



ZITA WEST

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# Acupuncture and Fertility

A review of the current literature.

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## 1. Introduction

The use of acupuncture with respect to managing fertility (naturally or during assisted reproductive techniques) or to treat gynaecological problems is gaining popularity but remains controversial. There appears much confusion over the impact this traditional Chinese medicine has on such health issues, and current studies are clearly conflicting. However, many Western based fertility or IVF clinics now offer acupuncture as an adjunct to other treatments and there is ongoing research into its effects and mechanism of action.

Despite its increasing use, currently there is a lack of published research. Western medicine places a high importance on animal research and randomised controlled trials before accepting a new medicine or technique into mainstream use. Acupuncture research has been criticised for failing to adhere to these design protocols, and consequently there is confusion and debate regarding its efficacy. However, in recent years there has been an increase in randomised controlled trials, and several studies using model animals to elucidate the mechanism of action. This report aims to summarise the current published works on acupuncture and several aspects of fertility including management of fertility and several gynaecological problems.

PubMed was searched using several search terms to identify original publications relevant to this report. Summaries are presented in Tables One to Five, references at the end of this document.

Table One: Acupuncture and fertility management in patients not receiving ART, supported by animal research.

Table Two: Acupuncture and IVF outcomes when used at times other than embryo transfer

Table Three: Acupuncture and IVF outcome when used at embryo transfer

Table Four: Acupuncture and effect on PCOS

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## 2. Acupuncture and Fertility Management

Traditional Chinese Medicine (TCM) is still a primary source of preventative medicine and treatment in many Asian Countries, and is comprised of acupuncture together with Chinese Herbal Medicines. TCM has been used in such cultures to treat gynaecological concerns for many years. As early as 1237 AD the first TCM book dedicated solely to gynaecology and obstetrics was published; *The Complete Book of Effective Prescriptions for Diseases of Women*. Since then TCM has been used for endometriosis, infertility, dysmenorrhea, abnormal uterine bleeding, premenstrual syndrome, menopausal syndrome, uterine fibroids and chronic pelvic inflammation, polycystic ovarian syndrome (PCOS), cervicitis and vaginitis. For a good review see Zhou & Qu, 2009.

A recent questionnaire study set by the British Acupuncture Council reported that 80% of UK acupuncture practitioners said the majority of their fertility-based work was related to assisted conception. (Bovey, et al., 2010) This is clearly different from its wide-spread use in Asian countries, and reflects how acupuncture is most commonly used as an adjunct to Western medicine, and is unlikely to constitute a primary source of treatment in Western countries.

As acupuncture has become more common in Europe, scientific research has also increased, albeit slowly. There is a bias towards research into acupuncture's use during ART, although there are a number of studies investigating its benefit and mechanism with regard to infertile patients not undergoing ART. Interestingly, while it has been reported that the use of acupuncture for males is uncommon (Bovey, et al., 2010) there appears to be a research bias towards investigating male fertility parameters in patients not receiving concomitant ART.

### 2.1 Fertility Management without assisted conception

#### 2.1.1 Female benefits

An early attempt to elucidate acupuncture's effect on hormonal profiles was published in 1976 in *The American Journal of Chinese Medicine (AJCM)*. (Aso, et al., 1976) Using fertile patients at various stages in their menstrual cycle, the authors concluded that properly performed electro-acupuncture stimulation might affect the female endocrine function. A later study more specifically focusing on 45 infertile patients concluded that auricular acupuncture would offer a valuable alternative therapy for female infertility due to hormone disorders, restoring normal ovulation. (Gerhard and Postneek, 1992) The authors saw that

various disorders of the autonomic nervous system normalised during acupuncture, and only matched-control patients receiving hormonal treatments suffered side-effects. Another study, using points Ganshu (UB 18), Shenshu (UB 23), Guanyuan (Ren 4), Zhongji (Ren 3), and Sanyinjiao (Sp 6) also concluded acupuncture could modulate the endocrine system to induce ovulation. (Mo, et al., 1993) Lastly, in 1997 Chen *et al* published their experiences of both human and animal studies into electro-acupuncture and ovulation, and concluded electro-acupuncture could possibly regulate endocrine dysfunction by several mechanisms, including influencing gene expression within the brain normalising secretion of GnRH, LH and oestrogen to restore normal and functional ovulation. (Chen, 1997)

