

INFERTILITY TREATMENT AND TRADITIONAL CHINESE MEDICINE

By

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## Abstract

Infertility treatments are sought after by about one in every ten women in the United States. In vitro fertilization (IVF) and intra-uterine insemination (IUI) are both relatively expensive and time consuming fertility options for patients and yet still cannot guarantee pregnancy will be achieved. Incorporating acupuncture into an IVF cycle creates a sympathoinhibitory effects, decreases pulsatility index, and promotes increased uterine artery blood flow and therefore increased endometrial thickness and increased likelihood of embryo implantation. Additionally, acupuncture normalizes hypothalamic-pituitary-ovarian axis dysfunction. Incorporating Chinese herbal medicine (CHM) into an IVF cycle promotes estrogenic effects including uterine support through the luteal phase. Incorporating CHM into an IUI regimen helps to alleviate the anti-estrogenic effects of the follicle stimulating pharmaceuticals prescribed. In randomized trials, acupuncture and CHM significantly increased endometrial thickness measurements and CHM significantly increased pregnancy and live birth rates when used alongside IVF. Most patients have negative perceptions regarding traditional Chinese medicine and are therefore not receptive to using it or incorporating it into their fertility treatment plan. Because some positive effects and no negative effects have been found, physicians should continue to recommend these complementary approaches to their patients, provided the addition of TCM is financially feasible for the patient.

## Introduction

Currently in the United States, about 10% of women between the ages of 15 and 44 are considered to be infertile, defined as difficulty getting pregnant and/or staying pregnant after one year of trying.<sup>12</sup> Approximately 11% of women seek fertility services. These women may include those with infertility, those seeking donor or gestational carrier services, and those in couples with male-factor infertility. Fertility services include both IVF and IUI.<sup>27</sup> The current success rate for IUI is approximately 10% per cycle for women under the age of 41. The average IUI cycle currently costs \$300-\$800. The current success rate for IVF in the United States averages around 43.2% (2012) per cycle, for women under the age of 35. These rates drastically decrease as patient age increases. The cost per cycle is approximately \$12,000 before medication, an additional \$3,000-\$5,000, and is typically not covered by insurance. The average IVF patient will undergo three cycles before reaching an 85% successful pregnancy rate or before seeking other options.<sup>26</sup> Because of the high costs and time investment of fertility treatment, this thesis proposes implementing Traditional Chinese Medicine (TCM), including acupuncture and Chinese herbal medicine, into the IVF and IUI regimens.

TCM dates back more than 2,500 years and has philosophical roots in Taoism. TCM includes acupuncture, moxibustion (the application of heat to acupoints), Chinese herbal medicine, Chinese therapeutic massage, dietary therapy, and tai chi. It is estimated twenty years ago, 10,000 practitioners in the United States served more than 1 million patients each year. Since then, these number have increased due to greater awareness of alternative and eastern-based medicine with the spread information through media such as the internet.<sup>2</sup>

By reviewing existing research, I aim to show that; a) the physiological effects of acupuncture include increased blood flow to the uterus and increased endometrial thickness and that b) the phytoestrogen compounds in Chinese herbal medicine extracts agonize the effects of estrogen and therefore increase endometrial thickness. The combination of these two TCM techniques improve IVF success rates while adding relatively low additional costs, in relation to the total costs of the fertility treatments.

### Acupuncture

The modern concept of acupuncture lies on the foundation of visceral meridians or “energetic lay lines.”<sup>7</sup> These internally flowing meridians have been mapped and are used regularly in practice to focus on specific systems of the body. The system of meridians has been deconstructed into twelve or thirteen “channels” symmetrically balanced across the body and each containing several methodical and particular points along its axis [see Figure 1]. By stimulating these calculated points, or “acupoints,” energy levels can be altered and therefore physiological changes be observed. When receiving acupuncture, a patient has a series of needles inserted at a subcutaneous to intramuscular depth range. Research shows that even at a subcutaneous depth, the mechanical force of having a needle inserted in loose connective tissue can cause an immediate biological response as seen in a study finding statistically significant improvement in motion-related pain, pain under pressure, and range of movement after receiving subcutaneous needling.<sup>16</sup> Additionally, this method of needling is preferential as the patient does not feel the needles being inserted or removed. The most common subcutaneous acupuncture is in the form of Fu’s Subcutaneous Needling (FSN). FSN

needles consist of a soft tube, a stainless-steel needle that is ten millimeters in diameter, and a handle; the needle is three millimeters longer than the tube, so it penetrates three millimeters deep [see Figure 2]. A traditional acupuncture needle penetrates both the subcutaneous layer and the muscular layer and is limited to axial rotation and vertical movement along the needle's axis. FSN needles can be moved smoothly in the horizontal direction in a swaying motion through the loose connective tissue. Additionally, FSN needling is beneficial in clinical studies as the relationship between needling and physiological results is focused on the exposure of a single layer to the needle, rather than multiple layers.<sup>29</sup>

Acupoints are known regions of the skin with high electrical conductance because of the presence of gap junctions in greater than normal density. These specific points are points of convergence for electromagnetic fields causing the cells in these regions to have a higher metabolic rate, higher temperature, and higher calcium concentration. These factors, along with the relatively great number of gap junctions produce greater chemical signaling at a higher rate.<sup>14</sup>

An essential concept central to all needling practices is tonification versus sedation. Tonification is defined as strengthening a slow physiological function while sedation is weakening hyperactive physiological function. Many specific needle motions are employed to create tonified or sedated states including speed of needle entry and direction of rotation.<sup>10</sup> By using electroacupuncture and an anode pulse stimulation on an acupoint, organ function is slowed and inhibited, providing a sedative effect. Conversely, by using a cathode pulse stimulation on an acupoint, organ function is enhanced, providing a tonified effect.<sup>14</sup>

