THE JOURNAL OF
Obstetrics and Gynaecology Research
The official Journal of Asia and Oceania Federation of Obstetrics and Gynaecology
Japan Society of Obstetrics and Gynecology
doi:10.1111/jog.12810 J. Obstet. Gynaecol. Res. Vol. 41, No. 12: 1905–1911, December 2015

Effects of transcutaneous electrical acupoint stimulation on ovarian reserve of patients with diminished ovarian reserve in *in vitro* fertilization and embryo transfer cycles

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Abstract

Aim: The aim of this study was to investigate the effect of transcutaneous electrical acupoint stimulation (TEAS) on ovarian reserve in patients with diminished ovarian reserve undergoing *in vitro* fertilization and embryo transfer.

Material and Methods: A total of 240 patients were randomly divided into the Han's acupoint nerve stimulator TEAS treatment (TES), comforting false Han's placebo (FHP), artificial endometrial cycle treatment (AEC), and control (CON) groups.

Results: Fifty-six patients in TES, 56 in FHP, 54 in AEC, and 60 in CON fulfilled the study, respectively. Antral follicle count and anti-Müllerian hormone levels were increased, whereas the estradiol level, follicle-stimulating hormone level, and follicle-stimulating hormone/luteinizing hormone ratio were significantly decreased after treatment in the TES and AEC groups. After treatment, the number of oocytes retrieved and average number of embryos transferred were higher in the TES and AEC than in the CON and FHP groups. Clinical pregnancy rate in the TES group was markedly higher than values obtained for the other three groups.

Conclusion: TEAS and AEC treatments could improve basal endocrine levels in patients, and increase the number of oocytes retrieved and high-quality embryos. TEAS treatment could improve the clinical pregnancy rate in patients with decreased ovarian reserve during *in vitro* fertilization and embryo transfer cycles.

Key words: acupuncture, follicle-stimulating hormone receptor, *in vitro* fertilization, poor ovarian reserve, transcutaneous electrical acupoint stimulation.

Introduction

The use of acupuncture for the treatment of female infertility has a long history. It was first proposed for the treatment of gynecological diseases based on the syndrome differentiation of traditional Chinese medicine by three gynecological monographs in a book named *Synopsis of Golden Chamber* compiled by Zhang Zhongjing at the end of the Eastern Han Dynasty. Since then, acupuncture has been used to relieve pain during egg retrieval, promote ovulation, improve endometrium, and enhance pregnancy rate by assisted reproductive technology (ART).[1–3]

In recent years, the incidence of infertility has increased. The number of infertile couples who turn to *in vitro* fertilization and embryo transfer (IVF-ET) and related technologies to achieve fertility is on the rise. One of the prerequisites for a successful pregnancy by ART

Received: April 08 2015.
Accepted: June 14 2015.
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is to maintain the ovaries in their natural state or induce adequate quantities of good-quality eggs by superovulation.[4,5] With increased work pressure, delayed child bearing, usage of hormone drugs, and the impact of environmental factors, such as electromagnetic radiation and air pollution, modern women increasingly show decreased ovarian reserve and adverse reactions to gonadotrophin (Gn).[6–9]

Ovarian reserve is the capacity of the primordial follicles in the ovarian cortex to develop into fertilized oocytes. It is usually evaluated by the number of follicles left in the ovarian cortex and the quality of oocytes to reflect a woman's fertility. Among patients undergoing IVF-ET therapy, some with poor ovarian reserve may be associated with female reproductive axis dysfunction and changes in ovarian microenvironment. The poor ovarian reserve manifests as decreased number of follicles in the ovarian cortex and egg quality. Many indicators have been used for the prediction of ovarian reserve, such as age, antral follicle count (AFC), basic endocrine hormones, anti-Müllerian hormone (AMH), uterine artery blood flow, and dynamics testing.[10–13] However, a gold standard for directly predicting ovarian reserve is lacking.

Many patients receiving IVF-ET have decreased ovarian reserve. However, only few effective modalities of treatment have been reported. In the past few years, studies have demonstrated that the transcutaneous electrical acupoint stimulation (TEAS) used for the treatment of patients undergoing IVF-ET can improve egg quality and increase pregnancy rate.[14] TEAS is an acupuncture point stimulation method based on electrical stimulation signal instead of traditional hand-twisted mechanical stimulation. It quantitatively controls stimulation time and stimulus intensity of acupuncture therapy, avoids the pain caused by acupuncture and topical skin tissue injury, and hence is easily accepted by patients. TEAS has been widely used in clinical treatment and research.

