

Use of acupuncture in female infertility and a summary of recent acupuncture studies related to embryo transfer

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Abstract

During the last five years the use of acupuncture in female infertility as an adjuvant to conventional treatment in assisted reproductive technology (ART) has increased in popularity.

The present paper briefly discusses clinical and experimental data on the effect of acupuncture on uterine and ovarian blood flow, as an analgesic method during ART, and on endocrine and metabolic disturbances such as polycystic ovary syndrome (PCOS).

Further it gives a summary of recent studies evaluating the effect of acupuncture before and after embryo transfer on pregnancy outcome. Of the four published RCTs, three reveal significantly higher pregnancy rates in the acupuncture groups compared with the control groups. But the use of different study protocols makes it difficult to draw definitive conclusions. It seems, however, that acupuncture has a positive effect and no adverse effects on pregnancy outcome.

Keywords

Electroacupuncture, infertility, anovulation, polycystic ovary syndrome, pain relief, embryo transfer.

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Introduction

Acupuncture, an ancient Chinese system of diagnosis and treatment, has been shown to alleviate a variety of conditions, including pain during ovum pick-up and male and female infertility. The delicate underlying mechanisms of acupuncture are usually described in the language of Traditional Chinese Medicine (TCM), but in later years the physiological background of acupuncture has been increasingly discussed.

The use of acupuncture as an adjuvant to conventional treatment in assisted reproductive technologies (ART) that aim to improve fertility is becoming more common. At the same time, the number of studies that investigate the effect of acupuncture during ART is beginning to increase. Despite this, acupuncture is still considered suspect in some circles.^{1,2} The studies are ‘dissected’, and many scientists claim that the higher pregnancy rates in the acupuncture groups compared with the other experimental and control groups may be due to placebo effects.

One reason for the criticism, and for the divergence in the evaluation of the studies, might be a lack of standardisation: most researchers design their own study protocols and have unique acupuncture recipes – they do not try to repeat and build on an existing, positive protocol. For this reason it is difficult to compare and evaluate various studies and to perform a homogeneous meta-analysis.

When debating if and how alternative treatments have been scientifically tested, one should realise that many treatments in conventional medicine also lack rigorous testing, a failing that the scientific community generally acknowledges must be remedied. It might also be argued that both conventional and alternative medicine rely on anecdotes, some of which are published as case reports in peer reviewed journals. Two major questions must be solved before acupuncture can be accepted to the same degree as conventional therapies: first, does acupuncture have a beneficial effect on any medical condition, and secondly, is this

outcome due to the specific effect of the needle or to a placebo effect.

In this paper, scientific publications will be discussed that in one or another way have evaluated the effect of acupuncture in women who suffer from infertility; all comments and views are our own.

Effect of acupuncture on uterine and ovarian blood flow

Our own group first investigated whether repeated acupuncture treatments given over a period of four weeks exerted a general inhibiting effect on uterine sympathetic tone, thereby reducing high blood flow impedance in the uterine arteries and increasing uterine blood flow and, hypothetically, endometrial receptivity.^{3,4} It is well known that successful in-vitro fertilisation (IVF) and embryo transfer (ET) requires optimal endometrial receptivity at the time of implantation. Arterial uterine blood flow impedance is considered a valuable method of assessing endometrial receptivity.

Measurements of arterial uterine blood flow impedance by doppler ultrasonography was used to elucidate the effect of eight electroacupuncture (EA) treatments (for specific points, see ref) in 10 infertile women with high uterine blood flow impedance.⁵ All women were down-regulated with gonadotropin-releasing hormone (GnRH) analogue to avoid the effect of endogenous hormones. We found that repeated EA treatments reduced blood flow impedance to normal levels.⁵

We then designed experimental studies on rats to determine whether EA increases ovarian blood flow.^{6,7} We found variations in ovarian blood flow depending on frequency and needle placement. The strongest ovarian blood flow response occurred when needles were placed in the abdominal muscles, that is, in the somatic innervations of the uterus and ovaries, or in the abdominal and leg muscles. Optimal frequency seems to be low, 2Hz burst frequency or 10Hz depending on the stimulator used. We were also able to demonstrate that the effect was mediated via ovarian sympathetic nerves, via supraspinal reflexes.

An interesting experimental observation in the literature is that EA stimulation at LI4 significantly reduced uterine motility in pregnant rats, most probably by inhibiting the expression of COX-2 enzyme in the endometria and myometria of pregnant rats.⁸ No attempts to replicate our observation that

repeated EA treatments in humans result in increased uterine blood flow have been made in a larger group.

