The Role of Acupuncture in in vitro Fertilization: A Systematic Review and Meta-Analysis

Chunjuan Shen^a Manxiang Wu^b Defeng Shu^a Xiaojie Zhao^a Ying Gao^a

^aDepartment of Obstetrics and Gynecology, and ^bInstitute of Integrated Traditional Chinese and Western Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Key Words

Acupuncture · In vitro fertilization · Clinical pregnancy rate · Embryo transfer · Systematic review

Abstract

Background/Aims: In recent years, acupuncture has become more and more popular in the management of subfertility. The aim of this study was to evaluate the impact of acupuncture during in vitro fertilization (IVF) treatment on the outcomes of clinical pregnancy in published randomized studies. **Methods:** This is a systematic review and meta-analysis. Data sources used were MEDLINE, Embase, Web of Knowledge and the Chinese Biomedical Database. **Results:** There was no statistically significant difference between the acupuncture group and no acupuncture (intervention) controls around the time of embryo transfer (ET; risk ratio, RR, 1.24, 95% confidence interval, CI, 1.02–1.50) or in unblinded trials, trials blinded to physicians and double-blind trials (95% CI 1.26–1.88, 0.82–1.33 and 0.89–1.25, respectively). This was also the case when comparing acupuncture with sham acupuncture controls around the time of ET (RR, 1.03, 95% CI 0.87–1.22) or when restricting to unblinded trials, trials blinded to physicians and double-blind trials (95% CI 0.80–2.02, 0.82–1.18 and 0.77–1.17, respectively). There was a statistically significant difference when performed at 30 min after ET and implantation phase (RR 1.76, 95% CI 1.22–2.55). There was also a statistically significant difference when performed

at follicle phase and 25 min before and after ET (RR 1.56, 95% CI 1.04–2.33). **Conclusion:** Our study showed that acupuncture did not significantly improve the IVF clinical pregnancy rate when performed only at the time of ET, while we found pooled benefit of acupuncture for IVF when performed at follicle phase and 25 min before and after ET, as well as 30 min after ET and implantation phase.

© 2014 S. Karger AG, Basel

Introduction

Over the past decade, much research has been devoted to increasing the in vitro fertilization (IVF) success rate, improving the quality of embryos, modulating the hormones, and managing the environment of the uterus. However, the pregnancy rate success remains low, so more and more couples affected by infertility try to seek other fertility cures. Acupuncture is an important part of traditional Chinese medicine and dates back at least 3,000 years. In recent years, acupuncture is more and more popular in the management of subfertility, but its effectiveness has remained controversial [1]. Some studies showed that acupuncture was significant in improving IVF outcomes [2–4]. The specific rationales were displayed as follows. First, psychological and environmental factors among Chinese are associated with early pregnancy [5]. The acupuncture regimen may abate stress around embryo transfer (ET)

and possibly improve pregnancy rates [6]. Second, acupuncture may enhance blood flow of the uterus and reduce uterine artery blood flow impedance [7]. Third, acupuncture treatment may enhance the hormonal balance of the embryo implantation stage of IVF in the treatment of infertility [4]. Another study also showed that acupuncture may promote the release of neurotransmitters, thereby mediating the development of hormones [8]. Fourth, acupuncture may regulate the levels of stem cell factor in follicular fluid and serum and improve oocyte quality [3]. However, the outcomes of recent studies have been adverse, and showed that the role of acupuncture in the IVF process was negligible or even nonexistent [9–11].

Many recent systematic reviews analyzed the effects of acupuncture among women undergoing IVF [1, 12–15]. These studies concluded conflicting results to different subgroups. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) involving different time points of acupuncture during IVF treatment to generate a more precise estimate of the effect of acupuncture on IVF outcome.

Materials and Methods

Literature Search

We searched PubMed (1977 to September 2013), Embase (1974 to September 2013), Web of Knowledge (Science) and the Chinese Biomedical Database. Medical subject headings (MeSH) included studies of acupuncture ('acupuncture', 'moxibustion' and 'electroacupuncture') and other studies of IVF and intracytoplasmic sperm injection (ICSI; 'in vitro fertilization', 'assisted reproduction', 'infertility' and 'embryo transfer'). We used 'AND' to connect the two parts.

In the Chinese Biomedical Database, we searched as follows: ZHEN JIU (which means 'acupuncture'), 'ZHEN CI' ('acupuncture'), 'TI WAI SHOU JING' ('in vitro fertilization'), 'FU ZHU SHENG ZHI JI SHU' ('assisted reproduction technology') and 'PEI TAI YI ZHI' ('embryo transfer').

