Adjunctive Role of Chinese Herbs and Acupuncture in an In Vitro Fertilization Cycle

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Abstract

In the past few years, several studies have been published showing effects of acupuncture to promote ovulation1 and improve in vitro fertilization (IVF) outcomes.2–4 However, physicians are highly concerned regarding the effects of combining Chinese herbs with pharmaceuticals that are powerful gonadotropin stimulators (GnRH)—the cornerstone of assisted reproductive techniques (ART).5–7 Patients must be closely monitored to ensure optimal ovarian performance and avoidance of complications,8–10 such as Ovarian Hyperstimulation Syndrome (OHSS), which if not properly managed can be fatal. Therefore the adjunctive use of Chinese herbs can be initially perceived as a clinical contraindication due to their function of potentiating or inhibiting gonadotropin medications. This case study will provide beginning clinical parameters for the safe and effective use of Chinese herbs within a larger IVF treatment plan.

Key words: IVF, acupuncture, Chinese herbs, traditional Chinese medicine, pregnancy rates

Background

Infertility is defined as when the inability to conceive after one year of unprotected intercourse in women less than 35 years old and after six months in women over 35.8, IVF may be pursued to assist conception. Since the mid 1990s there has been a steady upward trend in the U.S. in both the number of IVF procedures performed and associated pregnancies.11 The pregnancy rate average is 37.2% for a woman undergoing IVF with her own eggs that were conventionally fertilized (allowed to fertilize in a Petri dish).11 This is a significant increase from earlier times when the pregnancy rate was 28.1% for an IVF cycle.

In 2006, the CDC reported that women undergoing IVF age 41–42 had a 10% live birth rate and accounted for only 9.6% of all fresh non-donor IVF cycles.12 This is in comparison with the 35 years and below age bracket, which accounted for 41.9% of all procedures and had a 39% live birth rate nationally.

Risks involved with IVF include the aforementioned OHSS, which if monitored is a moderate to low occurrence. Additional risks with IVF include an increased likelihood of multiple pregnancies that can have deleterious effects on both the mother and children. In addition, the incidence of premature labor, premature delivery, maternal hemorrhaging, pre-eclampsia, eclampsia, and gestational diabetes are all increased. Mothers of high order multiples of three or more babies may choose to selectively reduce. There is also a slight increase in miscarriage and ectopic pregnancy with IVF related pregnancies.

IVF cycles are comprised of phases: suppression of ovarian function, ovarian stimulation, oocyte retrieval, insemination and culture, and embryo transfer. It should be noted that exact procedures vary from clinic to clinic and from patient to patient. In general, the suppression phase rests the ovaries so that they will respond to the stimulation medications. This is commonly done with oral contraceptive use for two weeks beginning once ovulation is confirmed. A GnRH agonist such as lupron may be added to ensure full “suppression” and inhibit follicular development prior to stimulation. After the suppression phase, a baseline ultrasound is done to evaluate antral follicle count. Blood levels confirm suppression. At this point, the estradiol (E2), luteinizing hormone (LH), and progesterone (P4) levels should be low, and the endometrium should be thin. This is similar to the start of the menstrual cycle, and there may or may not be the presence of uterine bleeding. If all is within normal parameters, then follicular stimulation medications or gonadotropins treatment will commence.

Stimulation medications act like follicular stimulating hormones (FSH) and promote multi-follicular development. They bypass the hypothalamus-pituitary-ovarian axis and strongly stimulate follicular growth. Harvesting multiple mature follicles increases the odds of success in IVF. Stimulation medications are counterbalanced with other medications to prevent early ovulation. Blood work and ultrasounds are done at least every other day to track the E2, LH, P4, follicular development, and endometrial thickness and quality. The E2 should increase to around 250pg/ml per mature follicle, while the LH and P4 are expected to stay low. Follicles should grow to 18mm to 22mm in size. The endometrium should become thick, between 8–10mm, and trilaminar in appearance.

Once this status is obtained, the E2 may be at least 2000 pg/ml. The ovaries at this point have enlarged due to the surface growth of the follicles, and there should be at least four primary follicles in the 18mm to 20mm range. Gonadotropin medications are discontinued and medication provided to promote follicle maturation, which occurs prior to oocyte retrieval 34–36 hours later.