The present study aimed to assess the effect of TEAS on the ovarian reserve in patients undergoing IVF-ET.

Methods

Subjects

A total of 240 patients with decreased ovarian reserve undergoing IVF-ET between July 2012 and July 2013 were enrolled at the Reproductive Center in the Second Affiliated Hospital of Shandong Traditional Chinese Medicine University (China). The patients were 26–47 years old and had infertility durations of 1–15 years. In all the patients, infertility was due to tubal-induced gamete transport barriers. Owing to the lack of a standard definition of ovarian reserve, the decreased ovarian reserve in patients was assumed based on previous reports[15–18] if they satisfied at least one of the following conditions: (i) AFCin bilateral ovarian total ≤ 5; (ii) basal follicle-stimulating hormone (FSH) levels ≥ 10 IU/L or FSH/luteinizing hormone (FSH/LH) ratio ≥ 3.6 detected at least twice, or age ≥ 35 years old; and (iii) a history of pelvic surgery. The patients were divided into the Han's TEAS treatment (TES group, $n = 60$), false Han's placebo (FHP, $n = 60$), and artificial endometrial cycle treatment (AEC, $n = 60$) groups. Meanwhile, patients unwilling to receive TEAS or artificial cycle treatment were selected as a control group (CON, $n = 60$). Patients with endometriosis, immune infertility, and intra-cytoplasmic sperm injection for male factor infertility were excluded from this study. The entire study was approved by the Ethics Committee of the Second Affiliated Hospital of Shandong Traditional Chinese Medicine University and all the participants provided written informed consent. The study was registered in the Chinese Clinical Trial Registry, and the Registration number is ChiCTR-TRC-14004523 (available online: http://www.chictr.org/cn/proj/show.aspx?proj=8103).

Artificial endometrial cycle treatment for patients in the AEC group

Patients induced by artificial cycle took oral tablets of estradiol valerate (Progynova, 1 mg/tablet, Bayer Pharmaceutical Company) at a dose of 2 mg/day for 21 days from the 5th day of menstruation. Ten days prior to the last dose, the patients received dydrogesterone tablets (Duphaston, 10 mg/tablet, Abbott Healthcare Products B.V.) at a dose of 20 mg/day for three cycles.

TEAS treatment for patients in the TES group

After the menstrual cycle, patients in the TES group were stimulated by Han's acupoint nerve stimulator (HANS) developed by the Neurological Institute of Peking University (Beijing, China), at a frequency of 2 Hz, and treatment was interrupted prior to the next menstrual cycle (a total of three courses). Prior to the treatment, the patients were required to empty their bladders and lie in the supine position. According to the national standard of China (Standard Acupoints), the acupoints for the TEAS treatment include the following:

1 Guanyuan (RN4): 3 cun below the umbilicus and on the anterior midline.
2 Zhongji (RN3): 4 cun below the umbilicus and on the anterior midline.

3 1Sanyinjiao (SP6): 3 cun above the medial malleolus of the foot and posterior to the edge of the tibia.
4 Zigong (EX-CA1): below the center of the umbilicus of the lower abdomen and 3 cun lateral to Zhongji.
5 Tianshu (ST25): 2 cun lateral to the center of the umbilicus.
6 Shenyu (BL23): below the spinous process of the second lumbar vertebra and 1.5 cun lateral to the posterior midline.
7 Yaoyangguan (DU3): in the depression under the fourth lumbar spinal process and on the posterior midline of the body.
8 Mingmen (DU4): in the depression under the second lumbar spinous process and on the posterior midline of the body.

The electrode patch of Han's device (Medical Technology Co., Ltd. Nanjing Jisheng) was affixed to the above acupoints. Treatment began at a frequency of 2 Hz and a tolerable strength of 20–25 mA; it lasted for 30 min and was given once a day. After three courses, the treatment continued during the ovulation cycle until the day of egg retrieval.

Treatment for patients in the FHP group

The false HANS is a scientific instrument similar to the actual HANS. However, regardless of the displayed electric current, its output current is stable at 5 mA. During the treatment, the electric current was turned on for 3 s and paused for 7 s. So the patients experienced alternate feelings of sensation and numbness in the acupoints. False HANS was used for patients in the FHP group by the same method used for those in the TES group.