Study Selection

First, we selected the RCTs. Second, the target population was women undergoing IVF with or without ICSI. IVF patients with a tendency for poorer prognosis were excluded. Women who began the IVF process but did not undergo ET were considered. This preserved the groups created by the randomization and reduced the chance of a type I error [13]. Third, some methods of acupuncture (needle, laser or electro) were accepted and compared with the no or sham (placebo) acupuncture group. In the acupuncture group, acupuncture could be needed into the traditional meridian points. The intervention was performed during the IVF or ICSI cycle. Fourth, any type of publication such as an abstract and full article was accepted, as well as any language of publication.

The acupuncture points used may be different but were chosen according to the principles of traditional Chinese medicine. Some

studies only included body acupuncture (even the body acupuncture points were variable), while some studies included body and ear acupuncture.

Data concerning the ongoing pregnancy rate and the live birth rate were not always integrated from these included trials. The clinical pregnancy rate (CPR) that almost all trials reported from a single IVF cycle per woman randomized to acupuncture or control intervention was more accurate than the chemical pregnancy rate. Therefore, we picked CPR to represent the effect of acupuncture on IVF. Clinical pregnancy was defined as the ultrasound identification of an intrauterine gestational sac after IVF treatment. Exclusion criteria: Retrospective studies, studies with a crossover design and studies with an obscure description of the CPR were excluded. Of course trials with no exact numbers of pregnancies and initials of all patients were also not considered. Since pain experience varies from individual to individual, the optimal method of conscious sedation may also be individualized [16]. Those studies that performed during oocyte retrieval to relieve pain were excluded.

Data Extraction

Two authors independently selected articles and extracted data. Data extracted included quality of the methods, participants, interventions and outcomes. Allocation concealment, blinding, sample size, population, protocol of intervention, type of control (no or sham acupuncture) and pregnancy outcomes were listed from the full-text articles and abstracts. The two authors discussed disagreement or contacted the corresponding authors with regard to the design and outcomes of their trials in order to clarify any ambiguities.

Data Synthesis and Analysis

The results were pooled and expressed as relative risks (RR) with 95% confidence intervals (CI). The heterogeneity of treatment effects was evaluated using a forest plot and statistically using I^2 . If the I^2 was higher than 50%, the random effect model was applied. In this paper, the type of control, acupuncture time and blindedness were used for sensitivity subgroup analyses.

We defined 3 broad groups of studies according to the different time points of acupuncture. The three time points were as follows: (1) 25 min before and after ET (around ET), (2) follicle phase and 25 min before and after ET and (3) 30 min after ET and implantation phase. We analyzed the sham-controlled and no intervention-controlled trials separately. Further, the double-blind, single-blind and unblinded trials were analyzed separately in the group around ET. The other 2 groups did not have enough trials, so we only analyzed the acupuncture and control trials.

Results

Overall, 21 RCTs with a total of 5,428 participants were contained in our review; 14 of the 21 included trials ($n = 3,971$) met standards when acupuncture was performed around the time of ET, while the remaining 8 trials ($n = 1,457$) fulfilled the criteria when acupuncture was performed before/after and around ET. See figures 1–4 for meta-analyses of all studies.

No intervention control group

Unblinded: no intervention control group

Blinded to physicians: no intervention control group

(For legend see next page.)

Double-blind: no intervention control group

Fig. 1. Meta-analysis of the studies evaluating the effect of acupuncture administered around the time of ET on the CPR in women undergoing IVF in the no intervention control groups. Values in parentheses are 95% CI. RR: Mantel-Haenszel method. n.a. = Not applicable.

Acupuncture Only around the Time of ET

In the study of Westergaard et al. [28], there were 2 acupuncture groups: ACU1 (patients who received acupuncture on the day of ET) and ACU2 (those who received acupuncture on the day of ET and again 2 days later). In this case, we put the ACU1 patients into the group of acupuncture around ET and the ACU2 subjects into the group of acupuncture after and around ET. There were 14 RCTs (n = 3,971) performing only around the time of ET. The quality of the included trials is summarized in table 1; 7 of the 14 studies were published as full reports [17–23], while the remaining 7 were published as conference abstracts [10, 11, 24–28]; 4 of the studies were in Europe (2 in Denmark [17, 18], 1 in Brazil [11], 1 in Germany [20]), 3 in China [21–23] and 7 in the USA [10, 18, 19, 24–27].