A study in 1996 also suggested acupuncture could modulate female fertility by virtue of the sympathetic nervous system. Ten women known to have high pulsatility indexes (PI) in uterine arteries were given acupuncture for one month, on top of gonadotrophin-releasing hormone down-regulation to remove any endogenous causes for changes in their PI. Post-acupuncture PI values were significantly reduced compared to their baseline values, and the authors suggested this was due to the acupuncture having a central inhibitory effect on the sympathetic nervous system. (Stener-Victorin, et al., 1996) A recent study found that manual acupuncture at bilateral SP6 could elicit immediate reductions in uterine PI values. (Yu, et al., 2010)

Since the mid 1990's there have only been a few studies focusing on sub-fertile patients not undergoing ART. However, they appear rather consistent in identifying benefits to acupuncture, with results regarding ovulation either equivalent or better than Western hormonal treatments, and similarly positive results regarding pregnancy rates. However, it should be noted that full text versions of these studies are currently unavailable so a complete critical analysis is not possible. The exact acupuncture timing and regime used is unknown, as are patient ages. The mechanism by which acupuncture achieves the results is likely not established by these studies. More research is needed to build on these preliminary results, but the current studies appear to have positive outcomes and improve patients' fertility without resorting to IVF. Studies using patients with PCOS suggest acupuncture may have some ability to restore normal ovulation.

Animal studies have also been used to help confirm the impact provided by acupuncture. A paper published in 2003 using a rat model concluded electro-acupuncture possibly mediated

its action by increasing GnRH cell numbers in the brain, resulting in a similar increase in blood oestrogen levels. They also stated corticotropin-releasing hormone (CRH) played an important role in electro-acupunctures capability to restore normal function of the hypothalamus-pituitary-ovarian axis. (Zhao, et al., 2003) Rat models also support a true benefit for acupuncture on implantation, as electro-acupuncture after conception can allow normal endometrium development, antagonising the effect of Mifepristone; a progesterone receptor antagonist used as an abortifacient if given during the first two months of pregnancy. (Liu, et al., 2007a) A further study by the same group concluded acupuncture may work by modulating both hormones and their receptor expression levels. (Liu, et al., 2007b) Later they concluded acupuncture's effect was mediated by increasing the levels of connexin 43 mRNA expression (Huang, et al., 2010).

Other rat models have reported increased *ovarian* blood flow responses to electro-acupuncture, mediated by a reflex response via ovarian sympathetic nerves (Stener-Victorin, et al., 2003) although this was later shown to be frequency dependent, and dependent on the stage of the oestrous cycle. (Stener-Victorin, et al., 2006) Others have reported acupuncture can regulate the function of hypothalamus-pituitary-ovarian axis by modulating the activity of numerous brain nuclei, measured by changes in C-fos expression. (Hu, et al., 1993) A rabbit model has also reported effects on brain activity, stating GnRH levels (which are pulsatile during ovulation) from the mediobasal hypothalamus (MBH) become amplified after acupuncture. (Yang, et al., 1994)

Consequently, while further validation is necessary, it is becoming accepted that acupuncture may improve fertility by modulating the sympathetic nervous system, affecting uterine and ovarian blood flow, and more directly interacting with the hypothalamic-pituitary-ovarian axis by affecting hormone (and receptor) expression level.

### **2.1.2 Male Benefits**

While investigations into acupuncture's ability to aid men whilst undergoing ART are very limited, there have been a number of studies investigating its ability to modulate natural fertility parameters in sub-fertile men. An early study reported significant improvements in total sperm count, concentration, motility and hormonal profiles (compared to baseline) after 28 males received 10 treatments over three weeks. (Fischl, et al., 1984) Another study using

28 men reported increases in sperm concentration and motility but not in volume, nor the men's psychological outlook as assessed by a written test. (Riegler, et al., 1984) The exact acupuncture protocol (timing, duration etc) is however unknown.