Outcome measurements of treatment

Treatment was assessed by AFC, basal estradiol (E2) level, basal FSH level, basal luteinizing hormone (LH) level, AMH level, FSH/LH ratio, ovarian artery resistance index (RI), ovarian artery pulsatility index (PI), and systolic/diastolic flow velocity ratio (S/D). These indicators were measured the day after the menstruation

Table 1 Clinical information on patients in the four groups

Group	CON	AEC	FHP	TES	*P*-value
Cases	60	54	56	56	
Age (years)	36.95 ± 4.34	36.85 ± 5.37	36.88 ± 4.65	36.05 ± 5.48	0.749
Body mass index (kg/m^2)	23.32 ± 2.85	23.87 ± 2.25	23.56 ± 2.63	24.14 ± 4.32	0.568
Duration of infertility (years)	5.25 ± 3.23	4.87 ± 2.43	4.75 ± 2.64	4.44 ± 2.98	0.388
Causes of infertility					
Primary infertility (*n*)	23	20	22	21	
Secondary infertility (*n*)	37	34	34	35	0.896
History of pelvic surgery	24	22	24	23	
Oophorocystectomy	22	21	23	21	0.880
Partial oophorectomy	2	1	1	2	
Antral follicle count	2.53 ± 1.24	2.17 ± 1.34	2.13 ± 1.38	2.13 ± 1.36	0.273
RI	0.63 ± 0.26	0.60 ± 0.11	0.62 ± 0.21	0.63 ± 0.12	0.694
PI	0.69 ± 0.05	0.70 ± 0.06	0.70 ± 0.05	0.69 ± 0.06	0.650
S/D	2.65 ± 0.32	2.66 ± 0.56	2.67 ± 0.43	2.69 ± 0.62	0.968

AEC, artificial endometrial cycle treatment group; BMI, body mass index; CON, control group; FHP, comforting false Han's placebo group; PI, ovary blood flow pulsation index; RI, ovary blood flow resistance index; S/D, systolic/diastolic blood flow velocity ratio; TES, Han's transcutaneous electrical acupoint stimulation treatment group.

Table 2 Indices of endocrine in patients of the four groups

Group	CON	AEC	FHP	TES	$P^{\dagger}$
Cases	60	54	56	56	
Basal E2 level (pmol/L)	201.20 ± 41.74	204.35 ± 59.11	203.50 ± 43.76	200.63 ± 62.78	0.978
FSH level (IU/L)	12.70 ± 2.15	12.95 ± 2.65	12.75 ± 2.45	12.82 ± 2.68	0.957
LH level (IU/L)	4.38 ± 1.27	4.25 ± 1.79	4.56 ± 1.44	4.94 ± 2.26	0.120
T level (nmol/L)	1.07 ± 0.47	1.15 ± 0.46	1.09 ± 0.45	1.10 ± 0.47	0.845
AMH level (ng/mL)	0.74 ± 0.42	0.69 ± 0.37	0.73 ± 0.41	0.74 ± 0.38	0.924

$^{\dagger}\chi^2$-test. AEC, artificial endometrial cycle treatment group; AMH, anti-Müllerian hormone; CON, control group; FHP, comforting false Han's placebo group; E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; T, testosterone; TES, Han's transcutaneous electrical acupoint stimulation treatment group.

cycle prior to treatment and in three treatment cycles using Bayer ACS-180SE automated chemiluminescence immunoassay system.

After oocyte retrieval, the number of oocytes, fertilization rate, cleavage rate, and high-quality embryo rate were calculated. Fertilization rate is the percentage of the number of fertilized eggs to the number of oocytes retrieved. Cleavage rate is the percentage of the number of fertilized eggs to the total number of eggs. High-quality embryo rate is the percentage of the number of high-quality embryos to the total number of embryos. Other indicators assessed included total Gn dosage, duration of Gn administration, the average number of embryos transferred, and clinical pregnancy and early abortion rates.

Statistical analysis

All data were expressed as mean ± standard deviation and analyzed using SPSS 19.0. Two independent samples' *t*-test and χ^2-test were used for comparison of baseline characteristics of subjects in different groups. For inter-group outcome data comparison, the Student–Newman–Keuls (SNK)-q test was used after χ^2-test and $P < 0.05$. D-values referred to differences between pre- and post-treatment indices of ovarian response. For all analyses, $P < 0.05$ was considered statistically significant.