Once all of the eggs are retrieved, they are washed in follicular fluid and prepared for insemination with sperm. Eggs are inseminated the same day either conventionally by mixing with sperm in a Petri dish or by intra-cytoplasmic sperm injection (ICSI), which is the manual injection of one sperm into an egg. Once the eggs are fertilized, they are incubated, and the patient will then begin progesterone therapy via injection. Three days later, each single fertilized egg should mature to an 8-cell embryo. The patient will then have one to two embryos transferred into the uterus. Approximately 10-12 days later a blood test is done to determine pregnancy. With pregnancy, a second blood test is done to ensure progression. Progesterone therapy will continue through week ten.

Thus far, TCM and IVF research trials have focused primarily on acupuncture for IVF support. However, study design and outcome measures have not been consistent. In the first randomized control trial (RCT) by Paulus et al., acupuncture was applied on the day of embryo transfer only. A standardized acupuncture protocol preformed the same day, before and after embryo transfer, significantly improved pregnancy rates over non-acupuncture.2 Three more RCTs were published later that were based on this germinal study with minor modifications. All reported improved IVF pregnancy rates with acupuncture, two significantly3,4 and one insignificantly.12

In contrast, Domar et al. replicated the original Paulus study in 2008 and reported no significant difference in outcomes between the acupuncture group and the control group.13 In 2009, a randomized double blind controlled trial from Hong Kong reported higher IVF clinical pregnancy rates in the placebo...
acupuncture group compared with the verum acupuncture group.14

As the body of research has grown, there have been four meta-analyses published. The first systematic review and meta-analysis of all peer-reviewed RCTs involving acupuncture and IVF reported a 65% improvement in outcomes.15 Two additional systematic review and meta-analyses that included abstracts found there was not sufficient evidence that acupuncture improves IVF outcomes.16-17 There has been little evidence showing acupuncture to be unsafe during an IVF.15-17

There has been little evidence showing Chinese herbalism improves fertility. The Yellow Emperor and Qibo Yet Chinese medicine provides thousands of acupuncture treatments and Chinese herbs, both of which were prescribed based on TCM differential diagnosis.18

Since the Paulus study was published,2 Colorado researchers consistently found that nine electro-acupuncture pretreatments combined with the Paulus protocol improved IVF pregnancy rates in the acupuncture group vs. the no acupuncture group.19-20 At this time, there is no consensus on the efficacy or effectiveness of acupuncture with IVF. However, more research is needed to elucidate the mechanism of action as well as how best to apply acupuncture to support an IVF cycle. Yet Chinese medicine provides thousands of years of clinical experience and insight into infertility. The Yellow Emperor and Qibo discussed the female fertility timeline in the Huang Di Nei Jing.21 And Chinese herbalism specializing in treating infertility dates back at least 700 years.6

Chinese medicine currently views infertility through the categorization of five primary pathologies with associated herbal formulas. (See Table 1) Treatment is directed to the Kidney as well as resolving stasis, supporting qi and blood, and transforming dampness.3-6 A recent survey showed that IVF patients predominately fall into Kidney vacuity patterns, with yang vacuity being the most prevalent, followed closely by yin vacuity.23 In TCM, the kidney essence (jing), yin, yang, and qi provide direction, energy, and substance to the reproductive system.3-6,21 The quality and balance of these energies determine egg health in the female and sperm health in the male. A decline in vital energies is a significant contributing factor for miscarriage, but not the primary reason. Naturally, essence, yin, yang, and qi decline with age, but this decline can be accelerated by poor quality of life including overworking, poor diet, drug/alcohol abuse, and/or excessive stress.

Case history

A 41-year-old female presented requesting support for IVF treatment. Secondary infertility due to advanced maternal age and diminished ovarian reserve had been diagnosed. She was utilizing an oral contraceptive to promote the suppression phase. The stimulation phase was to start in two weeks. She had two prior pregnancies which included one live birth without complication. She denied any long-term use of oral contraceptives.