Since then, a number of original research studies have been published. Although they are also conflicting with regard to what degree sub-fertility may be managed by acupuncture, they have all reported some positive results. Routine and biochemical semen parameters, levels of anti-sperm antibodies, testicular blood flow and scrotal temperature have all been suggested to be amenable to acupuncture.

The exact mechanism by which this occurs is not currently clear, and while the above studies do have several shortcomings, collectively they highlight the need for ongoing research to further validate the use of acupuncture in a male-fertility setting.

Acupuncture is likely to have a high psychological mechanism, as further discussed below. Consequently is a surprising that there is little research into acupuncture and ejaculation problems. A systematic review published last year identified just four suitable studies and concluded '*the evidence is insufficient to suggest that acupuncture is an effective intervention for treating erectile dysfunction (ED). Further research is required to investigate whether there are specific benefits of acupuncture for men with ED.*' (Lee, et al., 2009) Nonetheless, a thorough study using a diabetic-induced rat for a model of physiological erectile dysfunction noted that moxibustion at "Shenshu" (BL 23) and "Sanyinjiao" (SP 6) has a significant effect on the erectile function in the rats, which was related to improved blood sugars and promotion of the NO-cGMP pathway (a signalling transduction system) within the penis. (Yang, et al., 2007) Further research into this area is warranted to determine whether acupuncture can improve symptoms of erectile dysfunction, regardless of whether it develops for physiological or psychological reasons.

## **2.2 Assisted Reproductive Techniques**

Research into the benefits of acupuncture during IVF has gained some focus, with four original research studies being published this year. (Andersen, et al., 2010; Madaschi, et al., 2010; Moy, et al., 2010; So, et al., 2010) Collectively these studies have investigated pregnancy rates when acupuncture was given during stimulation or in conjunction with

embryo transfer, and all have reported finding no significance differences when using acupuncture.

The use of acupuncture during IVF is currently surrounded with confusion, and inconsistencies. While the majority of studies appear to satisfactorily match their control groups to treatment groups, the patient samples are highly heterogeneous in terms of age, fertility cause and previous number of ART cycles. Differing definitions of clinical pregnancy, ongoing pregnancy etc confuse direct comparisons. Each country has different laws regarding embryo selection and number of embryos routinely transferred, and this means each paper has highly contrasting IVF protocols, adding further difficulty to drawing conclusions based on multiple studies.

Studies have predominantly focused on performing acupuncture during the stimulation phase or pre- and post-embryo transfer in an attempt to improve pregnancy rates, although some have performed acupuncture solely after embryo transfer. Tables two and three discuss these original papers. While there have been a number of reviews, meta-analyses into acupuncture during IVF protocols are very limited, with some focusing solely on papers investigating acupuncture around embryo transfer. El-Toukhy *et al* conducted a meta-analysis using 13 relevant trials, including a total of 2500 women randomised to either acupuncture or control group. These patients received acupuncture either during oocyte retrieval or around the time of embryo transfer. On analysis of the data it was concluded acupuncture had no significant effect on clinical pregnancy rates or live birth rates, regardless of when the acupuncture was performed. (El Toukhy, et al., 2008) A similar review published by the same author one year later, now incorporating 14 trials including 2870 women came to the same conclusion (El-Toukhy and Khalaf, 2009).

While less researched than improvements in pregnancy rates, another suggested benefit of acupuncture is to reduce the risk of ovarian hyper-stimulation syndrome (OHSS). A study in 1997 reported the results of ten patients who had taken human menopausal gonadotrophin (HMG) and subsequently developed OHSS (to varying degrees). Each were given acupuncture instead of human chorionic gonadotrophin (HCG) for ovulation induction in an attempt to prevent exacerbation of the OHSS. Over 11 menstrual cycles (one patient had a reoccurrence of OHSS), 9 experienced a substantial remittance or disappearance of symptoms. Two pregnancies resulted when using acupuncture in the absence of HCG,



leading the authors to conclude acupuncture is effective in ovulation induction and allows OHSS to be managed effectively. (Cai, 1997) No other paper appears to directly discuss OHSS and acupuncture, although patients with PCOS are at high risk of OHSS and acupuncture in these patients has gained some focus, and is discussed later.