Results

Baseline information

During the treatment, six patients from the AEC group, four from the FHP group and four from the TES group withdrew from the study due to discontinued or intermittent medication. The baseline characteristics of patients who fulfilled the study are listed in Table 1. Endocrine indices of patients in the four groups are shown in Table 2. There was no significant difference (all *P*-values > 0.05) in age, duration of infertility, cause of infertility, body mass index, AFC prior to treatment, E2 values, FSH values, basic LH values, AMH level, RI, PI, and S/D among the four groups (Tables 1 and 2). In addition, patients with a history of pelvic surgery (oophorocystectomy or partial oophorectomy) were evenly distributed among groups (Table 1).

Ovarian response in patients of the TES, FHP, and AEC groups

Ovarian response, evaluated by various indicators, in patients of the TES, FHP, and AEC groups is shown in Table 3. After the treatment, AFC and AMH levels were

Table 3 Comparison of the number of antral follicles, endocrine hormones and ovarian artery blood flow before and after treatment in patients of the four groups

Group	AEC		$P^{\dagger}$	FHP		$P^{\dagger}$	TES		$P^{\dagger}$
	Before treatment	After treatment		Before treatment	After treatment		Before treatment	After treatment	
Cases	54	54		56	56		56	56	
Antral follicle count	2.17 ± 1.34	3.98 ± 1.34	<0.01	2.13 ± 1.38	2.14 ± 1.33	>0.05	2.13 ± 1.36	3.63 ± 1.51	<0.01
E2 level (pmol/L)	204.35 ± 59.11	152.09 ± 42.03	<0.01	203.50 ± 43.76	202.47 ± 45.69	>0.05	200.63 ± 62.78	150.91 ± 49.36	<0.01
FSH level (IU/L)	12.95 ± 2.65	9.57 ± 2.60	<0.01	12.75 ± 2.45	12.66 ± 2.48	>0.05	12.82 ± 2.68	9.24 ± 3.05	<0.01
FSH/LH	3.48 ± 1.40	2.68 ± 1.10	<0.01	4.56 ± 1.44	4.56 ± 1.42	>0.05	3.09 ± 1.54	2.26 ± 1.48	<0.01
AMH level (ng/mL)	0.69 ± 0.37	1.18 ± 0.61	<0.01	0.73 ± 0.41	0.72 ± 0.39	>0.05	0.74 ± 0.38	1.31 ± 0.78	<0.01
RI	0.60 ± 0.11	0.59 ± 0.09	>0.05	0.62 ± 0.21	0.63 ± 0.15	>0.05	0.63 ± 0.12	0.61 ± 0.09	>0.05
PI	0.70 ± 0.06	0.68 ± 0.06	>0.05	0.70 ± 0.05	0.69 ± 0.06	>0.05	0.69 ± 0.06	0.66 ± 0.16	>0.05
S/D	2.66 ± 0.56	2.51 ± 0.45	>0.05	2.67 ± 0.43	2.66 ± 0.58	>0.05	2.69 ± 0.62	2.74 ± 0.91	>0.05

†*t*-test. AEC, artificial endometrial cycle treatment group; CON, control group; E2, estradiol; FHP, comforting false Han's placebo group; FSH, follicle stimulating hormone; LH, luteinizing hormone; FSH/LH, follicle stimulating hormone/luteinizing hormone; AMH, anti-Müllerian hormone; RI, ovary blood flow resistance index; PI, ovary blood flow pulsation index; S/D, systolic/diastolic blood flow velocity ratio; TES, Han's transcutaneous electrical acupoint stimulation treatment group.

increased whereas E2 level, FSH level, and FSH/LH ratio were significantly decreased ($P < 0.01$) in the TES and AEC groups. These indicators did not differ ($P > 0.05$) prior to and post treatment in the FHP group. RI, PI, and S/D were not significantly different ($P > 0.05$) prior to and post treatment in the TES, FHP, and AEC groups. As shown in Table 4, differences between pre- and post-treatment indices of ovarian response (D-values) were compared using SNK-q test after χ^2-test. The results revealed that D-values of antral follicle count, E2 level, FSH level, FSH/LH, and AMH level were comparable between the AEC and TES groups ($P > 0.05$), but significantly different from FHP group values (all P-values < 0.05).

