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Original article

Acupuncture and Chinese herbal treatment for women undergoing intrauterine insemination

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Abstract

Aim: To assess the effect of traditional Chinese medicine (TCM, acupuncture and medicinal herbs) as a therapeutic adjuvant to ovulation induction with intrauterine insemination (IUI) procedures and evaluate its contribution to pregnancy and "take-home baby" rates.
Materials and methods: A comparative retrospective study was carried out in a university – affiliated municipal hospital. All women undergoing artificial insemination by donor spermatozoa (AID) and concomitantly treated with TCM were invited to participate. The enrolled women underwent weekly TCM in parallel with medical therapy. The treatment lasted between 2 and 36 cycles (equivalent to a time period ranging from one month to one year). The control group was comprised of women who underwent AID without TCM and whose data were retrospectively retrieved from hospital files. Pregnancy was assessed by human chorionic gonadotropin findings in blood 12–14 days after IUI. The birth rate was calculated during follow-up.
Results: A total of 29 women aged 30–45 years were enrolled in the study. The historical control group included 94 women aged 28–46 years. Women who combined TCM with the procedures for undergoing IUI had significantly higher pregnancy (OR = 4.403, 95% CI 1.51–12.835, $p = 0.007$) and birth rates (OR = 3.905, 95% CI 1.321–11.549, $p = 0.014$) than the control group.
Conclusions: TCM appears to be beneficial as an adjunctive treatment in IUI procedures. Randomized controlled trials are needed to further assess the role of acupuncture and herbs in this setting.
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Keywords: Traditional Chinese medicine; Infertility; IUI; Integrative medicine

Introduction

The term "infertility" is generally defined as the failure of a couple to conceive after 12 months of regular unprotected intercourse. Around 10–15% of couples have difficulty conceiving at some point in their reproductive lives and seek specialist fertility treatment [1]. In 2000, about 200,000 babies were conceived through in vitro fertilization (IVF) worldwide, and in 2003, over 120,000 treatment cycles were performed in clinics in the United States alone [2,3].

Two critical factors in establishing the prognosis, time course for evaluation and treatment are the age of the female partner and the duration of infertility. In general, there is a decrease in fertility with age. Studies show a decrease in monthly fecundity beyond age 30 with a more significant decline after age 35 [4]. The causes of this age-related decrease in conception have to do with chromosomal abnormalities, spontaneous abortions, aging of oocytes and luteal phase defects that are characteristic findings among older women. In terms of the duration of infertility, women who have not conceived after 2–3 years have a poor prognosis, although the advances in assisted reproduction therapies (ART) have greatly enhanced the likelihood for success.

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Originating 2500 years ago in China, acupuncture is one of the most widespread forms of complementary and alternative medicine (CAM) in the USA and Europe [5–7]. The general theory of acupuncture is based on the premise that disruptions of natural balanced energy flow (Qi) are responsible for disease pathogenesis. The use of acupuncture is aimed at correcting these imbalances and restoring health by the stimulation of anatomical points on the skin with thin metallic needles that are usually manipulated by the practitioner's hands or by electrical stimulation. The National Institutes of Health (NIH) Consensus Panel on Acupuncture (1997) concluded that acupuncture may be useful as an adjunct treatment or an acceptable alternative in a comprehensive management program for avoiding the use or reducing the dose of conventional medication [8]. Large clinical trials have shown that acupuncture is an effective treatment for a variety of conditions [9,10].

The topic of infertility and traditional Chinese medicine (TCM) has sparked much curiosity over the past few years. Paulus et al. evaluated the effect of acupuncture on the pregnancy rate in ART (IVF) by comparing a group of patients who underwent acupuncture treatment shortly before and after embryo transfer with a control group that did not have acupuncture [11]. Those authors' conclusions were that acupuncture seemed to be a useful tool for improving pregnancy rates after IVF. More recent randomized controlled studies evaluated the effect of acupuncture on reproductive outcome in patients treated with IVF/intracytoplasmic sperm injection (ICSI) [12,13]. Again, both studies showed that acupuncture on the day of embryo transfer significantly improved the reproductive outcome of IVF/ICSI compared with no acupuncture. A recently published systematic review and meta-analysis of randomized controlled trials suggested that acupuncture given concomitantly with embryo transfer improves the rates of pregnancy and of live births among women undergoing IVF [14]. A research team from Hong Kong further validated this claim [15]. In addition, acupuncture may be effective in restoring ovulation in patients with polycystic ovarian syndrome [16], thus contributing a positive effect on subfertility. In contrast, several other studies failed to show any beneficial role of acupuncture in this field [17,18]. One such example showed that placebo acupuncture was more effective than real acupuncture, drugs or other procedures in enhancing pregnancy rates during IVF treatments [19].