### *2.2.1 Effects when performed on day of embryo transfer*

In contrast to outcomes when used during stimulation, studies solely investigating the use of acupuncture with embryo transfer appear more promising. The first randomised, controlled, prospective study into the impact of acupuncture pre- and post-embryo transfer was performed in 2002 by Paulus et al. A total of 160 healthy women undergoing either IVF or ICSI due to a variety of reasons were recruited into the study, and randomised to receive either no acupuncture (n = 80) or acupuncture in two 25 minute sessions, one pre- and one post-embryo transfer (n = 80). The acupuncture points used were Cx6 (*Neiguan*), Sp8 (*Diji*), Liv3 (*Taichong*), Gv20 (*Baihui*), and S29 (*Guilai*) before embryo transfer. After embryo transfer, the needles were inserted at S36 (*Zusanli*), Sp6 (*Sanyinjiao*), Sp10(*Xuehai*), and Li4 (*Hegu*). In conjunction, auricular acupuncture was performed at ear point 55 (*Shenmen*), ear point 58 (*Zhigong*), ear point 22 (*Neifenmi*), and ear point 34 (*Naodian*). Two needles were inserted in the right ear, the other two needles in the left ear. The four needles remained in the ears for 25 minutes. The side of the auricular acupuncture was changed after embryo transfer. These points were chosen as ‘‘*Taiying* meridians (spleen) and *Yangming* meridians (stomach, colon) would result in better blood perfusion and more energy in the uterus. Stimulation of the body points Cx6, Liv3, and Gv20, as well as stimulation of the ear points 34 and 55, would sedate the patient. Ear point 58 would influence the uterus, whereas ear point 22 would stabilize the endocrine system.’’ (Paulus, et al., 2002) The measured outcome was clinical pregnancy rates at 6 weeks, and the rate of 42.5% in the acupuncture group was significantly higher than seen in the control group (26.3%). However, it should be noted that all patients were selected as they had good quality embryos, and the mean age in both groups was 32 years.

Since this preliminary study, a number of studies have attempted to replicate their findings. Some studies have reported a non-significant impact on pregnancy rates, although many report a trend to improving outcomes and they generally have a positive outlook on the use of acupuncture, deeming it safe and useful to reduce stress and improve optimism. (Johnson,

2006; Smith, et al., 2006) (Domar, et al., 2009) (Andersen, et al., 2010; Madaschi, et al., 2010). However, Paulus' results have been successfully replicated by some (Westergaard, et al., 2006) and Margerelli *et al* concluded that acupuncture improves pregnancy rates by modulating the stress response, evidenced by significantly different cortisol and prolactin levels in patients receiving acupuncture compared to controls. (Magarelli, et al., 2009). One paper performing acupuncture only after embryo transfer (on the day, and again 3 days later) also reported significant increases in pregnancy rates. (Dieterle, et al., 2006)

A meta-analysis specifically including only studies investigating acupuncture at the time of embryo transfer has recently been published. (Manheimer, et al., 2008) Seven trials with 1366 women undergoing in vitro fertilisation were included, and all studies were randomised controlled trials that compared needle acupuncture performed within one day of embryo transfer with sham acupuncture or no treatment. They concluded that there was preliminary evidence to suggest acupuncture given with embryo transfer improves rates of pregnancy and live birth. (Manheimer, et al., 2008) Another meta-analysis, also published in 2008, also agreed with this conclusion, stating if the aim of acupuncture is to improve pregnancy rates, it should be given on the day of embryo transfer. Acupuncture with oocyte retrieval reduced pain, but did not increase pregnancy rates. (Ng, et al., 2008)

It would appear that performing acupuncture around the time of embryo transfer may be more beneficial than if performed at any other time during the ART cycle, although individual papers are still conflicting and it is clear that more randomised controlled studies, incorporating a large sample size are necessary in order to prove this. However, as now discussed further, a number of studies have highlighted the important impact acupuncture may have on psychological parameters, predominately stress. Acupuncture may also have benefits for reducing pain during oocyte retrieval, and this may be particularly beneficial for some women but is not discussed further here.