At this time, we can only inform patients that EA treatment with needles placed in the abdominal and leg muscles, stimulated with low frequency EA prior to IVF will most likely increase uterine and ovarian blood flow with no apparent adverse effects.

Acupuncture in pain alleviation during oocyte aspiration

The next study we contemplated was designed to evaluate the pain relieving effect of acupuncture during oocyte aspiration. Pain during oocyte aspiration is caused by the passage of the needle through the vaginal wall and by mechanical stimulation of the ovary. The pain perceived during oocyte aspiration is often compared to the intense pain perceived during menstruation. Oocyte aspiration is usually quick, and the analgesic method used must be both effective and safe. Our own group has performed five studies to evaluate both the pain relieving effect of EA during oocyte aspiration and the effect of EA on IVF outcome, ie the number of pregnancies.⁹⁻¹³

EA was found to induce pain relief similar to that induced by a fast-acting opiate during oocyte retrieval and to have fewer negative side effects.^{9,10} In the first study, we found a significantly higher pregnancy rate in the acupuncture group than in the control group. After repeating the trial, however, with a larger number of patients based on a power analysis and with the primary aim of studying pregnancy rate, we observed no difference in pregnancy rate between the groups.¹⁰

Acupuncture effects on hormonal disturbances such as PCOS and anovulation

The approach used by most studies in this area is that of a single intervention trial with variables analysed on an intention-to-treat basis. Unfortunately, poor design and lack of valid outcome measures and diagnostic criteria, which make it difficult to interpret results, flaw most of these studies.

We recently conducted a study in patients with well defined and diagnosed polycystic ovary syndrome (PCOS) and anovulation to elucidate the effect of repeated low burst frequency (2Hz) EA treatments on endocrinological and neuro-endocrinological parameters as well as on

anovulation.¹⁴ This study showed that repeated EA treatments exert long lasting effects on both endocrinological parameters and anovulation. These results are in line with previous results, but they must be verified by randomised, comparative studies. These studies did not shed any light on the underlying mechanisms of EA, which for obvious reasons, are difficult to study because tissue samples from the ovaries and central nervous system are unobtainable.

Polycystic ovaries (PCO) experimentally induced by a single intramuscular injection of estradiol valerate (EV) in rats share many endocrinological and morphological characteristics of naturally occurring, human PCOS. We therefore used the steroid-induced rat PCO model to investigate the effects and possible mechanisms of repeated EA treatments under light anaesthesia. This was done by analysing concentrations of corticotrophin releasing factor (CRF),¹⁵ endothelin-1,¹⁶ and nerve growth factor (NGF) in the ovaries, the adrenal glands, and the central nervous system, respectively.^{16;17} We also analysed hypothalamic β -endorphin concentrations and immune function.¹⁸ Changes were found in the expression and distribution of α_1 -adrenoceptor subtypes after repeated EA treatments and four weeks of physical exercise.¹⁹⁻²¹

These results indicate that low burst frequency (2Hz) EA modulates activity in the sympathetic nervous system and that there is a functional interaction between activity in the nervous and the endocrine systems.

In conclusion, clinical and experimental evidence seem to indicate that acupuncture may have a beneficial effect on women with PCOS and anovulation. In a woman with PCOS, acupuncture may therefore be an alternative or a complement to pharmacological induction of ovulation that has no negative side effects. However, more randomised controlled trials (RCTs) in women with well defined diagnoses are needed.

Acupuncture before and after embryo transfer

At this time, only four RCTs have investigated the effect of acupuncture at the time of ET on the pregnancy rate of patients who undergo assisted reproductive therapies. Paulus et al (2002) performed the first prospective RCT.²² They randomised 160 patients to receive either acupuncture (n=80) 25

minutes before and after ET or a standard regimen with no acupuncture (n=80) but with bed rest 25 minutes after ET. A combination of traditional acupuncture and auricular acupuncture was used. The following acupuncture points were used:

- Before ET: CV6, SP8, LR3, GV20, and ST29
- After ET: ST36, SP6, SP10, and LI4.

Each treatment lasted 25 minutes, and the needles were stimulated to elicit the sensation of *de qi* twice. Further, two needles were inserted in the right ear and two in the left and remained in place for 25 minutes. After ET, the side of auricular acupuncture was changed and needles were left in place for 25 minutes. The ear points used were: 55 (*Shenmen*), 58 (*Zhigong*), 22 (*Neifenmi*), and 34 (*Naodian*). The acupuncture points used in the study were chosen according to TCM.