Of these trials, 2 included women with good quality embryos [20, 27], while the other trials included women without clear quality embryos; in 1 trial [11] all participants underwent ICSI, and not IVF, but all other trials reported using ICSI or IVF for participants – 10 trials included acupuncture and a no intervention control group. There were 4 unblinded trials [22, 24, 25, 28]. For 5 trials, the ET physicians were blinded to the treatment assignments [10, 11, 18, 20, 26]. For 1 trial, the ET physicians and patients were double blinded to the treatment assignments [26]. All studies used traditional needle acupuncture, and none used electroacupuncture. In addition, the study of Benson et al. [25] and Fratterelli et al. [26] included 5-arm groups (acupuncture, laser acupuncture, sham laser acupuncture, relax, no intervention), in which laser acupuncture was in 2 of the 5 arms of the trials. The

study of Zhang et al. [23] contained 3 groups (acupuncture, no acupuncture, sham acupuncture).

Of the 14 trials, 7 performed sham (placebo) acupuncture in the control group; 2 trials [23, 25] belonged to the unblinded trials group and 5 [17, 19, 21, 26, 27] belonged to the group of trials that were blinded to the physicians. Of the above 5 trials, all except the study of Paulus et al. [27] were double-blind trials. The methods of sham acupuncture were practiced in various ways: using superficial needling and blunt (placebo) needles on the true acupuncture points, using acupuncture on other places such as thighs and arms, or using laser sham acupuncture. But the principles of Chinese medicine implied in the sham acupuncture treatment had no influence on human fertility. In all trials, women received acupuncture on the day of ET, 25 min before and after the ET procedure.

In these trials there was similarity between the acupuncture group and the control group except for the study of Madaschi et al. [11], in which age was the essential factor in classifying the patients and some randomized women did not complete the treatment in the IVF process (i.e. no ET).

Acupuncture at Follicle Phase and 25 min before and after ET

A total of 4 trials were included in the subgroup. The characteristics of the included trials are summarized in table 2. Acupuncture at follicle phase only was used in 2 of the trials [29, 30], while the other 2 trials used acupuncture at follicle phase and around ET [31, 32]. All 4 trials were published as full reports – 1 in the UK [31], 1 in Australia [32] and 2 in China [29, 30].

Sham acupuncture group

Unblinded: sham acupuncture group

Blinded to physicians: sham acupuncture group

(For legend see next page.)

Double-blind: sham acupuncture group

Fig. 2. Meta-analysis of the studies evaluating the effect of acupuncture administered around the time of ET on the CPR in women undergoing IVF in sham control groups. Values in parentheses are 95% CI. RR: Mantel-Haenszel method.

Fig. 3. Meta-analysis of the studies evaluating the effect of acupuncture administered at 30 min after ET and implantation phase on the CPR in women undergoing IVF in placebo-controlled trials. Values in parentheses are 95% CI. RR: Mantel-Haenszel method.

Table 1. Characteristics of the studies in which acupuncture was performed 25 min before and after ET

First author	Number	Embryo	Allocation concealment	Blinding of patients	Placebo intervention	Comparable	Blinding of physicians	Acupuncture	Control	Aim
Andersen [17], 2010	635	yes	adequate	blinded	yes	yes	blinded	acupuncture 25 min before and after ET	patients received same points placebo acupuncture using the validated Streitberger placebo needle	ongoing pregnancy rates and live birth rates
Domar [18], 2009	146	yes	adequate	no	no	yes	blinded	acupuncture 25 min before and after ET	lay quietly	CPR, anxiety, optimism
Madaschi [11], 2010 ¹	455	ICSI	inadequate	no	no	age	blinded	acupuncture 25 min before and after ET	no acupuncture (unclear)	pregnancy, implantation and abortion rates
Moy [19], 2011	160	yes	adequate	blinded	yes	yes	blinded	acupuncture 25 min before and after ET	needling in nonacupuncture sites	CPR and clinical symptoms during ET
Omodei [24], 2010	168	IVF or ICSI	adequate	no	no	yes	no	acupuncture 25 min before and after ET	no acupuncture (unclear)	pregnancy rate
Paulus [20], 2002	160	IVF or ICSI with good quality embryos	adequate	no	no	yes	blinded	acupuncture 25 min before and after ET	no acupuncture, lay quietly	clinical pregnancy
Paulus [27], 2003	200	IVF or ICSI with good embryo quality	adequate	no	yes	unclear	blinded	acupuncture 25 min before and after ET	a placebo needle set was used without penetrating the skin, but at the same acupoints and after the same scheme.	clinical pregnancies
So [21], 2009	370	yes	adequate	blinded	yes	yes	blinded	acupuncture 25 min before and after ET	placebo acupuncture group received the Streitberger placebo needle acupuncture the same acupoints and time	pregnancy rate, ongoing pregnancy and live birth
Benson [25], 2006	258	no mention	unclear	no	yes	yes	no	acupuncture 25 min before and after ET	sham laser acupuncture, relaxation or no intervention	implantation and pregnancy rates
Craig [10], 2007	109	IVF or ICSI with good quality embryo	adequate	no	no	yes	blinded	acupuncture 25 min before and after ET	no acupuncture, lay quietly	clinical pregnancy, live birth
Westergaard [28], 2006	292	yes	adequate	no	no	yes	no	acupuncture 25 min before and after ET	no acupuncture	clinical pregnancy and ongoing pregnancy rates
Fratterelli [26], 2008	1,000	IVF or ICSI	adequate	double blind	yes	yes	blinded	acupuncture 25 min before and after ET	sham laser acupuncture, relaxation or no intervention	implantation, chemical and clinical ongoing pregnancy
Zhang [22], 2002	100	first IVF or ICSI	unclear	unclear	no	yes	unclear	acupuncture 25 min before and after ET	no acupuncture, lay quietly	clinical pregnancy
Zhang [23], 2003	210	IVF or ICSI	unclear	unclear	yes	yes	no	acupuncture 25 min before and after ET	Streitberger placebo needles, acupuncture at the same acupoints and time	clinical pregnancy