Menarche was at age 11, with regular cycles and 4 days of bright red bleeding followed by two days of light brown spotting. The blood flow was moderate but slightly thin. There were no clots or cramps. Prior to childbirth, she had moderate cramping at the onset of menses with mild, dull pain on the sacrum and some distension. She had not used ovulation predictor kits. She reported no noticeable cervical mucus and consistent mild vaginal dryness. Her blood work and baseline evaluation is outlined in Table 2.

Other notable subjective findings included: cold hands/feet, warm abdomen, gas and bloating post-prandial. Eats processed foods, craves and consumes sweets, soft bowel movements (2x/day, increases with stress), sleep is deep—difficult to wake up, irritability, sighing, night sweats, low back ache concentrated around sacrum, healthy libido, energy: 8/10, stress: 3/10

Objective findings at the initial visit were: pleasant but anxious to start treatment, slightly overweight, skin pale, rashes on nails, hands/feet felt warm, pulses: moderate rate (left: thready, deep, weak, right: deep, slippery in Spleen), tongue: dusky, thin and no coating. Poor diet and aging are the primary etiological factors. The Kidney yin and Liver blood naturally decline as a woman ages. Insufficient blood causes the Liver to be firm and stagnation easily arises. The poor diet weakens the Spleen, which is also unable to make sufficient amounts of blood and allows for an accumulation of pathological dampness.

Diagnosis: Kidney yin deficiency; Liver blood deficient with qi stagnation; Spleen qi deficiency leading to damp

Treatment Principle: nourish blood and yin; circulate qi; support the Spleen

Acupuncture: Key: + reinforcing technique, - reducing technique, = neutral technique

Front treatment: treatment 1 and 3.24-25
Zusanli ST-36 +: tonifies qi and blood, Guanyuan REN-4 +: nourishes yin, blood, strengthens yang, tonifies Kidney and benefits original qi. Zì Gōng +: promotes fertility via supporting the ovaries and uterus. Lieque Lu-7 –, Zhaohai KID-6 –. Together confluent points to support the Conception vessel.

Plus one of the following: Taibai SP-3 +: Yuan Source point of the Spleen, tonifies digestive aspect of Spleen with Zusanli ST-36 and resolves dampness; Sanyinjiao SP-6 +: tonifies Spleen, Stomach, resolves dampness; harmonizes the Liver and lower jiao. Calms shen and moves blood.

Auricular: Uterus to support the uterus and ovaries during the IVF cycle. Endocrine to support the endocrine system and response to the gonadotropic medications, Shenmen to calm the shen, and Liver to circulate Liver qi


A customized granular herbal formula was prescribed for three weeks—or through the stimulation phase of her IVF cycle. It was discontinued on the day of the retrieval and designed based on the treatment principle to nourish yin, circulate qi, support the Spleen, and drain dampness.

Dang Gui (Angelicae Sinensis Radix) 8; Bai Shao (Paeoniae Radix Alba) 12; Chai Hu (Bupleuri Radix) 6; Tu Si Zi (Cuscutae Semen) 12; Gou Qi Zi (Lycii Fructus) 8; Gui Ban (Testudinis Plastrum) 8; Shan Yao (Dioscorea Rhizoma) 8; Mai Ya (Hordei Fructus Germiiniatus) 12; Chen Pi (Citri Reticulatae Perciparium) 6; Fu Ling (Poria) 10; Chuan Niu Xi (Cyanthulai Radix) 6; Xiang Fu (Cyperi Rhizoma) 12; Fo Shou (Citri Sarcodactylis Fructus) 10.

The first three herbs are the ingredients to Xiao Yao San (Rambling Powder), which nourish the Liver blood and circulate the qi. Tu si zi (Cuscutae Semen) tonifies Kidney qi, yin and yang, and gou qi zi (Lycii Fructus) nourishes Kidney yin and Liver blood.27-28 Together they are said to support the jing. Because they are not strong enough, gui ban (Testudinis Plastrum) was added to benefit the jing while
sweats. Simultaneously clearing heat to stop night sweats. Shan yao (Dioscoreae Rhizoma) tonifies Kidney and Spleen qi and was combined with mai ya (Hordei Fructus Germiatus), chen pi (Citri Reticulatae Pericarpium) and ju ling (Poria) to address the middle jiao to drain damp. Chuan nia xi (Cytisulae Radix) moves blood and directs the actions of the herbs to the lower jiao. Xiang fu (Cyperi Rhizoma) circulates qi in the lower jiao and was combined with fo shou (Citri Sarcodactylis Fructus) to direct the action to the ovaries and uterus. Xiang fu (Cyperi Rhizoma) also works with chat hu (Bupleuri Radix) to soothe the Liver. In this particular advanced maternal-aged patient with diminished ovarian reserve, it was medically anticipated that she would not stimulate well based on low antral follicle count (AFC). The herbal formula was designed to address this concern.