Three main mechanisms have been suggested to explain the effect of acupuncture on subfertility: by regulating the hypothalamic–pituitary–ovarian axis thus affecting ovulation and the menstrual cycle [20], by affecting blood flow to the uterus [21] and by affecting endorphin production and secretion, thus inhibiting the central nervous system and reducing stress [22,23].

Herbal medicine is the other large branch of TCM. Similarly to acupuncture, herbal treatment aims at restoring balance and health by administering medicinal properties from plants, animals and minerals. The Chinese pharmacopoeia includes thousands of such herbal products, and their use in the field of gynecology and obstetrics both in China and in the west is widespread [24]. Some examples of these substances are Peonia Albae [25,26], Angelica Sinensis [27], Rehmannia [28,29] and Ligusticum Chuanxiong [30]. Both acupuncture and Chinese herbal medicine have been widely used for thousands of years in Eastern societies and are gaining rapid popularity in the west.

Aim of the study

To date, no studies have been done to assess effect of acupuncture in combination with Chinese herbs on patients undergoing intrauterine inseminations (IUI).

The present study employs a retrospective study, the first in our knowledge, to investigate the effect of both acupuncture and Chinese herbs as an adjunct to women undergoing AID.

Materials and methods

Design and participants

The Chinese Medicine Department is part of the Fertility Research Institute in the Tel Aviv Sourasky Medical Center (TASMC). It is an outpatient clinic that caters to both women and men undergoing fertility treatments. In order to form our study group, we included all the patients who underwent IUI by donor spermatozoa between the years 2002 and 2007. From 110 female patients treated in our clinic, 45 underwent artificial insemination by donor spermatozoa (AID). Excluding those who underwent IVF ($n = 16$), the remaining 29 women who underwent IUI treatments comprised our study group.

Treatment

A team of two accredited acupuncture practitioners selected acupuncture points and herbal formulae based on the TCM method of pattern discrimination. This method aims at harmonizing different organ systems based on symptoms (menses history, number of eggs in failed treatment protocols, basal body temperature, endometrial thickness and more) and signs (analysis of tongue and radial pulse, abdomen and body palpation). Once a pattern of disharmony has been determined, the treatment seeks to balance the body by acupuncture and herbal treatment. Tonification of the kidney system and of the spleen qi, tonification of the liver blood and heart blood, and harmonization of the liver are common treatment principles in many cases of infertility. They roughly correspond to anovulation patterns, thin endometrial lining and poor ovarian quality due to age.

The standard acupuncture intervention in our institution entails the insertion of disposable sterile 0.16-mm thick needles manufactured by "Seirin" company, Japan, and imported by "Medicin Bom" Co., with Israeli Health Department approval. Acupuncture is performed after alcohol wipe of the skin at the specific point. Needles are left in place and manipulated manually. Treatments generally last for 20–25 min and are administered weekly, with special attention given during the follicular phase. Treatment was sometimes given post-ovulation as well, such as in cases of luteal phase defect or frequent miscarriages for unknown causes.

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Table 1
Comparison of baseline data on women who underwent concomitant artificial insemination by donor spermatozoa (AID) and traditional Chinese medicine treatment (TCM, study Group) and women who underwent AID alone (controls).

	Study group	Controls
Total number of women	29	94
Mean age, years (SD)	39.43 (±4.1)	37.12 (±3.05)
Treatment cycles (SD)	9.1 (4.57)	6.01 (3.47)

Herbal formulae aimed at restoring balance and well-being are also tailored to specific needs. These formulae are frequently changed according to the menstrual cycle and medical interventions. Some examples of Chinese herbs that are used include Peonia Albae, Angelica Sinensis, Rehmannia and Ligusticum Chuanxiong. Herbal formulas are administered in powder or raw (dried) form and imported by "Zen Herbs", with Israeli Health Department approval.