¹ Acupuncture group (230, i.e. 208 + 22) + the no acupuncture group (225, i.e. 208 + 17), because it could be assumed that these participants without an ET did not achieve the clinical pregnancy outcome.

Fig. 4. Meta-analysis of the studies evaluating the effect of acupuncture administered at follicle phase and 25 min before and after ET on the CPR in women undergoing IVF. Values in parentheses are 95% CI. RR: Mantel-Haenszel method.

Acupuncture at 30 min after ET and Implantation Phase

In all, 4 trials [28, 33–35] were included when acupuncture was performed after and around the time of ET (1 in Germany [33], 1 in Denmark [28] and 2 in China [34, 35]). The characteristics of the included trials are summarized in table 2. The study of Zhang et al. [34] included 2 groups (mock transcutaneous electrical acupoint stimulation treatment: 30 min after ET; single transcutaneous electrical acupoint stimulation treatment: 30 min after ET). In the study of Westergaard et al. [28], there were 2 acupuncture groups: ACU1 (patients who received acupuncture on the day of ET) and ACU2 (those who received acupuncture on the day of ET and again 2 days later). In this case we put the ACU1 patients into the group of acupuncture around ET and the ACU2 subjects into the group of acupuncture after and around ET. The studies of So et al. [35] and Zhang et al. [34] used electroacupuncture in the trials, whereas the others used traditional needle acupuncture.

IVF Treatment Outcome

There was no statistically significant difference between acupuncture and no acupuncture (intervention) controls around the time of ET (RR 1.24, 95% CI 1.02–1.50, $I^2 = 64\%$, 10 trials, 2,226 participants) or when restricting to unblinded trials (RR 1.54, 95% CI 1.26–1.88, $I^2 = 0\%$, 5 trials, 757 participants) or trials blinded to physicians (RR 1.04, 95% CI 0.82–1.33, $I^2 = 67\%$, 5 trials, 1,469 participants) or double-blind trials (RR 1.05, 95% CI 0.89–1.25, $I^2 = 0\%$, 1 trial, 599 participants; fig. 2). The same was true when comparing acupuncture with sham acupuncture controls around the time of ET (RR 1.03, 95% CI 0.87–1.22, $I^2 = 59\%$, 7 trials, 2,010 participants) or when restricting to unblinded trials (RR 1.27, 95% CI 0.80–2.02, $I^2 = 55\%$, 2 trials, 245 participants) or trials blinded to physicians (RR 0.98, 95% CI 0.82–1.18, $I^2 = 61\%$, 5 trials, 1,765 participants) or double-blind trials (RR 0.95, 95% CI 0.77–1.17, $I^2 = 68\%$, 4 trials, 1,565 participants; fig. 3). There was no statistically significant difference between acupuncture and controls when combining all trials performed 30 min after ET (RR 1.12, 95% CI

Table 2. Characteristics of the studies in which acupuncture was performed at 30 min after ET and implantation phase/at follicle phase and 25 min before and after ET