### **2.3 Psychological Impact on Patients undergoing ART**

A search in PubMed using the term 'acupuncture, stress' returns 422 papers, indicating that its use for stress reduction is well researched. Stress has been linked to reducing fertility and, considering this association, the paucity of research specifically evaluating stress modulation in response to acupuncture during ART is surprising.

There is seemingly only one paper that measures the effect acupuncture has on stress hormones. Magarelli *et al*, found that acupuncture seemingly had a beneficial regulation of cortisol and prolactin in 67 patients undergoing IVF (Magarelli, et al., 2009). Cortisol and prolactin are indicative of stress, but clearly there is too little evidence to confirm acupuncture can inducing physiological changes in stress markers. The authors themselves made it clear they were unsure whether the increased pregnancy rates in the acupuncture group were due to reduced stress but it will be an interesting avenue for future research.

The ultimate goal of IVF is to increase take-home baby rates, and this seems to have resulted in the belief that all aspects of IVF should be contributing to this achievement. However, IVF itself is an extremely stressful period: daily injections, blood tests, ultrasounds, surgical procedures (oocyte retrieval, embryo transfer) and the ongoing possibility of failure place an enormous strain on already stressed patients. Heightened anxiety also places a burden on familial and working relationships. A poor support network and an inability to cope can lead to many women being unable to repeat the process after a failed cycle. Consequently, any method to relieve this aspect of treatment is highly desirable, and acupuncture may be able to offer important benefits for stress reduction. Even if acupuncture is shown not to directly increase pregnancy rates, if it can reduce anxiety and increase calmness and optimism patients may feel more in control and able to cope with IVF and multiple cycles, if necessary.

A few studies investigating acupuncture on physiological variables have also asked patients to report their feelings regarding the protocol. Interestingly, there are also conflicting results with regard to psychological parameters. A recent study has reported that acupuncture resulted in more negative feelings (pain etc) than the control group (Moy, et al., 2010), another stating that while anxiety was reduced it was not to a significant level. (So, et al., 2009) However, this is not a consistent finding; a recent paper stated increased feelings of calmness and optimism. (Domar, et al., 2009)

Despite a clear increase in acupuncture use, there is to date only two papers specifically designed to investigate patients' perceptions of acupuncture. A preliminary pilot study using semi-structured questionnaires evaluated the experiences of 8 patients who had used acupuncture during IVF. All women felt they had heard a lot of information about acupuncture and its potential benefits, perceived acupuncture to be more similar to

mainstream treatments than other complementary/alternative therapies (and felt re-assured by this) and to be safe. Importantly, while all women perceived the potential for acupuncture to help to be high, they also felt that even if acupuncture provided no benefits it would not interfere with their body or other Western drugs etc, and could do no harm. The two patients who became pregnant felt acupuncture had helped them, while those remaining childless stated acupuncture helped them cope. (de Lacey Sheryl, 2009)

Another small pilot study also found that acupuncture was associated with less stress both before and after embryo transfer, and that such patients had improved pregnancy rates. This study suggests that a reduction in stress may significantly impact on pregnancy rates, and that for some people this may be achieved by acupuncture. (Balk, et al., 2009)

Similar studies should follow, investigating a wide range of patients from different countries. Replication of the results may help further establish acupuncture as an appropriate adjunct therapy for use during IVF, or even during attempts to improve natural fertility by reducing stress.

### **3. Gynecological Problems**

#### **3.1 Polycystic Ovary Syndrome (PCOS)**

PCOS is one of the most common endocrine disorders in women, and is a leading cause of infertility despite its aetiology not being fully elucidated. Pharmaceutical interventions are not adequate for all patients, and may have adverse side-effects. Consequently, acupuncture has been used in an attempt to reduce the symptoms, and increase the fertility status of sufferers.