Measurements

Our primary outcome measure was a positive human chorionic gonadotropin (HCG) blood test carried out 12–14 days post-ovulation. We also measured the birth rates of the study and control groups during follow-up.

Study group

The study group consisted of 29 women who underwent AID concomitantly with TCM. Primary infertility accounted for 58.6% of these cases. Their average age was 39.43 years (ranged 30–45), and they had previously undergone an average of nine AID cycles before seeking Chinese medical intervention. They continued the course of TCM for an average of five more cycles before discontinuing it.

Control group

The control group for this study was retrieved from a large pool of women who underwent AID in our Fertility Research Institute. We randomly retrieved patients' files between 2002 and 2007 and selected the women who were between 30 and 45 years of age at the beginning of AID treatments. Excluded were women diagnosed as having cancer or clotting irregularities as well as those who had undergone AID treatments for more than two consecutive years. A total of 94 women fulfilled these criteria. Their average age was 37.12 years and they had undergone an average of six AID treatments. Ten of these women (11%) had conceived in the past. All women in study and control groups had a hormonal profile that supported ovulation.

Table 1 summarizes the baseline characteristics of patients in both groups.

Statistical analysis

The patients' records were retrospectively reviewed for demographic information, such as age and number of previous cycles. We used the *t*-test to assess for differences in independent variables at baseline between intervention and control groups. The Fisher exact test was used to compare pregnancy and birth rates between the groups. We performed multiple regression to test for primary outcomes (pregnancy and birth rates) between the intervention and control groups, while controlling for independent variables (age, number of IUI cycles). All outcome measures were analyzed separately, with a p-value <0.05 indicating statistical significance. Statistical analyses were performed using SPSS version 17.

Table 2
Multi-variant analysis for primary outcomes (A) pregnancy (B) birth rates comparison between the intervention and control groups, while controlling for independent variables taken at baseline. All outcome measures were analyzed separately, with a p-value <0.05 indicating statistical significance.

	Odds ratio (95% CI)	p value
Pregnancy rates		
Age	0.82 (0.716–0.939)	0.004
Number of AID cycles	1.036 (0.934–1.149)	0.504
TCM intervention	4.403 (1.51–12.835)	0.007
Birth rates		
Age	0.81 (0.703–0.933)	0.004
Number of AID cycles	0.973 (0.97–1.09)	0.641
TCM intervention	3.905 (1.321–11.549)	0.014

Results

Nineteen of the twenty-nine women in the study group conceived (65.5%), of whom twelve delivered and six miscarried. Thirty-seven of the ninety-four women in the control group conceived (39.4%), of whom twenty-five delivered (26.6%) and twelve miscarried.

A multi-variant analysis for differences between the intervention and control groups, for primary dependent variables of pregnancy and birth rates while controlling for possible confounders (age, number of IUI treatments) has demonstrated that acupuncture group resulted in higher rates of both pregnancies (OR = 4.403, 95% CI 1.51–12.835, $p = 0.007$) and birth rates (OR = 3.905, 95% CI 1.321–11.549, $p = 0.014$). Table 2 summarizes the comparison of pregnancy and birth rates of the 29 patients who underwent concomitant TCM and AID and those of the 94 historical controls.

Six women (20.7%) in the acupuncture intervention group and twelve (12.8%) of the control comparison group had miscarriages. This had no statistical significance ($p = 0.367$).

There were no adverse effects caused by either the acupuncture needles or herbal formulae in the TCM patients.

Discussion

The results of this comparative study demonstrated that TCM may be effective in enhancing fertility of women undergoing AID. The study group showed a significantly higher ($p = 0.019$) cumulative pregnancy rate (65.5%) over an average 4.5-month treatment period compared to the control group (39.4%). In comparison, a retrospective analysis of 6139 AID cycles conducted

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in our facility between 1980 and 1997 showed a cumulative pregnancy rate of 36%, 53%, and 75% for 3, 6 and 12 months, respectively [31]. It should be noted that the average age of the women who underwent combined TCM and AID was 39 years, which is two years older than the average age of the control group. As shown in Table 2A this age difference has statistical relevance and makes the results more meaningful, given that fertility decreases as women age.

The birth rate of the study group was also higher than the control group (41.4% vs. 26.9%, respectively, $p = 0.014$).