Treatment outcome

As shown in Table 5, the average Gn dosage and average duration of Gn administration were lower in the TES and AEC groups than in the CON and FHP groups, and lower in the TES group than in the AEC group ($P < 0.05$). The patients in the TES, FHP, and AEC groups were similar ($P > 0.05$) in their clinical indicators and basic endocrine indicators. After treatment, the number of oocytes and average number of embryos transferred were higher ($P < 0.05$) in the TES and AEC groups than in the CON and FHP groups, but not significantly different ($P > 0.05$) between the TES and AEC or CON and FHP groups. Clinical pregnancy in the TES group was markedly higher ($P < 0.05$) than in the other three groups. No significant difference ($P > 0.05$) was found in fertilization, cleavage, and high-quality embryo rates among the four groups.

Adverse reactions

There were three cases of mild liver function abnormalities, seven cases of dizziness, and three cases of fatigue in the AEC group. There were one and two cases of mild allergy in the FHP and TES groups, respectively.

Discussion

The present study demonstrated that the clinical pregnancy rate in the TES group was significantly higher than in the other three groups ($P < 0.05$). It was apparent that TEAS treatment could significantly improve the clinical pregnancy rate of patients undergoing IVF-ET with decreased ovarian reserve. As the pregnancy of some patients was less than a month and the frozen-thawed embryo transfer not completed, the miscarriage rate of patients in the middle and advanced stage of pregnancy is not described here. Stener-Victorin *et al*.[19,20] found that electro-acupuncture, similar to fast-acting anesthetics, is effective for pain relief during oocyte retrieval and can result in higher embryo transfer, pregnancy, and birth rates, in agreement with our findings. Other studies[21,22] also showed that electro-acupuncture can increase the ovulation rate in patients with PCO. In agreement, Stener-Victorin *et al*.,[21] and Paulus *et al*.[23] reported higher clinical pregnancy rates in patients receiving acupuncture treatment prior to and post embryo transfer during IVF-ET cycles. Similar findings were reported by Westergaard *et al*.,[2] who found an increased rate of positive pregnancy tests, and clinical and ongoing pregnancy rates in patients receiving acupuncture treatment prior to and post embryo

Table 4 Comparison of the difference between pre- and post-treatment indices in Table 3 (D-value) in patients of AEC, FHP and TES groups

Group	D-value of AEC (A)	D-value of FHP (B)	D-value of TES (C)	$P^{\dagger}$	$PAB^{\ddagger}$	$PAC^{\ddagger}$	$PBC^{\ddagger}$
Cases	54	56	56				
Antral follicle count	1.81 ± 0.70	0.02 ± 0.52	1.50 ± 0.87	0.000	0.000	0.052	0.000
E2 level (pmol/L)	−52.25 ± 30.22	−0.91 ± 15.12	−49.72 ± 24.04	0.000	0.000	0.629	0.000
FSH level (IU/L)	−3.38 ± 2.41	−0.92 ± 1.01	−3.53 ± 0.93	0.000	0.000	0.656	0.000
FSH/LH	−0.797 ± 1.32	0.003 ± 0.56	−0.71 ± 1.79	0.001	0.000	0.772	0.006
AMH level (ng/mL)	0.48 ± 0.47	−0.01 ± 0.55	0.56 ± 0.53	0.000	0.000	0.382	0.000
RI	−0.02 ± 0.13	0.01 ± 0.22	−0.02 ± 0.15	0.626			
PI	−0.02 ± 0.05	−0.01 ± 0.08	−0.03 ± 0.16	0.650			
S/D	−0.15 ± 0.48	−0.01 ± 0.63	0.05 ± 1.01	0.355			

$^{\dagger}\chi^2$-test. ‡SNK-q test. AEC, artificial endometrial cycle treatment group; D-values referred to differences between pre- and post- treatment indices of ovarian response. E2, estradiol; FHP, comforting false Han's placebo group; FSH, follicle stimulating hormone; LH, luteinizing hormone; FSH/LH, follicle stimulating hormone/luteinizing hormone; AMH, anti- Müllerian hormone; RI, ovary blood flow resistance index; PI, ovary blood flow pulsation index; S/D, systolic/diastolic blood flow velocity ratio; TES, Han's transcutaneous electrical acupoint stimulation treatment group.