Acupuncture stimulates a significant increase in  $\beta$ -endorphin production during treatment and for up to 24 hours afterwards.  $\beta$ -endorphin is derived from pro-opiomelanocortin in the arcuate nucleus, the pulse generator for gonadotropin releasing hormone (GnRH), which affects peripheral gonadotropin levels. For this reason, acupuncture normalizes hypothalamic-pituitary-ovarian axis dysfunction and acts as a replacement for hCG, which mimics LH in ovulation induction.  $\beta$ -endorphin levels are higher in the follicular fluid of healthy ovulatory women compared to circulating plasma levels, which indicates the association between  $\beta$ -endorphin and ovulation induction and therefore acupuncture and ovulation induction.<sup>25</sup>

Acupuncture is often not perceived as a valid form of medicine or scientifically welcomed field due to the variation and inconsistencies amongst practitioners, although it is widely accepted by some cultures. For example, many sources believe there are twelve meridians while others identify thirteen or even more. Figure 1 depicts thirteen meridians, including the notable “conception vessel” which contains acupoints for irregular menstruation, uterine prolapse, and infertility. Other figures from varying schools of teaching provide different depictions with different meridian names.<sup>8</sup> The conception vessel begins at the pubic area and runs up the anterior midline of the body to the mouth. Because it is located on the ventral portion of the body it is said to contain yin energy, which is nourishing, moistening, and growth oriented. A yin deficiency is correlated with infertility; therefore, by needling along a yin meridian, such as the conception vessel, you can enhance yin energy and suppress the symptoms of reproductive infertility. The conception vessel contains 24 acupoints, eight of which are

located at or beneath the umbilicus and control symptoms related to fertility [see Table 1].<sup>15</sup>

### Chinese Herbal Medicine

Chinese Herbal Medicine (CHM) is used commonly as a complementary health approach by people in the United States. Because the herbs used in TCM are often regarded as dietary supplements and not pharmaceuticals, they are not strictly regulated by the FDA, while acupuncture needles are.<sup>2</sup> Medicines are prescribed by a TCM practitioner as either a single form or a formula combining a variety of compounds. The practitioner must take into account negative and positive interactions within the formula and between the compounds and other drugs being taken by the patient. The medicines are typically dried, powdered, and encapsulated for easy consumption. CHM is used to treat a variety of conditions including insomnia, fatigue, chronic headaches, skin disorders, anxiety, arthritis, and infertility.<sup>6</sup>

CHM is a common aspect of TCM that can be incorporated into fertility treatment. The most common CHM compounds contain phytoestrogens, which are similar to estrogen disrupting compounds and act agonistically or antagonistically to estrogens, including estradiol (E2) on estrogen receptors (ER $\alpha$  and ER $\beta$ ) to activate E2 dependent gene transcription. CHM compounds support fertility treatments by agonizing estrogenic effects on the uterus and therefore increasing endometrial thickness.

Estrogens, including estradiol (E2), are endogenously produced in the granulosa cells of ovarian follicles, the corpus luteum, and adipose tissue. As gonadotropins stimulate follicle development through the follicular phase of the menstrual cycle, E2

levels slowly increase. Because follicles produce E2, E2 is sensed by the pituitary as an indication of sufficient follicular development and therefore inhibits gonadotropin release at the pituitary level. On day 14 of the cycle, luteinizing hormone levels spike, triggering ovulation. Through the luteal phase, E2 levels begin to rise again as the corpus luteum develops and to support the proliferative uterine phase and building of the endometrium.<sup>9</sup>

Phytoestrogens are derived from plants and can be broken down into compounds with estrogenic activity. Phytoestrogens include both flavonoids and non-flavonoids. Flavonoids include isoflavones (obtained through soy products), coumestans, prenyl flavonoids; non-flavonoids include lignans. ER $\alpha$  and ER $\beta$  are nuclear receptors that bind E2. ER $\alpha$ , the primary estrogen receptor expressed in the uterus, hydrogen bonds the hydroxyl on the E2 A-ring with the carboxyl of Glu353, the guanidinium of Arg 394, and structural water. The hydroxyl on the E2 D-ring hydrogen bonds to His524 of ER $\alpha$  [see Figure 4]. The binding of E2 by ER $\alpha$  receptors on the uterus elicits a response including increased uterine weight, epithelial cell height, gland number, and lactoferrin expression.<sup>18</sup>

The isoflavone genistein binds to ER $\alpha$  in an identical manner to E2 and elicits the same responses [see Figure 5]. ER $\beta$  has a similar structure to ER $\alpha$  but with different binding affinities; coumestrol binds with ER $\beta$  with 7-fold higher affinity than to ER $\alpha$ , and a 20-30-fold higher affinity for genistein, spigenin, kaempferol.<sup>9</sup> Genistein has a 20-30-fold higher affinity for ER $\beta$  than ER $\alpha$  but only a slight preference for gene activation through ER $\beta$ , when studied on a mouse model. Unlike the uterus which primarily expresses ER $\alpha$ , the ovaries express both ER $\alpha$  and ER $\beta$  and when genistein binds to

receptors on the ovaries, it exhibits a dose-dependent increase in multi-oocyte follicle development compared to controls.

Once phytoestrogens bind to ERs, they initiate transcription through estrogen response elements or by binding early transcription factors c-Jun and c-Fos. The rapid and transient activation of second messenger pathways causes increased intracellular calcium levels, increased cyclic-AMP, and therefore increased signal transduction for neuronal signaling and differentiation. This promotes the effect of increased endometrial thickness as endometrial cells proliferate and differentiate.<sup>22</sup> Other CHM compounds include *Cimicifuga racemosa*, *Cinnamomum cassia*, *Curcuma longa*, *Glycyrrhiza* spp., *Matricaria chamomilla*, *Mentha piperita*, *Paeonia lactiflora*, *Silybum marianum*, *Tribulus terrestris* and *Vitex agnus-castus*, and are often found in combinations with one another.<sup>18</sup>