The primary focus of the study was clinical pregnancy rate, and only patients with good embryo quality were included in the study. In addition, the pulsatility index (PI) for each uterine artery was calculated immediately before and after ET in all patients. A maximum of three embryos were replaced. Luteal phase support was given in the form of progesterone administered vaginally three times a day.

There were no between-group differences regarding patient characteristics, numbers of previous IVF and intra-cytoplasmic sperm injection (ICSI) treatments, endometrial thickness on the day of transfer or PI before and after ET. The clinical pregnancy rate, however, was significantly in favour of acupuncture: 26.3% (control) versus 42.5% (P=0.03). The authors concluded that acupuncture at the time of ET improves the clinical pregnancy rate in IVF/ICSI patients, but they recommended that future studies should include a third arm – involving placebo needles to rule out possible psychological or psychosomatic effects of acupuncture.

Interestingly, the same group performed a placebo-controlled trial using the Streitberger placebo needle.^{23;24} In total, 200 patients were randomised to ET with acupuncture (n=100) or ET with placebo needling (n=100). The experimental setup was the same as in the first study except that the control group received placebo needling; the same acupuncture

points, selection, and stimulation were used in both groups. A third arm – a control group – was missing.

The clinical pregnancy rate was 43% in the acupuncture group versus 37% in the placebo needling group, and this difference was not significant. The authors concluded that the reason why acupuncture was not significantly better than placebo needling might be due to methodological problems – that the placebo model was not a ‘real’ placebo model. The placebo needle used induced an acupressure effect, thus leading to a higher pregnancy rate than in a population with no complementary treatment. Unfortunately, this trial has only been presented and published as an abstract.

This year (2006), three prospective RCTs were published in the May issue of *Fertility and Sterility*; the studies investigated the effect of acupuncture on the reproductive outcome of IVF/ICSI patients at the time of ET.²⁵⁻²⁷

In the study by Westergaard et al,²⁵ patients were randomised on the day of oocyte retrieval into one of three groups: to receive acupuncture on the day of ET (ACU 1), to receive acupuncture on the day of ET and again two days later (ACU 2), or to receive no acupuncture (control). According to the authors, the rationale for the ACU 2 group was to explore whether an additional acupuncture treatment closer to the time of implantation improves the quality of the endometrium due to a positive effect on uterine blood flow, which would further improve pregnancy and implantation rates. The primary focus of this study was to compare rates of positive pregnancy tests, clinical pregnancy rates, and on-going pregnancy rates between the three groups. Unlike the study by Paulus et al,²² no additional auricular acupuncture was used. The 273 patients were allocated to one of three groups: ACU 1 (95 patients), ACU 2 (91 patients), or control (87 patients). The acupuncture in ACU 1 was given 25 minutes before and 25 minutes after ET. In ACU 2, patients were treated according to the same protocol used in ACU 1 but received a third acupuncture treatment of 25 minutes duration two days after ET. In the control group, patients had bed rest for one hour after ET.

The following acupuncture points were used in ACU 1 and ACU 2:

- Before ET: GV20, ST29, SP8, PC6, and LR3.
- After ET: ST36, SP6, SP10, and LI4.

The following points were used in ACU 2:

- Two days after ET: GV20, CV3, ST29, SP10, SP6, ST36, and LI4.

A maximum of three embryos were transferred, and luteal support in the form of progesterone was administered vaginally three times a day in combination with 2mg estradiol orally twice a day.

No differences in patient characteristics, ovarian stimulation regimen, total consumption of gonadotrophins, or numbers of transferable and transferred embryos were observed. The pregnancy rate, clinical pregnancy rate, and on-going pregnancy rate, however, were significantly higher in ACU 1 than in the control group (42% versus 28%, $P=0.044$; 39% versus 24%, $P=0.038$; 36% versus 22%, $P=0.049$). Although all parameters in ACU2 tended to be higher than in the control group, differences were not significant. When the acupuncture groups were combined, a significant overall improved outcome was seen in the acupuncture groups compared to the control group. Interestingly, there seemed to be an age specific limit of 38 years in ACU 1 regarding a positive effect of acupuncture. Patients younger than 38 years had significantly higher clinical and on-going pregnancy rates compared to the control group, whereas in women aged 38 and older, differences compared to the control group were not significant. Finally, rates of early pregnancy loss tended to be higher in ACU 2 compared to ACU 1 and the control group, but again, these differences were not significant.