First author	Number	Participation	Randomization	Blinding of patients	Placebo intervention	Comparable	Acupuncture	Control	Aim
di Villahermosa [31], 2013	84 (28 in each)	IVF or ICSI with at least 2 good embryos	adequate	unclear	yes	yes	performed on days D1, D7, on the day before ovarian puncture and on the day after ET	sham group, needle insertion was performed in the arm and thigh, not corresponding	biochemistry CPR
So [35], 2010	226	FET	adequate	blinded	yes	yes	a single session of real acupuncture for 25 min immediately after FET, sterile disposable stainless steel needles	placebo acupuncture for 25 min immediately after FET, Streitberger placebo needles, the same acupoints	rates of overall pregnancy, clinical pregnancy, ongoing pregnancy, live birth and implantation
Westergaard [28], 2006 ¹	292	IVF or ICSI	adequate	no	no	yes	1 group of patients received acupuncture on the day of ET, another group on ET day and again 2 days later	no acupuncture	clinical pregnancy and ongoing pregnancy rates
Zhang [34], 2011 ²	216	FET or fresh IVF	adequate	blinded	yes	yes	single TEAS treatment: 30 min after ET	mock TEAS treatment: 30 min after ET	clinical PR, embryos implantation rate, live birth rate
Dieterle [33], 2006	225	IVF/ICSI	adequate	blinded	yes	yes	applied for 30 min immediately after ET and again 3 days later	the placebo acupuncture treatment was designed not to influence fertility	clinical and ongoing pregnancy rates
Smith [32], 2006 ³	228	IVF or ICSI	adequate	no	yes	yes	the first undertaken on day 9 of stimulating injections, the second before ET, and the third immediately after ET	sham acupuncture points located close to but not on the real acupuncture points	pregnancy, implantation
Cui [29], 2006	94	IVF or ICSI	unclear	no	no	yes	in the mid-follicular phase until oocyte revival, every time every day	no acupuncture	clinical pregnancy
Ho [30], 2009	44	IVF or ICSI	adequate	no	no	yes	twice a week for 2 weeks, from day 2 of the study to the day before oocyte retrieval	no acupuncture	clinical pregnancy and pulsatility index of right and left uterine arteries

FET = Frozen ET; TEAS = transcutaneous electrical acupoint stimulation.

¹ ACU1 (100 patients: contains 5 patients that did not undergo ET); ACU2 (99 patients: contains 8 patients that did not undergo ET); control group (93 patients: contains 6 patients that did not undergo ET).

² Mock TEAS (106 patients: contains 7 patients that did not undergo ET), single TEAS (110 patients: contains 0 patients that did not undergo ET).

³ Acupuncture (110 patients: contains 13 patients that did not undergo ET); sham acupuncture (118 patients: contains 17 patients that did not undergo ET).

0.60–2.11, $I^2 = 85\%$, 2 trials, 442 participants), but there was a statistically significant difference between acupuncture and controls when combining all trials performed 30 min after ET and implantation phase (RR 1.76, 95% CI 1.22–2.55, $I^2 = 14\%$, 2 trials, 417 participants). When performing at follicle phase, there was no statistically significant difference between acupuncture and controls (RR 1.29, 95% CI 0.83–2.02, $I^2 = 0\%$, 2 trials, 138 participants). When performing at follicle phase and around ET, there was also a statistically significant difference between acupuncture and controls (RR 1.56, 95% CI 1.04–2.33, $I^2 = 50\%$, 2 trials, 284 participants).

Discussion

The outcomes of our review showed no significant improvement in clinical pregnancy when acupuncture was performed around the time of ET. According to our results, in sham-controlled trials, we found no statistically significant pooled benefits of acupuncture administered around the time of ET in IVF; when restricting to unblinded or double-blind trials, there was also no statistically significant improvement in clinical pregnancy. In no treatment-controlled trials, when restricting to unblinded trials, there was a more statistically significant difference. However, when restricting to trials blinded to physicians or double-blind trials, we found no statistically significant pooled benefits. We also found statistically significant pooled benefits when treatment was administered 30 min after ET and implantation phase. The effect of acupuncture administered at follicle phase and around ET on the CPR in women undergoing IVF was statistically significant.

Blinding of the physicians performing the ET was a potential source of bias. Our study showed bias between acupuncture and controls when combining all trials performed around the time of ET (fig. 2, 3). For the no intervention-controlled trials the RR descended gradually in the unblinded trials, trials blinded to physicians and double-blind trials (RR 1.54, 1.04 and 1.05, respectively). Comparing the acupuncture group with sham acupuncture controls when performed around the time of ET, the outcome was the same as the no intervention-controlled trials (RR 1.27, 0.98 and 0.95, respectively).

There were some reasons for the distinct results of our systematic review. First, as mentioned, blinding of the physicians performing the ET was a potential source of bias. We separated the blinding and no blinding groups to decrease the risk of bias. Second, we used sh-

am-controlled trials to rule out the possibility that acupuncture produces only psychological or psychosomatic effects [27]. Third, we concluded the effects of acupuncture at different time points. The times of acupuncture intervention were always another potential source of bias [8].