### In Vitro Fertilization

In vitro fertilization (IVF) came to fruition when Gregory Pincus, a scientist at Harvard, first successfully completed the treatment in rabbits in 1934. At the time, the mere suggestion that this technology could be implemented in humans was so absurd that Pincus was ridiculed for his work and denied tenure by the university. However, in the short span of ten years, this exact absurdity was accomplished as John Rock and Miriam Menkin, Pincus's assistant, who successfully fertilized four human ova in vitro, marking this the first effective in vitro fertilization using human ova and sperm. In 1968, British scientist Robert Edwards and gynecologist Patrick Steptoe used Steptoe's new laparoscopic surgery technology to retrieve mature human eggs (a technique described

in the egg retrieval section below) from infertile women and fertilize them externally. Continuing their work, Edwards and Steptoe report the first successful IVF pregnancy in 1975, although the pregnancy was ectopic and the baby was lost. In November of 1977, Lesley Brown and her husband sought the assistance of Steptoe after learning of Lesley's blocked fallopian tubes and, understanding that this would prevent Lesley from carrying ectopically, Steptoe urged IVF. Steptoe laparoscopically removed Lesley's eggs, fertilized them with her husband's sperm, and implanted an eight-cell embryo into her uterus two days later. In July of 1978, the Browns gave birth to their daughter, Louise Joy, the first successfully born "test tube baby." By 1980, the U.S. approved federal funding for IVF research and the first IVF clinic was opened stateside. Since then, the technology and pharmaceutical fertility drugs have led to steadily increasing IVF success rates; however, physicians and researchers have been continually seeking means to improve these rates.<sup>30</sup>

In vitro fertilization is defined as fertilization of an egg by sperm to create an embryo outside of the female's body. IVF is considered to be the most successful as well as the most expensive and intensive assisted reproductive technology (ART).<sup>4</sup> The process of an IVF cycle can be split into three major phases: ovarian stimulation and egg retrieval, fertilization and intra-cytoplasmic sperm injection (ICSI; if necessary), and embryo transfer and luteal phase support.<sup>5</sup>

#### 1) Ovarian Stimulation and Egg Retrieval:

For a patient to begin IVF, baseline testing is performed on cycle day two or three and consists of an ultrasound and a blood test for follicle stimulation hormone (FSH) and E2 levels. The patient will then begin taking daily oral

contraceptives to begin ovarian suppression for two to four weeks. This time period varies as clinics typically try to align all their patients for the month in one cycle. To do so, a patient seen earlier in the cycle will take oral contraceptives longer as means to suppress her ovarian function while other patients are being tested and beginning the process. Patients using an agonist protocol will begin taking Lupron, a daily injection, 14 days before anticipated ovarian stimulation. Lupron is a gonadotropin releasing hormone (GnRH) agonist that, after long term use, downregulates luteinizing hormone (LH) release, preventing the patient from getting her own LH surge, which could cause premature ovulation. At this point, another ultrasound and blood test should be performed to confirm ovarian downregulation. After two weeks, Lupron's dosage is lowered as daily fertility medication injections are incorporated into the program to encourage ovarian stimulation. These medications include Follistim, Menopur, and Gonal-F; these are manufactured forms of FSH, and, in some cases, LH, that regulate egg growth and development within the ovaries. The different types contain different ratios of FSH and LH. Follistim and Gonal-F, for example, are solely FSH while Menopur is an equal mixture of FSH and LH. Starting five days into stimulation, the patient will receive ultrasound monitoring and blood tests daily or once every other day. When ultrasound monitoring confirms that enough follicles have been matured, typically between days eight and 12, the patient self-administers an injection of human chorionic gonadotropin (hCG), also known as the "trigger shot" to induce ovulation. This trigger shot mimics a natural LH surge that promotes ovulation. The exact time of the trigger shot must be precise as the egg

retrieval procedure must be performed exactly 36 hours after the shot is administered, just prior to ovulation. At this 36-hour mark, the patient will arrive at the office, be placed under anesthesia, and have their follicles aspirated and eggs retrieved using a minimally invasive procedure.<sup>5</sup> An ultrasound and needle are inserted vaginally, and the needle is passed through the vaginal wall and ovarian wall and inserted into each individual follicle where the contents, including a mature egg and surrounding cumulus complex, are aspirated out and into collection tubes, which are given to the embryologist in the lab. The goal of this procedure is to gather all eggs located within each follicle [see Figure 3].<sup>26</sup>

## 2) Fertilization and ICSI:

Sperm from the male partner is acquired on the day of egg retrieval. It is typically suggested that the male partner abstain from ejaculation for one to two days prior to the official sperm collection, in order to assure optimal sperm quantity and quality. Once the egg retrieval procedure has been completed, an embryologist will analyze the aspirated product with a microscope, rinse it with cultured media, and place it in dishes. Typically, eight to 12 eggs will be retrieved. At this point, any number of eggs or count of sperm can be cryopreserved for future use, if desired. Sperm will be introduced to the dish for natural fertilization. In specific cases of male infertility, including oligospermia and teratozoospermia, intracytoplasmic sperm injection (ICSI) will be performed in which specific individual sperm will be selected and injected through the outer shell of the egg and the egg membrane and into the cytoplasm. Once an embryo has formed, approximately three to five days after fertilization, it can be prepared for transfer

to the uterus, undergo assisted hatching, and, if desired, undergo a preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS) procedure. At this point, viable embryos that will not be transferred to the uterus can be cryopreserved. Assisted hatching is performed when the zona pellucida is considered to be too thick or the embryo has excessive fragmentation or slow rate of division, marking it as low quality. The process consists of the injection of an acidic solution into the zona pellucida, which slightly digests it and creates a small hole. This essentially creates a higher quality embryo that can more easily be implanted in the uterus when transferred. PGD testing is performed to scan for single gene defects, such as cystic fibrosis, in cases where this may be a concern. PGS is the same procedure but calls for overall chromosomal screening, not specific disease screening. PGS is used to diagnose chromosomal abnormalities and disorders such as Down syndrome. This allows patients and physicians to implant only genetically and/or chromosomally normal and theoretically healthy embryos when test results come back. The PGD or PGS procedure typically calls for the excision of a portion of the zona pellucida as well as one to two cells from the three-day embryo or five to ten cells from the blastocyst. These cells are then sent to a lab where they are screened for various and specific genetic sequences.<sup>5,26</sup>

