Pregnancy outcomes of women randomized to receive real versus placebo acupuncture on the day of fresh or frozen-thawed embryo transfer

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Abstract

Introduction: Acupuncture is commonly used in various aspect of Western medicine in recent years including in-vitro fertilization (IVF) treatment. Although there are many clinical trials of acupuncture in IVF and the Cochrane meta-analysis did not find benefit of adjuvant acupuncture for IVF, there is no report on the pregnancy outcomes of women who had received acupuncture during their IVF treatment.

Objectives: To compare the pregnancy outcomes of women randomized to receive real versus placebo acupuncture during their IVF treatment.

Methods: A retrospective chart review was performed on the 212 women with on-going pregnancies after receiving real or placebo acupuncture by sterile disposable stainless steel needles or Streitberger's placebo needles to the acupoints before and after the embryo transfer on the day of fresh or frozen-thawed embryo transfer. The pregnancy outcomes were obtained from the Hospital Authority Clinical Management System for deliveries in the public sector or from a self-returned questionnaire if those in the private sector.

Results: No significant differences were found between the demographics of the two groups including their age, gravida, parity and the duration of subfertility. Maternal adverse outcomes including gestational diabetes and hypertensive disorder were comparable for the real acupuncture group (35.3% and 4.4% respectively) and the placebo acupuncture group (39.7% and 5.5% respectively). None of the patients had

placenta accreta. The preterm delivery (<37 weeks gestation) rate in the real acupuncture group (23/86, 26.7%) was similar to that in the placebo acupuncture group (25/97, 25.8%). No statistical significant difference was found in the mode of delivery. There were no significant differences between the two groups for in the Apgar scores and birthweight.

Conclusion: Acupuncture during IVF treatment does not influence pregnancy outcomes

Background:

Acupuncture is commonly used in various aspect of Western medicine in recent years including in in-vitro fertilization (IVF) (1-2). The Cochrane meta-analysis did not find benefit of adjuvant acupuncture for IVF (3). Even though there were reported outcomes of IVF with acupuncture, there is no report on the pregnancy outcomes of women who had received acupuncture during their IVF treatment.

In 2008 and 2010, we have published two randomized controlled trials on the pregnancy rates of women who were randomized to receive real or placebo acupuncture during fresh (4) and frozen-thawed embryo transfer cycles (5). The miscarriage rates and live birth rates were comparable in the real and placebo acupuncture groups. The on-going pregnancy rates were 39.9% (119/298) and 31.2% (93/298) for the placebo and real acupuncture groups respectively (RR 1.280, CI 1.028 – 1.592). However, we did not report the pregnancy outcomes of those who had on-going pregnancies in these two randomized trials.

Mechanisms of acupuncture including improvement for ovarian and uterine circulation, modulation for neuro-hormone and cytokine for better implantation and effect on stress reduction were believed to be able to bring short-term and long term benefit to IVF pregnancy (6). However, many studies in reproductive medicine only focus on the pregnancy rate without reporting the obstetrics and perinatal outcomes (3). After the publication of the Improving the reporting of clinical trials of infertility treatments (IMPRINT) by the Harbin Consensus Conference Workshop Group in 2014 (7), it

became more and more important for pregnancy outcomes to be reported and evaluated. Therefore, we aim to compare the pregnancy outcomes of women randomized to receive real versus placebo acupuncture on the day of fresh or frozen-thawed embryo transfer.