Women with previous IVF failure had lower clinical pregnancy outcomes than those undergoing treatment in their first cycle [36]. Patients should be included in the same IVF cycle in order to reduce a potential bias of baseline pregnancy rate. However, across all trials, the included patients were undergoing IVF or ICSI that included the first cycle or the repeated cycle. Many authors did not report how many previous cycles the patients underwent. Therefore we did not evaluate this in our design. In addition, the subgroup analysis of the review paper by Manheimer et al. [37] showed that such factors have not been shown to be strong predictors of pregnancy rate and none of these factors seemed to correlate well with the variability in baseline rate.

The efficacy of acupuncture given may vary in the included RCTs. High dosages of acupuncture could have a higher efficacy of acupuncture than the low dosage of acupuncture used in IVF [38, 39]. However, the definitive efficient dosages are still unknown. Future research should consider the efficacy of dosage to reach an available outcome.

The protocol of many studies was as close as possible to the protocol used in the study of Paulus et al. [20]. Hence what the studies were doing was attempting to manifest the efficacy of performing around ET on the success rate in IVF. In fact, when only performed at one time point, acupuncture did not develop perfect function. Brenner [40] stated that this is a widespread issue with acupuncture trials as a one-size-fits-all protocol; these trials only give information on that protocol and not on the possibility of success with acupuncture. In the study of di Villahermosa et al. [31], acupuncture was performed on the 1st and 7th day of ovulation induction, on the day before ovarian puncture and on the day after ET. The study showed that the CPR in the acupuncture group was significantly higher than that in the control and sham groups. Our study inferred that acupuncture performed during controlled ovarian hyperstimulation and around ET would promote clinical pregnancy, and that performing acupuncture at 30 min after ET and implantation phase would have some effect on pregnancy outcomes.

Conclusion and Future Research

Our study showed that acupuncture increased pregnancy rates when performed at follicle phase and 25 min before and after ET or 30 min after ET and after the implantation phase in the IVF process. However, there was no statistically significant difference in women undergoing IVF between treatment performed only around the time of ET, follicle phase or implantation phase. The study of Zheng et al. [14] also showed that the pooled CPR result around the time of ET showed no significant differences between all acupuncture groups and the control groups. However, the CPR result of acupuncture performed around the time of controlled ovarian hyperstimulation showed a significant difference. The potential impact of acupuncture in the treatment of female infertility on the hypothalamic-pituitary-ovarian axis and on the uterus was significant, but the specific mechanism was still unknown [41]. Many medications such as oral contraceptive pills have no influence on increasing the pregnancy rate [42] and have some side effects, while acupuncture on patients undergoing IVF is a relatively simple procedure without side effects. Moreover, it was an inexpensive treatment for many couples affected by infer-

tility [10, 43]. Perhaps if more individualized acupuncture programs are used, more positive effects from acupuncture in IVF can be achieved [14]. The effects of acupuncture changed according to the endocrine system of patients, and so we should use acupuncture at different time points successively in the controlled ovarian hyperstimulation process according to individual characteristics. In addition, with some couples affected by infertility, lifestyle behavior also plays an essential role when pursuing assisted reproductive technology [44].

For future trials, the baseline rate of pregnancy, the dosage of acupuncture and individual characteristics should be considered. The protocol of efficient acupuncture should be well explored.

Acknowledgments

We are grateful to the members of the Department of Epidemiology and Biostatistics, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, who helped with the statistical analysis.

No specific funding was received for the study, but the Department of Obstetrics and Gynecology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology supported us throughout the study period and manuscript preparation.