### 3) Embryo Transfer and Luteal Phase Support:

Embryo transfers are considerably less invasive procedures than egg retrieval. Patients typically take a Diazepam to relax their muscles and produce a calming effect. Before the transfer, the patient and physician will discuss how many

embryos they want transferred, typically dependent on many variables including the patient's age, PGD/PGS results, embryo quality, and history of miscarriages. Typically, three to five days after egg retrieval, when the embryo is four to eight cells on day three or a full blastocyst on day five, the embryo will be transferred into a catheter and inserted into the uterus, usually monitored using an abdominal ultrasound. The embryo(s) is(are) released from the catheter at the center of the uterine cavity. It is important to ensure the catheter does not penetrate the endometrial surface. Once this procedure is complete, the patient will begin vaginal progesterone suppositories twice daily until the end of the first trimester or until negative pregnancy tests have been confirmed. High levels of progesterone are maintained to ensure the endometrium remains thick and is optimal for implantation of the blastocyst, as this sometimes happens up to 48 hours after embryo transfer. Blood will be drawn around days nine and 12 to monitor hCG levels and officially confirm or rule out pregnancy.<sup>5,26</sup>

For a couple undergoing a cycle of IVF, the egg and sperm can be obtained from the female and male partner. Many other unique forms of IVF exist to benefit a variety of patients in a variety of circumstances. These include the use of gestational carriers to provide an adequate uterine environment for embryo implantation, egg and/or sperm donation from an anonymous or known donor, and cryopreservation of egg and/or sperm samples or embryos allowing for future fertilization or implantation.<sup>4</sup>

In vitro fertilization is clearly a lengthy and intensive process that is physically, mentally, and monetarily demanding; and, even with the continually evolving technologies and drugs, the process has a pregnancy rate of only about 40% per cycle.

This relatively low success rate, considering the expense, is exactly why complimentary programs, including acupuncture and Chinese herbal medicine, could be implemented more regularly, to improve outcomes.

### Intra-Uterine Insemination

Intra-uterine insemination (IUI) was first researched as a method to treat infertility around the same time as IVF but it was available earlier is a less expensive and less invasive method to treat infertility. The procedure is most useful for patients under the age of 41 who do not exhibit tubal blockages or damage, ovarian failure, severe male-factor infertility, or severe endometriosis. Because IUI is highly dependent on ovarian reserves, patient age and day three FSH levels are the primary determinants in the relative possibility and success of IUI. Elevated day three FSH levels indicate reduced ovarian reserve.<sup>25</sup>

To begin, physicians aim to increase the patient's LH and FSH levels to stimulate follicle growth and warrant multiple follicles to mature. IUI focuses on enhanced follicular development and timed ovulation. Pharmaceuticals including clomiphene citrate (CC) or Letrozole are used to stimulate follicular development. CC is an estrogen antagonist that acts by inhibiting the negative feedback of E2 on the pituitary and therefore promoting additional FSH release and follicular stimulation. CC antagonizes estrogen by downregulating estrogen receptors at the level of the hypothalamus and pituitary. Letrozole prevents the conversion of androgens to estrogens by inhibiting the enzyme aromatase and therefore allows for more FSH and LH secretion because E2 levels are maintained relatively low to prevent negative feedback by E2 on the pituitary. Once

follicular development, monitored by vaginal ultrasound, is complete, ovulation is induced by using an hCG trigger shot, in the same manner used for IVF. Ovulation will occur 36 hours after the injection. At this time, a sperm sample will be collected, washed and suspended in media, and placed in the uterus using a catheter. Two weeks later, a pregnancy test can be performed.<sup>28</sup>

IUI has approximately a 10-15% chance of pregnancy per cycle for up to three cycles, dependent on the use of pharmaceuticals. Studies suggest that CC may actually allow for multiple eggs to ovulate, not just one predominate one, and therefore an increased chance of fertilization. If pregnancy is not achieved using IUI after three months, it is typically advised that they then move to IVF. IVF has much higher success rates than IUI but is also considered significantly more invasive and more expensive.<sup>15</sup>

## Discussion

Chinese herbal medicine has been proven to be effective for both patients undergoing IUI and IVF. There are primarily only studies showing the applicability of acupuncture for IVF patients although the net effects of increase endometrial thickness should be beneficial to any patient intending to become pregnant, regardless of the method.

Anovulation is responsible for 20-40% of infertility in patients. Clomiphene citrate, Letrozole, and gonadotropin agonists (LH and FSH) are the primary pharmaceuticals used for ovulation induction in IUI. According to a 2011 study, CC induced ovulation in 70.9% of women and pregnancy was achieved in 17.9%. Gonadotropin agonists induced ovulation in 89.89% and pregnancy was achieved in 17.9%. Letrozole induced ovulation in 67.5% and pregnancy was achieved in 15.2%. CC is considered to be anti-

estrogenic because of its ability to downregulate estrogen receptors and inhibit negative feedback by E2 at the pituitary level. These anti-estrogenic effects also act on the uterus downregulate estrogen-dependent gene transcription in uterine cells and therefore decrease endometrial thickness. The phytoestrogenic effects of CHM in turn relieve the anti-estrogenic effects on the uterine lining. The addition of CHM to CC increased occurrence of a thicker endometrial lining of the uterus by 78% compared to CC alone and pregnancy rates by 50% compared to CC alone. In this specific study, the main CHM substances used were *Rehmannia glutinosa*, *Angelica sinensis*, *Paeonia lactiflora*, and *Ligusticum chuanxiong*. Amongst CHM practitioners, these herbs are known for qualities including hematopoietic actions, induced suppression of the sympathetic nervous system, and decreased physiological stress. The outcomes of the trial finding significant improvement in both endometrial thickness and pregnancy rates is supported by these qualities.<sup>24</sup>