Materials and methods

A total of 370 women, who were undergoing IVF treatment in the Centre of Assisted Reproduction and Embryology, The University of Hong Kong – Queen Mary Hospital between August 2006 and July 2007, were randomly allocated on the day of fresh embryo transfer to either real or placebo acupuncture according to a computer-generated randomization list in sealed opaque envelopes. All patients gave informed consents prior to participating in the acupuncture studies, which were approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKCTR-236 and HKCTR-686; HKClinicalTrials.com). The methodology was previously described (4-5). Single embryo transfer was encouraged if the woman is <35 years old, undergoing the first IVF cycle with endometrial thickness >8mm with 2 good quality embryos (embryo of >/= 4cells, grade 1 or 2). Women received 25 minutes of real or placebo acupuncture by sterile disposable stainless steel needles or Streitberger's placebo needles to the acupoints before and after the embryo transfer. The acupoints used before embryo transfer were PC6 (Neiguan), SP8 (Diji), LR3 (Taichong), GV20 (Baihui) and ST29 (Guilai). After the embryo transfer, the acupoints used were ST36 (Zusanli), SP6 (Sanyinjiao), SP10 (Xuehai) and LI4 (Hegu). All acupuncture treatments were performed in the same way by the same certified acupuncturist who had completed the degree of Chinese Medicine and had 2 years of experience in acupuncture. In the real acupuncture group, 59 women had on-going pregnancy and 55 women had a live birth whereas in the placebo acupuncture group 75 women had on-going pregnancy while 71 of them had a live birth (4).

Between October 2006 and November 2007, 226 women undergoing frozen-thawed embryo transfer treatment were also randomized in the same way to receive real or placebo acupuncture before and after the transfer. In the real acupuncture group, 34 women had on-going pregnancy and 33 women had a live birth while 44 and 40 women, in the placebo group had an on-going pregnancy and a live birth, respectively (5).

A retrospective study was conducted for these 212 women with on-going pregnancy. An ethics approval was obtained from Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster for this retrospective study. Pregnancy outcomes were obtained from the Hospital Authority Clinical Management System (CMS) or the self returned questionnaire from the in-charge doctor for the women who did not deliver with the public system. A retrospective review of the database was performed for all women. A database was set up with Microsoft Excel for Windows and the Statistical Product and Service Solutions (SPSS 21.0; SPSS, Inc., Chicago, IL) to facilitate data entry, retrieval and analysis. Demographic data, pregnancy outcomes including gestation at the time of delivery, birth weights, Apgar scores and presence of pregnancy complications were recorded. Birth weights were charted according to the gestational age specific birth weight of Chinese (8). Neonatal outcomes were analysed by the number of babies (9).

The outcomes were the rate of preterm delivery, defined as delivery before 37 completed gestational weeks; gestational diabetes, defined as fasting glucose >/= 7.0 mmol/l or 2 hour glucose >/= 7.8 after a 75-gram oral glucose tolerance test;

hypertensive disorder, defined as diastolic blood pressure >/= 90mmHg 4 hours apart with or without proteinuria; and placenta accreta diagnosed by imaging or intra-operatively; of women randomized to receive real versus placebo acupuncture on the day of fresh and frozen-thawed embryo transfer. These maternal outcomes were analysed by number of on-going pregnancy (9).

Results

Among the 596 women undergoing real or placebo acupuncture, 212 women had on-going pregnancy, 39.9% (119/298) and 31.2% (93/298) for the placebo and real acupuncture groups, respectively (RR 1.280, CI 1.028 – 1.592). 199 women had live birth, 37.2% (111/298) and 29.5% (88/298) for the placebo and real acupuncture groups (RR 1.261, CI 1.003 to 1.586). No significant differences were found between the demographics of the two groups including their age, gravida, parity, smoking status, number of embryos transferred, multiple pregnancy rate and the duration of subfertility (Table 1). All six patients who received single embryo transfer ended up with singleton pregnancies. For the patients receiving two embryos during the fresh or frozen-thawed embryo transfer cycles, the multiple pregnancy rate was 21.7%. There was no difference observed between the real or placebo acupuncture groups (25.8% (24/93) in the real group versus 18.4% (22/119) in the placebo group, RR 0.716, 0.430 to 1.194). 146 women delivered in the public hospital with the pregnancy outcome obtained from the Hospital Authority Clinical Management System, 37 women had deliveries in the public sector and the delivery outcome obtained from a self-returned questionnaire if those in the private sector.