Table 5 Comparisons of the number of oocytes, fertilization rate, cleavage rate, high-quality embryo rate, number of embryos transferred, clinical pregnancy rate and early abortion rate in the patients among the four groups

Group	CON (A)	AEC (B)	FHP (C)	TES (D)	$P^{\dagger}$	$PAB^{\ddagger}$	$PAC^{\ddagger}$	$PAD^{\ddagger}$	$PBC^{\ddagger}$	$PBD^{\ddagger}$	$PCD^{\ddagger}$
Cases	60	54	56	56							
Average dosage of Gn (U)	2238.67 ± 426.17	2056.78 ± 408.74	2340.56 ± 433.75	1762.64 ± 376.52	0.000	0.022	0.205	0.000	0.001	0.000	0.000
Average duration of Gn administration (days)	10.52 ± 0.66	9.43 ± 0.68	10.36 ± 0.64	8.62 ± 0.82	0.000	0.000	0.188	0.000	0.000	0.000	0.000
Number of oocytes	2.38 ± 1.55	4.53 ± 3.24	2.43 ± 1.55	4.87 ± 3.47	0.000	0.000	0.875	0.000	0.000	0.580	0.000
Fertilization rate (% (*n*))	72.73 (104/143)	76.99 (184/239)	72.79 (99/136)	80.59 (220/273)	0.000	0.350	0.990	0.067	0.364	0.319	0.073
Cleavage rate (% (*n*))	93.27 (97/104)	93.48 (172/184)	93.94 (93/99)	94.56 (208/220)	0.000	0.945	0.845	0.648	0.880	0.651	0.828
Number of high-quality embryos	63	112	60	135							
High-quality embryo rate (% (*n*))	64.95 (63/97)	65.12 (112/172)	64.52 (60/93)	64.90 (135/208)	0.001	0.978	0.950	0.994	0.922	0.966	0.948
Average number of embryos transferred	1.28 ± 0.39	1.81 ± 0.46	1.32 ± 0.43	1.94 ± 0.37	0.000	0.000	0.731	0.000	0.000	0.123	0.000
Clinical pregnancy rate (% (*n*))	21.57 (11/51)	32.0 (16/50)	22.00 (11/50)	42.31 (22/52)	0.000	0.236	0.958	0.024	0.260	0.282	0.028
Early abortion rate (% (*n*))	9.09 (1/11)	6.25 (1/16)	9.09 (1/11)	4.55 (1/22)	0.000	0.782	1.000	0.606	0.782	0.816	0.606

†χ^2-test. ‡SNK-q test. AEC, artificial endometrial cycle treatment group; CON, control group; FHP, comforting false Han's placebo group; Gn, gonadotrophin; TES, Han's transcutaneous electrical acupoint stimulation treatment group.

transfer. Moreover, Smith *et al.*[3] demonstrated that the pregnancy rates in patients with three sessions of acupuncture treatment prior to and post embryo transfer on the ninth day of controlled ovarian hyperstimulation are increased by 1.5% when compared with those receiving placebo acupuncture treatment. Dieterle *et al.*[24] revealed that the clinical pregnancy rate in patients with acupuncture treatment immediately after and on the third day after embryo transfer is significantly increased when compared to those with placebo acupuncture treatment. Dieterle *et al.*[24] analyzed the role of acupuncture in the treatment of patients in the luteal phase, and found that the clinical pregnancy and ongoing pregnancy rates in the acupuncture group are significantly higher than the placebo acupuncture group. Our data presented here corroborate these findings, demonstrating the potential of TEAS in augmenting ovarian reserve, which ultimately increases clinical pregnancy rates.

Adverse reactions of patients undergoing acupuncture mainly include tissue and organ damage, cross-infection, physiological and psychological responses (e.g., weakness and allergic reactions), and other unforeseen circumstances and aggravated diseases caused by clinical errors.[25] TEAS could avoid adverse reactions caused by traditional acupuncture, such as skin damage, infection, and fainting, and produce persistent stimulation. In addition, it is quantitative and easy to operate. Follow-up study in patients treated with TEAS demonstrated that only two patients had mild allergic reactions at electrode sites.

In conclusion, TEAS could improve ovarian reserve in patients with diminished ovarian reserve in IVF-ET cycles, reduce the dosage and duration of Gn administration, increase oocytes and high-quality embryo number, accrue the average number of embryos transferred, and improve the clinical pregnancy rate without leading to obvious adverse reactions.

Acknowledgments

This study was supported by a grant from the National Natural Science Foundation of China (No. 81273996); the Scientific Research Fund of Public Welfare Profession of Ministry of Health, China (No. 201302013).

Disclosure

None declared.

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