Infertility treatments are becoming increasingly more common. Women who seek medical interventions are exposed to varying amounts of hormones, ultrasound examinations, blood tests and, in the case of IVF, general anesthesia. These treatments also occasionally give rise to unwanted side effects, such as hot flashes, thinning of the endometrial lining, ovarian hyperstimulation, weight gain and mental disturbances [32–34]. There were no adverse effects associated with the use of acupuncture needles or herbal formulae in any of our patients, in agreement with the findings of large-scales studies in which side effects associated with acupuncture tended to be uncommon, mild and reversible [35,36].

TCM treatments that are tailored for specific diagnoses try to restore balance to the body by changing acupuncture points and herbal formulae as needed. This is also the main reason why it is so difficult to execute a randomized double blind standardized study in which all patients undergo one unmodified treatment protocol. One example of this difficulty is described in a recent work that allocated real or placebo acupuncture on the day of embryo transfer to 370 randomly selected patients. The results unexpectedly showed an overall pregnancy rate that was significantly higher in the placebo acupuncture group than that in the real acupuncture group [19]. We therefore believe that retrospective studies such as these, based on TCM differential diagnosis, will serve as base for double blind randomized controlled studies on those set of acupoints that have shown positive results. Chinese herbal formulas based on accepted TCM differential diagnosis can be formulated as well. A generally accepted TCM diagnosis with a standard set of acupoints and herbal formulas will allow widespread use of these ancient techniques.

Limitations of the study: First, the number of patients enrolled in this study is relatively small. Secondly, our department serves as an out-patient clinic for women who have an hormonal profile that support their ovulation. Since many women undergo their follow up at their HMO, we do not have access to the complete hormonal profile of the comparative control group. Finally, the methodology of the study is a comparative retrospective study, which needs to be further validated by randomized controlled trials.

In conclusion, our study was the first to combine acupuncture treatment with Chinese herbal medicine and demonstrated that this approach is safe and promising as an effective adjunctive therapy to conventional care for infertility patients. Randomized controlled trials are needed to further assess the role of TCM as part of treatment management for increasing the number of healthy pregnancies among women who undergo intrauterine insemination.

Conflict of interest

None.

References

[1] Evers JL. Female subfertility. Lancet 2002;360:151–9.
[2] Centers for Disease Control and Prevention. Assisted reproductive technology success rates: national summary and fertility clinic reports 2003. Atlanta, GA: US Department of Health and Human Services; 2005.
[3] Adamson GD, De Mouzon J, Lancaster P, Nygren KG, Sullivan E, Zegers-Hochschild F. World collaborative report on in vitro fertilization, 2000. Fertil Steril 2006;85:1586–622.
[4] Bongaarts J. Infertility after age 30: a false alarm. Fam Plann Perspect 1982;14:289–90.
[5] Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, et al. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. J Am Med Assoc 1998;280:1569–75.
[6] Ernst E. Prevalence of use of complementary/alternative medicine: a systematic review. Bull World Health Organ 2000;78:252–7.
[7] Barnes PM, Bloom B, Nahin R. CDC National Health Statistics Report #12. Complementary and Alternative Medicine Use Among Adults and Children: United States, 2007. December 10, 2008 NIH.
[8] Consensus Development Panel of Acupuncture. JAMA 1998;280:1518–24.
[9] Berman BM, Lao L, Langenberg P, Lee WL, Gilpin AM, Hochberg MC. Effectiveness of acupuncture as adjunctive therapy in osteoarthritis of the knee: a randomized, controlled trial. Ann Intern Med 2004;141:901–10.
[10] Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR. Acupuncture for tension-type headache. Cochrane Database Syst Rev 2009;1:CD007587.
[11] 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;77:721–4.
[12] Westergaard LG, Mao Q, Krogslund 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 trail. Fertil Steril 2006;85:1341–6.
[13] 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;85:1347–51.
[14] Manheimer E, Zhang G, Udoff L, Haramati A, Langenberg P, Berman BM, et al. Effects of acupuncture on rates of pregnancy and live birth among women undergoing in vitro fertilisation: systematic review and meta-analysis. Br Med J 2008;336:545–9.
[15] 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.
[16] Stener-Victorin E, Waldenström U, Tägnfors U, Lundeberg T, Lindstedt G, Janson PO. Effects of electro-acupuncture on anovulation in women with PCOS. Acta Obstet Gynecol Scand 2000;79:180–8.
[17] Pinborg A, Loft A, Andersen AN. Acupuncture with in vitro fertilisation. Br Med J 2008;336:517–8.
[18] El-Toukhy T, Khalaf Y. The impact of acupuncture on assisted reproductive technology outcome. Curr Opin Obstet Gynecol 2009;21:240–6.
[19] 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;24:341–8.
[20] Ferin M, Vande Wiele R. Endogenous opioid peptides and the control of the menstrual cycle. Eur J Obstet Gynecol Reprod Biol 1984;18:365–73.
[21] Stener-Victorin E, Waldenström U, Andersson SA, Wikland M. Reduction of blood flow impedance in the uterine arteries of infertile women with electro-acupuncture. Hum Reprod 1996;11:1314–7.
[22] Ku YH, Chang YZ. Beta-endorphin- and GABA-mediated depressor effect of specific electroacupuncture surpasses pressor response of emotional circuit. Peptides 2001;22:1465–70.