It is important to ensure the yin is enriched during ovarian stimulation, as this is much like the follicular phase of a menstrual cycle. However, care must be taken as to not engender dampness. Herbs that move qi and drain damp were specifically chosen for this reason. An overabundance of yin can engender damp accumulation, which significantly inhibits the flow of qi. If too much dampness accumulates, qi stagnates and heat can develop, which if left unchecked will damage yin and Blood. From a biomedical perspective, it can lead to more bloating, nausea, and abdominal cramping during the stimulation phase. In extreme cases, ovarian hyperstimulation may result, which is why it cannot be stressed enough: extreme care must be taken when combining herbs with IVF.

The patient took IVF stimulation medications for 10 days. Estradiol peaked at 2000 pg/ml and the endometrial lining was 11mm and trilaminar. Ten mature eggs were obtained on the day of oocyte retrieval, and seven fertilized normally. She received acupuncture the day before her transfer. The Paulus pre-IVF protocol was followed with one addition: Baihui GV-20 clears the senses and calms the shen. It also lifts qi, treats all types of prolapase and any pre and post partum issues. Its inclusion may be for calming the shen and supporting the lifting action of the qi to support implantation.

Guilai ST-29 is traditionally indicated for infertility, amenorrhea and influences the ovaries and vagina. Of note, Guilai ST-29 can also treat inflammation of the adnexa, which is an inevitable side effect in an IVF fresh cycle with one’s own eggs. Neiguan P-6 is a common point to calm the Heart and shen. It can also suppress pain and regulate qi. Additionally, it can influence the cervix and promote its opening and relaxation.

Dii SP-8 harmonizes the blood and regulates the uterus. It is an ideal point for minimizing uterine cramping from the transfer itself, as well as for treating abdominal distension, another inevitable side effect of IVF stimulation medications. Taichong LIV-3 is an ideal point to circulate qi, move and open the channels. It pacifies the Liver and influences the genitals. The latter functions are important for the actual procedure of speculum insertion and Liver-type anxiety.

Qhui CV-6 was added because it regulates qi and reinforces the Kidney. It also reinforces the actions of Baihui GV-20. It is indicated for abdominal distension and dysmenorrhea as well. This addition was made to directly address the Kidney via an extraordinary meridian, since the original Paulus et al. protocol did not do so.

**The ear points:** The left ear was needled with Brain and Shenmen. The Brain point adaptively regulates excitation or inhibition of the cerebral cortex and is used for endocrine and urogenital systems. In the Right ear, Uterus and Endocrine were needled. The Uterus point is self-explanatory as it supports the uterus. The Endocrine point supports not only the reproductive endocrinological functions of the body but is also used for urogenital and gynecological diseases. It also has anti-allergic and anti-rheumatic functions.

The clinic suggested a day three embryo transfer, in which she had the following: five 8-cell embryos, two 7-cell embryos, one 6-cell embryo. Four 8-cell embryos were transferred that day. No post IVF treatment was done, and the patient did not return to the acupuncture clinic. In a follow-up contact, she reported she delivered a healthy girl the following year at 41.3 weeks, weighing 9.58 lbs.

**Discussion**

Reproductive endocrinologists remain very concerned about combining IVF medication and Chinese herbs because the mechanism of action is not understood. In addition, there is no peer-reviewed research to support this clinical approach. Despite this, the patient in this case participated in a limited number of acupuncture treatments, took Chinese herbs, utilized IVF, became pregnant, and delivered a healthy baby girl at 41.5 weeks gestation.

There has been very little written about this treatment strategy in Western peer-reviewed journals. The other texts outlining TCM treatment with IVF are based on clinical observation or anecdotal evidence.