References

- 1 Ng EH, So WS, Gao J, Wong YY, Ho PC: The role of acupuncture in the management of subfertility. *Fertil Steril* 2008;90:1–13.
- 2 Dalton-Brewer N, Gillott D, Atalla N, Menabawey M, Wright P, Thornhill A: Use of acupuncture before and after embryo transfer. *Hum Fertil* 2009;12:247.
- 3 Chen J, Liu LL, Cui W, Sun W: Effects of electroacupuncture on in vitro fertilization-embryo transfer (IVF-ET) of patients with poor ovarian response. *Zhongguo Zhen Jiu* 2009;29:775–779.
- 4 Cavalla H: Acupuncture and electroauriculotherapy treatment for infertility. *Med Acupunct* 2010;22:49–52.
- 5 Sun L, Tao F, Hao J, Su P, Xu R, Liu F: Vaginal bleeding in early pregnancy and associations with physical, psychological and environmental factors among Chinese women: from the C-ABC cohort study. *Gynecol Obstet Invest* 2012;73:330–336.
- 6 Balk J, Catov J, Horn B, Gecsi K, Wakim A: The relationship between perceived stress, acupuncture, and pregnancy rates among IVF patients: a pilot study. *Complement Ther Clin Pract* 2010;16:154–157.
- 7 Cakmak YO: Electroacupuncture reduces uterine artery blood flow impedance. *Taiwan J Obstet Gynecol* 2010;49:390, author reply 391.
- 8 Guo J, Li D, Zhang QF: Acupuncture intervention combined with assisted reproductive technology: its different effects at different time points during the in vitro fertilization-embryo transfer course (in Chinese). *Zhong Xi Yi Jie He Xue Bao* 2008;6:1211–1216.
- 9 Rashidi BH, Tehrani ES, Hamedani NA, Pirzadeh L: Effects of acupuncture on the outcome of in vitro fertilisation and intracytoplasmic sperm injection in women with polycystic ovarian syndrome. *Acupunct Med* 2013;31:151–156.
- 10 Craig LB, Criniti AR, Hansen KR, Marshall LA, Soules MR: Acupuncture lowers pregnancy rates when performed before and after embryo transfer. *Fertil Steril* 2007;88(suppl 1):S40.
- 11 Madaschi C, Braga DP, Figueira Rde C, Iaconelli A Jr, Borges E Jr: Effect of acupuncture on assisted reproduction treatment outcomes. *Acupunct Med* 2010;28:180–184.
- 12 El-Toukhy T, Sunkara SK, Khairy M, Dyer R, Khalaf Y, Coomarasamy A: A systematic review and meta-analysis of acupuncture in in vitro fertilisation. *BJOG* 2008;115:1203–1213.
- 13 Manheimer E, van der Windt D, Cheng K, Stafford K, Liu J, Tierney J, Lao L, Berman BM, Langenberg P, Bouter LM: The effects of acupuncture on rates of clinical pregnancy among women undergoing in vitro fertilization: a systematic review and meta-analysis. *Hum Reprod Update* 2013;0:1–10.
- 14 Zheng CH, Zhang MM, Huang GY, Wang W: The role of acupuncture in assisted reproductive technology. *Evid Based Complement Alternat Med* 2012;2012:1–15.
- 15 El-Toukhy T, Khalaf Y: The impact of acupuncture on assisted reproductive technology outcome. *Curr Opin Obstet Gynecol* 2009;21:240–246.
- 16 Stener-Victorin E: The pain-relieving effect of electro-acupuncture and conventional medical analgesic methods during oocyte retrieval: a systematic review of randomized controlled trials. *Hum Reprod (Oxford)* 2005;20:339–349.
- 17 Andersen D, Lossl K, Nyboe Andersen A, Furbringer J, Bach H, Simonsen J, Larsen EC: Acupuncture on the day of embryo transfer: a randomized controlled trial of 635 patients. *Reprod Biomed Online* 2010;21:366–372.

