgesic effect in humans is 30 min (Research Group of Acupuncture Anesthesia, Peking Medical College, 1974). The effect remained during the period of stimulation, and started to decrease exponentially along with the termination of stimulation. When the

electrical stimulation lasted for more than 40–60 min, the analgesic effect started to decline gradually, a phenomenon known as “acupuncture tolerance” (Chen and Han, 1992; Cheing *et al.*, 2003). It should also be pointed out that one single session of EA merely increases the release of brain opioid peptides, while consecutive sessions of EA obviously up-regulate both the mRNA level and the content of opioid peptides in the central nervous system (Liang *et al.*, 2010). Taken together, 30 min seemed to be convenient for a single session and multiple sessions are necessary for chronic disorders.

While the analgesic effect of EA/TEAS is mainly mediated by opioid peptides and can be blocked by opioid receptor antagonist naloxone, this may not be the sole determinant for acupuncture-induced analgesia (Sun *et al.*, 2003). Monoamines have been known to play significant roles (Zhang *et al.*, 2012). Recent studies showed that signal integrators, such as transient receptor potential vanilloid type 1 and purinergic receptor P2X3, play important roles in acupuncture analgesia (Xu *et al.*, 2011; Jiang *et al.*, 2013).

Concerning the choice of acupoints, Hegu (LI 4) is the most commonly used acupoint for analgesia, and Neiguan (PC 6) is known to be effective for antiemetic effect (Lee *et al.*, 2013; Zhang *et al.*, 2013). The combined stimulation of Hegu (LI 4) and Neiguan (PC 6) may meet the needs of the present study.

7 Application of EA/TEAS in treating diminished ovarian reserve

According to TCM, the pathological situation of ovarian dysfunction is “deficiency of kidney, disharmony of Chong and Ren, stagnation of Qi and blood”. Therefore, invigorating kidney, promoting Qi, circulating blood, and regulating Chong and Ren are the principles for the treatment of diminished ovarian reserve (DOR). The commonly used acupoints include Guanyuan (CV 4), Tianshu (ST 25), Zhongji (CV 3), Zigong (EX-CA1), Sanyinjiao (SP 6), Shenshu (BL 23), Mingmen (GV 4), and Yaoyangguan (GV 3) (Mi *et al.*, 2013). EA at 2 Hz has a significant effect in strengthening the ovarian reserve (Qiu *et al.*, 2012).

8 Application of EA/TEAS in improving the pregnancy rate after ET

A previous study found a single session of TEAS for 30 min after ET could increase the pregnancy rate by 13% (Zhang *et al.*, 2011). Two sessions of TEAS (24 h before ET and 30 min after ET) could increase it by 20% (Zhang *et al.*, 2011). Low frequency (2 Hz) electric stimulation is better than high frequency (100 Hz) stimulation, and the acupoints located in the trunk, such as Guilai (ST 29), Zigong (EX-CA1), Guanyuan (CV 4), and Shenshu (BL 23), are more helpful for embryo implantation and pregnancy than acupoints located in the limbs, such as Xuehai (SP 10), Dijii (SP 8), Zusanli (ST 36), and Taixi (KI 3). Patients at age of 30–45 years find more benefits than those below 30 years.

9 Application of EA/TEAS in treating oligospermia and asthenospermia

In a randomized, single-blind, placebo-controlled study reported by Dieterle *et al.* (2009), a significantly higher percentage of motile sperm, but no effect on sperm concentration, was found after acupuncture, compared with placebo acupuncture. In a previous small sample clinical study, TEAS also could improve the sperm activity and the ratio of forward motile sperm in patients with oligospermia and asthenospermia after 2-month treatment at acupoints with Shenshu (BL 23), Zusanli (ST 36), and Guanyuan (CV 4) (Jin *et al.*, 2016b). In the rat model of asthenozoospermia induced by intragastric administration of ornidazole (400 mg/(kg·d)) once a day for 14 d, EA was significantly effective on all of the sperm motility indexes but not the sperm concentration, and EA treatment once every other day was more effective than treatment once per day (Jin *et al.*, 2016a). TEAS can increase the seminal content of neutral α -glucosidase, fructose, and the level of zinc, which maybe one of the mechanisms of EA/TEAS acting on sperm motility.

10 Conclusions

The use of EA/TEAS combined with modern reproductive medicine makes acupuncture more

popular in the field of assisted reproduction. In particular, TEAS is widely favored by patients owing to its advantages of easy-operation, non-invasive nature, and painless procedures. It might be regarded as a model of the integrated application of TCM and modern medicine.

Compliance with ethics guidelines

Fan QU, Rong LI, Wei SUN, Ge LIN, Rong ZHANG, Jing YANG, Li TIAN, Guo-gang XING, Hui JIANG, Fei GONG, Xiao-yan LIANG, Yan MENG, Jia-yin LIU, Li-ying ZHOU, Shu-yu WANG, Yan WU, Yi-jing HE, Jia-yu YE, Song-ping HAN, and Ji-sheng HAN declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题目: 电针和经皮穴位电刺激技术在生殖医学中的应用: 专家共识

概要: 本文从传统针刺治疗不孕症的选穴依据与现代电针/经皮穴位电刺激技术的相关原理着手, 从最优刺激参数选择、穴位辨证、疗程与治疗次数的确定及基本原理等方面阐述了电针/经皮穴位电刺激技术在多囊卵巢综合症、取卵镇痛、卵巢储备功能降低、胚胎移植以及男性少/弱精症等生殖领域中的具体应用。首次对电针/经皮穴位电刺激技术在生殖领域优势病种中的应用进行了系统的分析和总结, 在最优刺激参数选择、穴位辨证、疗程与治疗次数的确定等方面提出了一系列专家共识, 并为临床实践提供了指导意见和理论依据。

关键词: 电针; 经皮穴位电刺激; 生殖医学; 专家共识