The combination of acupuncture, including electro-acupuncture with Chinese herbs, helped this woman conceive with IVF. Her doctor was not opposed to this approach, which is uncommon. The electro-acupuncture, which was based on research, increases blood flow to the uterus and ovaries. It is hypothesized that this increase in ovarian blood flow will increase ovarian response to the medications. Other research has found electro-acupuncture pre-treatment significantly impacts cortisol and prolactin levels, which in turn improve IVF pregnancy outcomes.

The Chinese herbal formula was designed to nourish yin and blood and protect the jing, which would support the biomedical process of folliculogenesis due to ovarian hyperstimulation. The oocyte is strongly influenced by yin and jing, and the endometrium by blood. If the yin, jing and/or blood is/are insufficient or weak, then egg quality will be affected, and the lining will not be thick enough to sustain a full term pregnancy.

In general, tonifying herbs are contraindicated for the following conditions which easily cause hyperstimulation:

1. Polycystic Ovary Syndrome – PCOS
2. High antral follicle count
3. Patients with normal fertility factors, who are nonetheless undergoing IVF
4. Patients who have never undergone an ovarian stimulation cycle and are unproven responders.
5. The physician opposes any herbal intervention: It is not clinically appropriate to triangulate the patient between the acupuncturist and the doctor.

**Conclusion**

While this is only one case, it demonstrates that both herbal and acupuncture treatments were safely integrated with an IVF cycle and resulted in a healthy live birth. More rigorous research is needed to examine safety parameters, appropriate patient demographics, dosage, and duration of TCM treatment when combined with IVF and accompanying guidelines.
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References

Table 1. Infertility TCM Diagnosis Patterns and Recommended Herbal Therapeutics

<table>
<thead>
<tr>
<th>Primary TCM diagnosis</th>
<th>Common herbal treatment 5,22</th>
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<tbody>
<tr>
<td>Kidney deficiency or vacuity</td>
<td>Yin Xu – Gui Shao Di Huang Tang, [Zuo Gui Wan (Left Metal Pill)]</td>
</tr>
<tr>
<td>Gi and blood deficiency vacuity</td>
<td>Bu Zhong Yi Qi Tang (Tonify the Middle and Augment the Qi or Decocation), Ba Zhen Tang (Eight Treasure Decocation)</td>
</tr>
<tr>
<td>Blood stagnation or stasis</td>
<td>Shao Fu Zhu Yu Tang (Drive Out Blood Stasis in the Lower Abdomen Decocation), Tao Hong Si Wu Tang (Four Substance Decotion with Saflower and Peach Pill)</td>
</tr>
<tr>
<td>Qi Stagnation</td>
<td>Xiao Yao San (Rambling Powder), Si Ni San (Frigid Extremities Powder)</td>
</tr>
<tr>
<td>Damp-phlegm accumulation</td>
<td>Can Fu Dao Tan Wan (Atractylodes Cyperus Conducting Phlegm Pill), Xiong Gui Ping Wei San (Ligusticum Angelica Balancing the Stomach Powder)</td>
</tr>
</tbody>
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Table 2. Baseline Hormone and Ultrasound Findings

<table>
<thead>
<tr>
<th>Test</th>
<th>Menstrual Cycle Day (CD) of test</th>
<th>Findings</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH</td>
<td>CD 3</td>
<td>10.2 mIU/mL</td>
<td>&lt;10 mIU/mL</td>
</tr>
<tr>
<td>E2</td>
<td>CD 3</td>
<td>42 pg/ml</td>
<td>25-75 pg/ml</td>
</tr>
<tr>
<td>LH</td>
<td>CD 3</td>
<td>5.3 mIU/mL</td>
<td>&lt;7 mIU/mL</td>
</tr>
<tr>
<td>FSH</td>
<td>CD 10 [CCCT]</td>
<td>13.8 mIU/mL</td>
<td>&lt;10 mIU/mL</td>
</tr>
<tr>
<td>AFC L</td>
<td>CD 3</td>
<td>3 – 5</td>
<td></td>
</tr>
<tr>
<td>AFC R</td>
<td>CD 3</td>
<td>2 – 3</td>
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