Please cite this article in press as: Sela K, et al. Acupuncture and Chinese herbal treatment for women undergoing intrauterine insemination. Eur J Integr Med (2011), doi:10.1016/j.eujim.2011.04.020

[23] Kim JH, Nam D, Park MK, Lee ES, Kim SH. Randomized control trial of hand acupuncture for female stress urinary incontinence. Acupunct Electrother Res 2008;33:179–92.
[24] Maciocia G. Obstetrics and gynecology in Chinese medicine. New York: Churchill Livingston; 1998.
[25] Hsu FL, Lai CW, Cheng JT. Antihyperglycemic effects of paeoniflorin and 8-debenzoylpaeoniflorin, glucosides from the root of Paeonia lactiflora. Planta Med 1997;63:323–5.
[26] Takeuchi T, Nishii O, Okamura T, Yaginuma T. Effect of paeoniflorin, glycyrrhizin and glycyrrhetic acid on ovarian androgen production. Am J Chin Med 1991;19:73–8.
[27] Lau CB, Ho TC, Chan TW, Kim SC. Use of dong quai (Angelica sinensis) to treat peri- or postmenopausal symptoms in women with breast cancer: is it appropriate? Menopause 2005;12:734–40.
[28] Guo LM, Zhang RX, Jia ZP, Li MX, Wang J, Yin Q. Effects of Rehmannia glutinosa oligosaccharides on proliferation of HepG2 and insulin resistance. Zhongguo Zhong Yao Za Zhi 2007;32:1328–32.
[29] Chao SL, Huang LW, Yen HR. Pregnancy in premature ovarian failure after therapy using Chinese herbal medicine. Chang Gung Med J 2003;26:449–52.
[30] Tuttle RS, Marmelstein L, Trad T, Reddy S, Radley T. In vitro uterine response to tetramethylpyrazine, the active constituent of chung chong (a traditional Chinese medicine). Am J Obstet Gynecol 1989;161: 1319–23.
[31] Botchan A, Hauser R, Gamzu R, Yogev L, Paz G, Yavetz H. Results of 6139 artificial insemination cycles with donor spermatozoa. Hum Reprod 2001;16:2298–304.
[32] Haritha S, Rajagopalan G. Follicular growth, endometrial thickness, and serum estradiol levels in spontaneous and clomiphene citrate-induced cycles. Int J Gynaecol Obstet 2003;81:287–92.
[33] Kahnberg A, Enskog A, Brännström M, Lundin K, Bergh C. Prediction of ovarian hyperstimulation syndrome in women undergoing in vitro fertilization. Acta Obstet Gynecol Scand 2009;88:1373–81.
[34] Huisman D, Raymakers X, Hoomans EH. Understanding the burden of ovarian stimulation: fertility expert and patient perceptions. Reprod Biomed Online 2009;19 Suppl. 2:5–10.
[35] White A, Hayhoe S, Hart A, Ernst E. BMAS and AACP. British Medical Acupuncture Society and Acupuncture Association of Chartered Physiotherapists. Survey of adverse events following acupuncture (SAFA): a prospective study of 32,000 consultations. Acupunct Med 2001;19: 84–92.
[36] Melchart D, Weidenhammer W, Streng A, Reitmayr S, Hoppe A, Ernst E, et al. Prospective investigation of adverse effects of acupuncture in 97,733 patients. Arch Intern Med 2004;164:104–5.

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