- 18 Domar AD, Meshay I, Kelliher J, Alper M, Powers RD: The impact of acupuncture on in vitro fertilization outcome. *Fertil Steril* 2009; 91:723–726.
- 19 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;95:583–587.
- 20 Paulus WE, Zhang M, Strehler E, El-Danasouri I, Sterzik K: Influence of acupuncture on the pregnancy rate in patients who undergo assisted reproduction therapy. *Fertil Steril* 2002;77:721–724.
- 21 So EW, Ng EH, Wong YY, Lau EY, Yeung WS, Ho PC: A randomized double blind comparison of real and placebo acupuncture in IVF treatment. *Hum Reprod* 2009;24:341–348.
- 22 Zhang M, Huang G, Lu F, El-Danasouri I, Sterzik K: Effect of acupuncture on rate of pregnancy among women undergoing embryo transfer. *Zhongguo Zhen Jiu* 2002;22: 507–509.
- 23 Zhang M, Huang G, Lu F, El-Danasouri I, Sterzik K: Effect of acupuncture on rate of pregnancy among women undergoing embryo transfer: a prospective randomized placebo controlled trial. *Zhongguo Zhen Jiu* 2003;23:3–5.
- 24 Omodei U, Piccioni G, Tombesi S, Dordoni D, Fallo L, Ghilardi F: Effect of acupuncture on rates of pregnancy among women undergoing in vitro fertilization. *Fertil Steril* 2010; 94(suppl 1):S170.
- 25 Benson MR, Elkind-Hirsch KE, Theall A, Fong K, Hogan RB, Scott RT: P-18: impact of acupuncture before and after embryo transfer on the outcome of in vitro fertilization cycles: a prospective single-blind randomized study. *Fertil Steril* 2006;86:S135.
- 26 Fratterelli JL, Leondires MR, Fong K, Theall A, Locatelli S, Scott RT: Laser acupuncture before and after embryo transfer improves art delivery rates: results of a prospective randomized double-blinded placebo controlled five-armed trial involving 1,000 patients. *Fertil Steril* 2008;90(suppl):S105.
- 27 Paulus WE, Zhang M, Strehler E, Seybold B, Sterzik K: Placebo-controlled trial of acupuncture effects in assisted reproduction therapy. *Hum Reprod* 2003;18:18–19.
- 28 Westergaard LG, Mao Q, Kroglund M, Sandrini S, Lenz S, Grinsted J: Acupuncture on the day of embryo transfer significantly improves the reproductive outcome in infertile women: a prospective, randomized trial. *Fertil Steril* 2006;85:1341–1346.
- 29 Cui W, Sun W, Liu L, Wen J: Effects of electroacupuncture on patients undergoing in vitro fertilization and embryo transplantation. *Zhongguo Fu You Bao Jian* 2006;22:3403–3405.
- 30 Ho M, Huang LC, Chang YY, Chen HY, Chang WC, Yang TC, Tsai HD: Electroacupuncture reduces uterine artery blood flow impedance in infertile women. *Taiwan J Obstet Gynecol* 2009;48:148–151.
- 31 di Villahermosa DIM, dos Santos LG, Nogueira MB, Vilarino FL, Barbosa CP: Influence of acupuncture on the outcomes of in vitro fertilisation when embryo implantation has failed: a prospective randomised controlled clinical trial. *Acupunct Med* 2013;31:157–161.
- 32 Smith C, Coyle M, Norman RJ: Influence of acupuncture stimulation on pregnancy rates for women undergoing embryo transfer. *Fertil Steril* 2006;85:1352–1358.
- 33 Dieterle S, Ying G, Hatzmann W, Neuer A: Effect of acupuncture on the outcome of in vitro fertilization and intracytoplasmic sperm injection: a randomized, prospective, controlled clinical study. *Fertil Steril* 2006;85: 1347–1351.
- 34 Zhang R, Feng XJ, Guan Q, Cui W, Zheng Y, Sun W, Han JS: Increase of success rate for women undergoing embryo transfer by transcutaneous electrical acupoint stimulation: a prospective randomized placebo-controlled study. *Fertil Steril* 2011;96:912–916.
- 35 So EW, Ng EH, Wong YY, Yeung WS, Ho PC: Acupuncture for frozen-thawed embryo transfer cycles: a double-blind randomized controlled trial. *Reprod Biomed Online* 2010; 20:814–821.
- 36 Chiara R, Carolina B, Franco C: Effect of acupuncture on pregnancy rate in selected women undergoing IVF. *Eur J Integr Med* 2012;4: 52.
- 37 Manheimer E, Zhang G, Udoff L, Haramati A, Langenberg P, Berman BM, Bouter LM: Effects of acupuncture on rates of pregnancy and live birth among women undergoing in vitro fertilisation: systematic review and meta-analysis. *BMJ* 2008;336:545–549.
- 38 Humaidan P, Brock K, Bungum L, Stener-Victorin E: Pain relief during oocyte retrieval – exploring the role of different frequencies of electro-acupuncture. *Reprod Biomed Online* 2006;13:120–125.
- 39 Anderson BJ, Rosenthal L: Acupuncture and IVF controversies. *Fertil Steril* 2007;87:1000.
- 40 Brenner Z: Acupuncture and IVF trial. *Fertil Steril* 2009;92:27, author reply 28.
- 41 Kim J, Shin KH, Na CS: Effect of acupuncture treatment on uterine motility and cyclooxygenase-2 expression in pregnant rats. *Gynecol Obstet Invest* 2000;50:225–230.
- 42 Bozdog G, Esinler I, Yerali H: Pretreatment with oral contraceptive pills does not influence the pregnancy rate in the long leuprolide acetate protocol. *Gynecol Obstet Invest* 2012; 73:53–57.
- 43 Rosenthal L, Anderson B: Acupuncture and in vitro fertilisation: recent research and clinical guidelines. *J Chin Med* 2007;84:28–35.
- 44 Domar AD, Conboy L, Denardo-Roney J, Rooney KL: Lifestyle behaviors in women undergoing in vitro fertilization: a prospective study. *Fertil Steril* 2012;97:697–701.