Using CHM as a complementary approach for IVF patients has similar outcomes. Twenty studies (from 2013) were reviewed using CHM either “before” (four trials), “during” (12 trials), “after” (three trials), “during and after” (three trials), or “before, during, and after” (one trial) in infertility cases classified as either tubal, PCOS, or endometriosis related. “Before” was defined as two to three days prior to beginning IVF, “during” was defined as starting on the first day of GnRH or FSH injections, and “after” was defined as post-oocyte retrieval or post-embryo transfer. In these trials, the herbs included *Radix rehmanniae preparata* (16 trials), *Radix angelicae sinensis* (15 trials), and *Radix paeoniae alba* (12 trials). According to CHM practitioners, these herbs were selected based on the ability to “nourish yin,” “tonify kidney,” “regulate qi,” and “activate

blood.” As discussed with acupuncture, tonification is important is activating slow physiological systems. Because a yin deficiency is associated with infertility, is it important that the herbs helps to diminish these effects by nourishing yin.<sup>13</sup>

Incorporating CHM significantly increased clinical pregnancy (presence of at least one gestational sac with or without a fetal pole), implantation rate (percentage of embryos implanted compared to number of embryos transferred), ongoing pregnancy (evidence of a gestational sac with fetal heart beats at twelve weeks), and live birth (delivery of a live fetus after 20 completed weeks of gestation). There was no significant impact on the number of miscarriages when using CHM before acupuncture but when using CHM after IVF, with the intention of protecting the fetus, it significantly decreased the miscarriage rate.<sup>13</sup> *Semen cuscutae*, specifically, increases estrogen receptor expression at the hypothalamus and pituitary and LH receptor expression at the ovaries. It regulates the proliferation and apoptosis of the decidua and cytotrophoblast to prevent spontaneous abortion, suggesting that CHM is important in protecting the fetus and maintaining the pregnancy, post-IVF.<sup>19</sup> Additionally, there were no reported adverse effects. It is believed that “Giving CHM earlier and for a longer duration may be more helpful in improving the clinical outcomes of IVF and therefore the mechanism of CHM in IVF may involve improving the quality of oocytes or embryos.”<sup>13</sup>

A study including 45 women suffering from oligomenorrhea and/or luteal phase defect performed auricular acupuncture and found a significant increase of in the resumption of ovulatory cycles compared to the control group with bromocriptine, dexamethasone, levothyroxine, clomiphene citrate, or gonadotropin; however, there was no significant difference in the pregnancy rates between the groups. This indicates

that using acupuncture as an alternative therapy to follicle stimulating drugs does not increase pregnancy rates. When using acupuncture as a complementary therapy for IVF patients, results were significant. When IVF patients (average age of 32.8) receive acupuncture 25 minutes prior to embryo transfer, the pregnancy rate was 42.5%, which is significantly higher than the control group rate of 26.3% (IVF alone). Pulsatility index, inversely related to vasodilatory effects, was measured before, after, and two weeks after acupuncture was performed. Uterine artery pulsatility index significantly decreased in both the after and two weeks after measurements, indicating immediate and long term vasodilatory effects of acupuncture and supporting the hypothesis that blood flow to the uterine artery increases.<sup>25</sup>

Both acupuncture and CHM improve blood flow to the uterus, hematopoietic actions, and induce suppression of sympathetic nervous system action. However, only 19% of IVF patients using acupuncture are currently using CHM as well.<sup>24</sup>

### Conclusion

Acupuncture normalizes hypothalamic-pituitary-ovarian axis dysfunction by promoting the release of  $\beta$ -endorphins. Acupuncture is sympathoinhibitory and therefore decreases pulsatility index and vasoconstriction. It leads to a significant increase in uterine artery blood flow and therefore endometrial thickness. Patients using acupuncture as a complementary treatment with IVF saw a 1.6-times higher pregnancy rate.

Chinese herbal medicine utilizes the phytoestrogenic properties in plants and soy products to promote estrogenic effects for IVF patients. By binding to estrogen

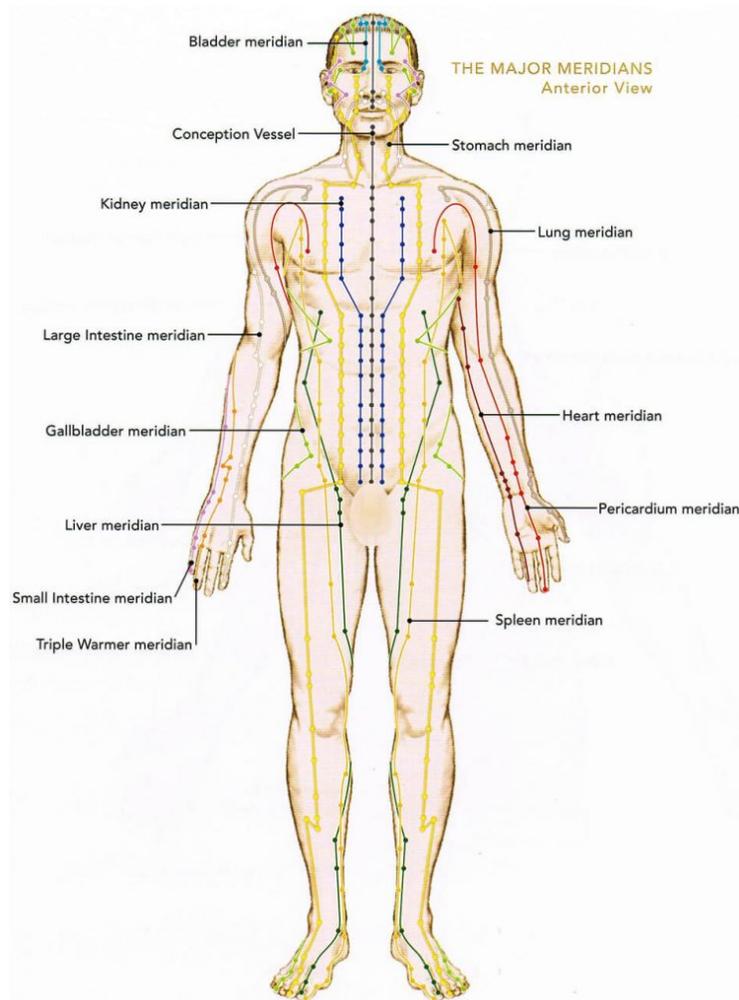
receptors and inducing estrogen-dependent gene transcription, flavonoid phytoestrogens stimulate glandular endometrium development leading to increased uterine weight, epithelial cell height, gland number, and lactoferrin expression. Chinese herbal medicine creates similar outcomes in IUI patients by relieving the anti-estrogenic effects of clomiphene citrate on the uterus by agonizing E2 binding to estrogen receptors. The use of CHM after IVF or IUI further promotes fetal protective effects by regulating proliferation and apoptosis of uterine cells and preventing spontaneous abortion.