Outcomes for maternal complications were available in 141 women, 68 in the real group and 73 in the placebo group. Gestational diabetes was observed in 35.3% (24/68) in the real acupuncture group and 39.7% (29/73) in the placebo group (RR 1.242 (0.821 – 1.878)) while hypertensive disorder was found in 4.4% in real acupuncture group versus 5.5% in placebo acupuncture group (RR 1.242 (0.288 – 5.348)) respectively. None of the patients had placenta accreta (Table 2). Mode of delivery was available in 166 women (77 in real acupuncture group versus 89 in placebo group). No statistical significant difference was found in the mode of delivery (table 3), however, it was noted to have a higher than usual Caesarean delivery rates in both groups when compared to the general population rate of 20-30% in our unit.

Details about gestation at delivery were available in 183 women, 86 in the real acupuncture group and 97 in the placebo group. The preterm delivery (<37 weeks gestation) rate was 26.7% (23/86) in the real acupuncture group and 25.8% (25/97) in the placebo acupuncture group (RR 0.964 (0.593 – 1.567)). There was no difference in the preterm delivery rate with singleton or multiple pregnancies (Table 4).

Congenital anomaly was present in three patients, 2 in real acupuncture group and 1 in placebo group, p = 0.59). 2 patients had fetocide for the abnormal twin in the second trimester for complex congenital heart disease. The third patient with mild fetal tricuspid regurgitation carried on with her pregnancy and gave birth at term. Birth weights were available in 224 babies (105 in real acupuncture versus 119 in placebo group) and were

charted according to the gestational age specific birth weight of Chinese (8) (Table 5). Apgar scores were available in 178 babies (84 in the real acupuncture group and 94 of the placebo acupuncture group), 1 baby in each group had Apgar score <4 at one minute (1.2% in the real acupuncture group versus 1.1% in the placebo acupuncture group, RR 0.893 (0.059 – 14.065)) and no babies had Apgar score <4 at five minutes of life. There was no significant difference in their birth weights and Apgar scores.

Discussion

Acupuncture during IVF treatment does not influence pregnancy outcomes. This echoes with the current literature when acupuncture was used at other times during pregnancy.

Acupuncture has been used in different aspects of IVF treatment and during pregnancy (1-3, 10-12) despite its actual mechanism still remained unclear and the quality of reporting of adverse event remained poor (13-14). For women receiving acupuncture around the time of oocyte retrieval, mainly live birth rate, on-going pregnancy rate, clinical pregnancy rate and miscarriage rate were reported. Multiple pregnancy rate and other pregnancy complications were not being reported (3). As for women receiving acupuncture around the time of embryo transfer, there were only two trials reporting on the multiple pregnancy rates on top of the above outcome measures (3).

Acupuncture was also being used in other timing during pregnancy for treatment of hyperemesis (11) and during induction of labour (10). However, only one study in 2004

by Habek et.al reported on the preterm birth rate and the stillbirth and neonatal death rate, which the quality of evidence was rated as low (11).

It was evaluated that most of the adverse events were unlikely the consequence of acupuncture treatment (12-14). Also, most of the studies excluded the groups in which acupuncture was used during assisted reproduction (13) as it was uncertain whether the use of acupuncture used at the time of conception would lead to long term consequence affecting perinatal outcomes.

The reason why there was no significant difference observed between both groups may be related to the brief period of acupuncture lasting 25 minutes in two sessions, which was unlikely to pose any long lasting effects to the pregnancy. As implantation only occurs 4-5 days later and the organogenesis happens even later, the impact of such brief acupuncture could have worn off by then. However, we cannot be certain about the impact if acupuncture was given in multiple sessions, especially after embryos have already been transferred. Long term data and larger studies would be needed to look at the safety of acupuncture applied at different time points during pregnancy.

The present study has the strength of involving randomized subjects with acupuncture done by a single acupuncturist on site. The limitations of the study include it being a retrospective analysis of two randomized studies. The sample sizes are too small for comparison of obstetric outcomes. Both fresh and frozen transfer cycles were included. Also the pregnancy outcomes of patients not delivering in the public sector were

obtained from a self-returned questionnaire from the doctor in charge for the women, which may also pose some bias with the reporting.

Conclusion

Acupuncture during IVF treatment does not influence pregnancy outcomes.

Conflict of interest

The authors have no conflict to report.

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