The design of this study included no arm with placebo needles. The authors concluded that acupuncture given on the day of ET significantly improves the reproductive outcome of IVF/ICSI patients, supporting the findings of Paulus et al.²²

In the study by Smith et al,²⁶ 228 patients were randomised to receive acupuncture ($n=110$) or placebo acupuncture with the Streitberger needle ($n=118$). The acupuncture treatment protocol was a modification of the protocol used by Paulus et al.²² Three acupuncture treatments were given, the first on day nine of stimulation injection, the second and third immediately before and after ET. Women in the placebo group received placebo needling at points located close to but not at the real acupuncture points.

Differences in pregnancy outcome between the acupuncture group (31%) and the placebo group (23%) were not significant. The authors concluded that although the odds for achieving a pregnancy were 1.5 higher in the acupuncture group compared with the placebo group, the result was not significant. But a minor positive treatment effect could not be excluded.

Dieterle et al randomised 116 patients to receive acupuncture (n=116) or placebo acupuncture (n=109).²⁷ Both groups received two acupuncture treatments, one after ET and a second one three days later. The points in the placebo acupuncture group were designed not to influence fertility.

The following points were used in the acupuncture group:

- After ET: CV4, CV6, ST29, PC6, SP10, and SP8
- Three days after ET: LI4, SP6, ST36, KI3, and LR3

The following points were used in the placebo group:

- After ET and 3 days after ET: TE9, TE12, GB31, GB32, and GB34

Moreover, a seed with a special Chinese medical herb (*Caryophyllaceae*) was placed on the patients' ears in both groups.

The pregnancy outcome differed significantly between the acupuncture group (28.4%) and the placebo group (13.8%) (P=0.01). The pregnancy rate in the placebo group, however, must be considered very low. The authors do not report whether this was a normal outcome for their clinic. Interestingly, although the success rate decreases with the number of previous ART attempts, the benefits imparted by the acupuncture appear to increase. However, the numbers of patients undergoing ≤ 3 attempts were low.

They conclude that acupuncture significantly improves the IVF/ICSI outcome and that acupuncture might be a complementary option for patients undergoing IVF/ICSI even though further evidence is needed.

Of the four published RCTs, three reveal significantly higher pregnancy rates in the acupuncture groups compared with the control

groups. But again, the use of different study protocols makes it difficult to draw definitive conclusions. It seems, however, that acupuncture has a positive effect and no adverse effects on pregnancy outcome. Two large on-going RCTs, one in Denmark and one in the US, are currently evaluating the efficacy of acupuncture on pregnancy outcome, and we have to await the results of these studies to draw firm conclusions.

Finally, two retrospective studies evaluated the effects of acupuncture on IVF outcomes using a combination of protocols reported by Stener-Victorin et al,^{5,28,29} with eight EA treatments during hormonal stimulation, and the protocols of Paulus et al,²² described above. In one study,²⁶ 147 patients considered to be poor responders were included; 53 received acupuncture as described and 94 received no acupuncture (control). The pregnancy rate in the acupuncture group was significantly higher than in the control group, 53% versus 38% (P=0.01). In the other retrospective study,²⁵ 114 infertile patients were included; 53 received acupuncture and 61 received no acupuncture. The pregnancy rate was significantly higher in the acupuncture group compared with the no acupuncture group, 51% versus 38% (P=0.05). The authors concluded that the combination of the Stener-Victorin and the Paulus EA protocols has a positive effect on pregnancy outcome in IVF.^{5,22}

The results of these two studies, although retrospective, combining acupuncture during the down-regulation and stimulation period of IVF with acupuncture at embryo transfer are interesting, as this opens the possibility of a positive impact of adding weekly acupuncture to the IVF protocol. Clearly RCT's are needed to evaluate this new concept.

General comment

Acupuncture is a safe intervention in the hands of competent practitioners,³⁰ and material costs are low. Few topics are as controversial as acupuncture, especially within the scientific community. The evidence seems to be split down the middle between negative and positive results. Proponents and opponents do not speak the same language and seem to be missing each other's points. The lack of well designed studies on acupuncture only increases the scepticism of the opponents. Whether or not acupuncture has a true effect, the chance that it might

is a compelling reason for the scientific community to investigate the method, particularly as there is a plausible biological action.

Summary points

The use of acupuncture in female infertility has increased in popularity

Acupuncture appears to have some effect on uterine and ovarian blood flow

Acupuncture has been used successfully as an analgesic method during oocyte retrieval

Acupuncture may modify the endocrine and metabolic disturbances in polycystic ovary syndrome

Acupuncture appears to have a positive effect and no adverse effects on pregnancy outcome, although the data are rather heterogeneous

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