As shown, CHM and acupuncture significantly increase both endometrial thickness and pregnancy rates in clinical trials. However, these outcomes have not been documented in clinical practice. This absence of information is dependent on the inability to regulate conditions for patients between practices, the irregularities of practice exhibited between practitioners, additional costs incurred by the patient, and the negative perceptions most patients in the United States have towards traditional eastern medicine. A 2016 study states that to enhance the use of herbal medicine, practitioners must first provide “convincing information to enhance the initiation of herbal medicine use,” considering the greatest factors inhibiting herbal medicine use are negative perceptions and attitudes and inconsistent effectiveness of some products.<sup>11</sup>

An interview with Dr. Scot Hutchinson of the Reproductive Health Center in Tucson, Arizona exposed both the benefits and concerns of incorporating acupuncture into IVF treatments, from a physician’s perspective. Dr. Hutchinson noted that for his patient population with a decreased uterine lining thickness, acupuncture is greatly advocated for and anecdotally appears to be incredibly beneficial for this patient

population. He said, “When we have people with whom we can’t get a good uterine lining for an embryo transfer – if we do not get it in a couple of months we will typically refer them to acupuncture twice a week and then repeat the protocols to get better results.” Additionally, for patients who choose to have acupuncture on the day of embryo transfer, he recommends going at least several times prior to this date in order to gain awareness of what exactly they should expect the day of and reduce any additional anxiety on that day. He mentioned that from his personal experience, he has learned that, if you are going to get acupuncture treatments, you should go twice a week for several weeks. He compared it to exercise saying that working out just once a month will not provide any benefits while working out twice a week will provide great benefits. The greatest downside to incorporating acupuncture into IVF treatments for all patients is simply cost. Acupuncture runs around \$60 per session and, although in the scheme of a \$15,000 treatment it is not substantial, it is enough to be a barrier for most people. The average income in Tucson is below that of the United States, so for many of his patients, this \$60 will price them out of the possibility. As a whole, Dr. Hutchinson will always recommend acupuncture to his IVF patients so long as they can afford it. There are no known negative effects so for many patients, especially those with decreased endometrial thickness, it cannot hurt to try (S. Hutchinson, personal communication, November 1, 2016).