Rat models of PCOS have been created either by a single injection of oestradiol valerate or by continuous release of DHT. Neither model fully replicates the symptoms seen in human patients, but they do exhibit some of the morphological, endocrine and metabolomic alterations of PCOS. Such models have been used to implicate the sympathetic nervous system (in response to altered nerve growth factor (NGF)) and immune abnormalities in the development and maintenance of PCOS, as such rats show abnormalities in these variables compared to controls. Acupuncture interventions are generally very successful, reversing most of the symptoms seen in model rats. This has been achieved in some groups by

decreasing elevated NGF levels therefore limiting the hyperactivity of the sympathetic nervous system. However, exercise also has similar effects, and is possibly even more effective in causing weight loss, which is of particular importance to women wishing to become pregnant. Other groups report acupuncture can modulate corticotropin-releasing hormone (CRH), endothelin-1 (ET-1),  $\beta$ -endorphins and various serum hormonal levels, therefore improving PCOS-like symptoms. Yet, these results are not seen by all groups and since rat models are not fully representative of human PCOS, extrapolating evidence to humans should be done with care.

Although there are some human studies investigating acupuncture's effect on certain symptoms of PCOS (insulin resistance, obesity etc) there are less that explicitly investigate women with diagnosed PCOS. Such studies do however report improvements in most symptoms and signs of PCOS such as leptin, fat and insulin abnormalities and reproductive hormone abnormalities. Menstrual and ovulation are restored in many cases, and some even report acupuncture's ability to aid weight loss. As for murine models though, exercise also has a similar effect, so acupuncture is perhaps best applied to patients who are also counseled appropriately on diet and exercise choices to improve their symptoms. However, one paper found that after 6 cycles the symptoms returned to patients receiving domiphen and chorionic gonadotrophin, but not to those receiving acupuncture, which suggests that acupuncture may have better long term effects on some patients than pharmaceutical interventions. (Chen, et al., 2007)

Ongoing studies into acupuncture and PCOS relief are needed, but it appears that acupuncture may be a beneficial adjunct to patients receiving treatment, especially when patients make lifestyle changes to reduce their symptoms.

### **3.2 Endometriosis**

Acupuncture's effect on endometriosis is less well researched than for PCOS, and most studies focus on an ability to reduce dysmenorrhea. While the analgesic effect of acupuncture is supported in these patients, as in others with chronic pain conditions, it should be remembered that a reduction in pain does not necessarily reflect a concomitant improvement in fertility status. No clear effect on improving fertility in patients with endometriosis is seen by the current literature due to a lack of specific investigations. However, there is some promise offered by a murine model that concludes that acupuncture may be capable of *curing*

endometriosis by acting on matrix metalloproteinase-2 levels to inhibit endometrial tissue invasion. This is a bold claim, and much more research is needed in order to validate it. (Chen, et al., 2008) There is however one recent paper that found that acupuncture, in conjunction with ‘medicine’ can significantly improve oocyte retrieval, implantation and pregnancy rates in endometriosis patients undergoing IVF. While the medicine referred to is unclear in the abstract, this is an interesting finding and should be further investigated.

#### **4. Conclusion**

Although acupuncture has been used for centuries in some countries, its use in Western areas is more recent, and growing. This increase in use means acupuncture is expected to be exposed to the rigorous testing applied to all Western medicines. While more studies are being done, it is fair to say that many do not adhere to the strict guidelines of randomised, controlled studies; the ‘gold standard’ of Western medicine. Blinding is a particular problem in many papers, and is seen by some to invalidate the results. A direct comparison of many of the papers is also difficult. Different studies use different acupuncture protocols, timings and durations. The causes of infertility and sub-fertility are numerous even within a single study. The disparity between papers does make drawing a clear and logical conclusion complicated, and this may be reflected in the lack of meta-analyses.

However, it may not be fair to even subject acupuncture to such research designs; it is not after all a Western medicine. It is likely to always be seen as an adjunct to other interventions, most evidently when used alongside IVF. Although the benefits of acupuncture may not be clear, there are little if no reports of harm arising from acupuncture. It is interesting that critics often state that any benefits from acupuncture are arising from a placebo effect. Yet if something modulates an outcome positively, it should not matter if this is from a physiological or psychological mechanism. More studies into patients’ perceptions are needed in order to help strengthen acupuncture’s place as an adjunct to Western medicine.

If a patient believes a treatment will work, and feels supported in this belief by practitioners, this may have a beneficial impact on the course of their treatment. This is particularly important in a fertility setting, where psychological improvements such as stress reduction or pain relief will have far reaching effects, and may well have a biological impact on conception rates.



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