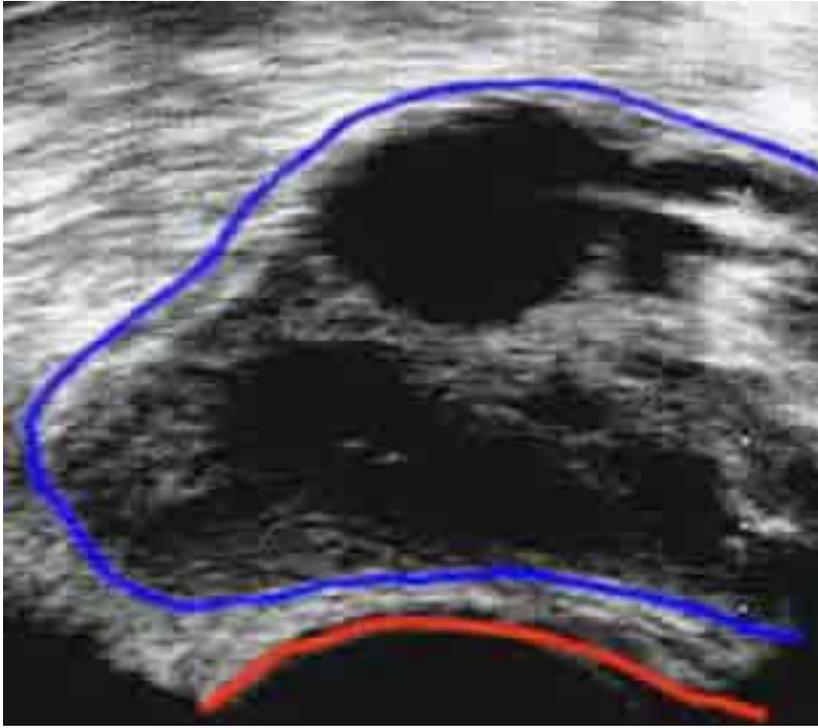
## Tables and Figures



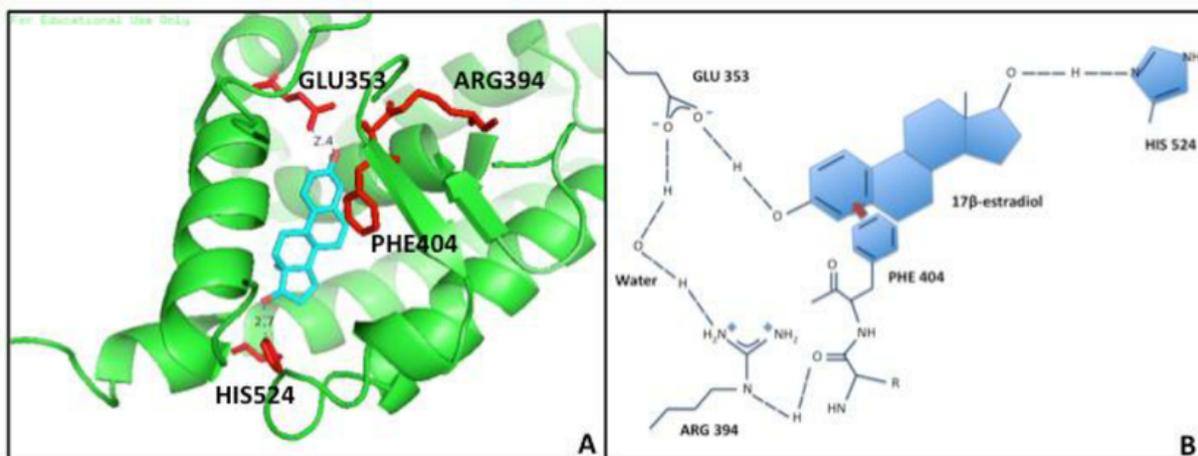
<sup>8</sup>Figure 1: Pictorial representation of thirteen meridians of the human body and associated acupoints, anterior view.



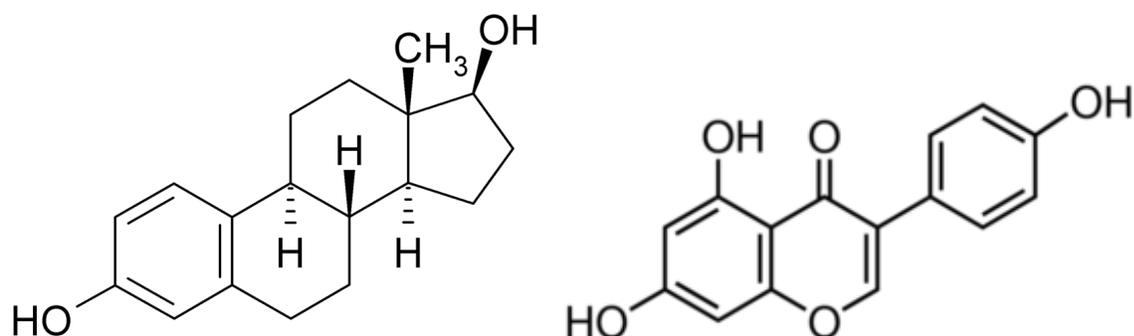
<sup>29</sup>Figure 2: Fu's Subcutaneous Needle. Image (A) shows the assembled needed that is inserted subcutaneously. Image (B) shows the 3mm difference between the stainless steel needle and the cap.



<sup>26</sup>Figure 3: An ultrasound image of egg aspiration. The ovary is outlined in blue, the top of the vagina is outlined in red. The white structure on the right is the needle inserted into the follicle, the large black circle, and collecting its contents.



<sup>20</sup>Figure 4: The binding of 17β-Estradiol (E2) to ERα.



<sup>1,3</sup>Figure 5: The structure of 17 $\beta$ -Estradiol on the left and the structure of genistein on the right, showing the similarity in structure and hydrogen bonding abilities.

Point	Location	Function
1	Directly anterior to anus	Amenorrhea, irregular menses, infertility and sterility, frigidity, prolapse of uterus
2	Just superior to pubic bone, over bladder	Menses: irregular, metrorrhagia, menorrhagia Uterine haemorrhage
3	4 cun below the umbilical cord	Dysmenorrhoea Itching, pain, swelling and heat in the genitals or cervix Irregular menses Sterility Vaginal itch and pain Vaginal discharges Prolapse of the uterus
4	Abdominal midline, 3/5 of the way down from the umbilicus to the superior edge of the pubic bone	Impotence, infertility, vaginal discharge, irregular menses, amenorrhea
5	2 cun inferior to to the center of the umbilicus	Raises sinking qi of weakly functioning uterus, uterine prolapse, prolonged vaginal discharge, continuous but light menstrual bleeding
6	1.5 cun inferior to the center of the umbilicus	Tonify kidney qi to support infertility, raise sinking qi from prolapsed uterus or vagina, uterine haemorrhage, regulate irregular menses and dysmenorrhea
7	1 cun inferior to the center of the umbilicus	Regulates heavy or light bleeding or amenorrhea, irregular menses, infertility
8	Center of the umbilicus	Supports yang deficiency related to infertility and frequent miscarriage

<sup>15</sup>Table 1: Acupoints 1-8 on the conception vessel. (Note: 1 cun is equal to 3.715cm)

## References

- <sup>1</sup>(2008, April 24). *Definition and Structure of Estradiol*. Retrieved from <http://itech.dickinson.edu/chemistry/?cat=101>
- <sup>2</sup>(2013, October). *Traditional Chinese Medicine: In Depth*. Retrieved from <https://nccih.nih.gov/health/whatiscam/chinesemed.htm>
- <sup>3</sup>(2015, April 21). *What is Genistein*. Retrieved from <http://www.best-dietary-supplements.com/genistein-99>
- <sup>4</sup>(2016, June 16). *In Vitro Fertilization (IVF) – Overview*. Retrieved from <http://www.mayoclinic.org/tests-procedures/in-vitro-fertilization/home/ovc-20206838>
- <sup>5</sup>(2017). *IVF Cycle Details*. Retrieved from <http://uscfertility.org/fertility-treatments/ivf-cycle-details/>
- <sup>6</sup>*Acupuncture and Chinese Medicine*. Retrieved from <http://www.acupuncture.org.au/AcupunctureandChinesemedicine/ChineseHerbalMedicine.aspx>
- <sup>7</sup>Acupuncture Theory. *Academy of Classical Oriental Sciences*. Retrieved from <http://www.acos.org/articles/acupuncture-theory/>
- <sup>8</sup>Acupuncture for Life. (2016). [Pictorial illustration Acupuncture Meridians and Nomenclature April 25, 2016]. Retrieved from <http://acupunctureforlife.co.uk/acupuncture-meridians/>
- <sup>9</sup>Albini, A., Rosano, C., Angelini, G., Amaro, A., Esposito, A. I., Maramotti, S., ... Pfeffer, U. (2014). Exogenous Hormonal Regulation in Breast Cancer Cells by

Phytoestrogens and Endocrine Disruptors. *Current Medicinal Chemistry*, 21, 1129–1145. <http://doi.org/10.2174/09298673113206660291>

<sup>10</sup>Amaro, John A. Acupuncture Needle Techniques. *International Academy of Medical Acupuncture*. Retrieved from

[http://www.iama.edu/Articles/Acupuncture\\_NeedleTech.htm](http://www.iama.edu/Articles/Acupuncture_NeedleTech.htm)

<sup>11</sup>Aziato, L., & Antwi, H. O. (2016). Facilitators and barriers of herbal medicine use in Accra, Ghana: an inductive exploratory study. *BMC Complementary and Alternative Medicine*, 16, 142. <http://doi.org/10.1186/s12906-016-1124-y>

<sup>12</sup>Brumbaugh K, Eisenberg E. (2012, July 16). *Infertility fact sheet*. Retrieved from <https://www.womenshealth.gov/publications/our-publications/fact-sheet/infertility.html>

<sup>13</sup>Cao, H., Han, M., Ng, E. H. Y., Wu, X., Flower, A., Lewith, G., & Liu, J.-P. (2013). Can Chinese Herbal Medicine Improve Outcomes of In Vitro Fertilization? A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *PLoS ONE*, 8(12), e81650. <http://doi.org/10.1371/journal.pone.0081650>

<sup>14</sup>Chang R, Chung PH, Rosenwaks Z. Role of acupuncture in the treatment of female infertility. *Fertil Steril* 2002;78:1149– 1153.

<sup>15</sup>The Conception Vessel (Ren Mai) Power Behind Reproduction but... Much More (2013). *Acupuncture Points*. Retrieved from <http://www.acupuncture-points.org/conception-vessel.html>

<sup>16</sup>Fu, ZH & Wang, JH & Sun, JH & Chen, XY & Xu, JG (2007). Fu's subcutaneous needling: possible clinical evidence of the subcutaneous connective tissue

- in acupuncture. *PubMed*. Retrieved from  
<https://www.ncbi.nlm.nih.gov/pubmed/17309377>
- <sup>17</sup>Gibreel A, Maheshwari A, Bhattacharya S. Clomiphene citrate in combination with gonadotropins for controlled ovarian stimulation in women undergoing in vitro fertilization. *Cochrane Database of Systematic Reviews* 2012, Issue 11. Art. No.: CD008528. DOI: 10.1002/14651858.CD008528.pub2
- <sup>18</sup>Henley, D. V., & Korach, K. S. (2010). Physiological effects and mechanisms of action of endocrine disrupting chemicals that alter estrogen signaling. *Hormones (Athens, Greece)*, 9(3), 191–205.
- <sup>19</sup>Hung, Y.-C., Infertility in Taiwan: A Population-Based Cohort Study. *Medicine*, 95(11), e3075. <http://doi.org/10.1097/MD.0000000000003075>
- <sup>20</sup>Miller C. (2015, October). *A brief on the structure and function of estrogen receptor alpha (BCMB8010 Enzyme Project)*. [Pictorial illustration Ligand binding pocket of estrogen receptor alpha October 2015]. Retrieved from  
[https://www.researchgate.net/figure/282878976\\_fig2\\_Figure-3-Ligand-binding-pocket-of-estrogen-receptor-alpha-Figure-A-displays-the-4-amino](https://www.researchgate.net/figure/282878976_fig2_Figure-3-Ligand-binding-pocket-of-estrogen-receptor-alpha-Figure-A-displays-the-4-amino)
- <sup>21</sup>Moy I, Ekpo G. (2011, April 1). Clomiphene citrate use for ovulation induction: When, why and how? Retrieved from  
<http://contemporaryobgyn.modernmedicine.com/contemporary-obgyn/news/clinical/clinical-pharmacology/clomiphene-citrate-use-ovulation-induction-wh?page=full>

- <sup>22</sup>Patisaul, H. B., & Jefferson, W. (2010). S. (2010). Physiological effects and mechanisms of action of endocrine disrupting chemicals that alter estrogen signaling. *Hormones (Athens, Greece)*, 9(3), 191–205., 31(4), 400–419.  
<http://doi.org/10.1016/j.yfrne.2010.03.003>
- <sup>23</sup>Rheumatology. *Oxford Journals*. (2004) 43 (5): 662-663.[doi:10.1093/rheumatology/keg005](https://doi.org/10.1093/rheumatology/keg005)
- <sup>24</sup>See, McCulloch, Smikle, Gao (2011). Chinese Herbal Medicine and Clomiphene Citrate for Anovulation: A Meta-Analysis of Randomized Controlled Trials. *The Journal of Alternative and Complementary Medicine*. DOI: 10.1089/acm.2010.0254
- <sup>25</sup>Sherbahn R. (2017). *Artificial insemination for infertility, intrauterine insemination – IUI*. Retrieved from <http://www.advancedfertility.com/insem.htm>
- <sup>26</sup>Sherbahn, R. (2017). *In Vitro Fertilization, IVF – the Process and Procedures*. Retrieved from <http://www.advancedfertility.com/ivf.htm>
- <sup>27</sup>Sifferlin A. (2017, March 14). *Millions of Women Don't Have Access to Fertility Treatments in the U.S.* Retrieved from <http://time.com/4701023/fertility-treatments-ivf/>
- <sup>28</sup>Weinstein, R. *Session 14 ART* [PDF document].
- <sup>29</sup>Zhong-Hua Fu, Jin-Han Wang, Jian-Hua Sun, Xin-Yuan Chen, Jian-Guo Xu (2007). Fu's Subcutaneous Needling: Possible Clinical Evidence of the Subcutaneous Connective Tissue in Acupuncture. *The Journal of Alternative and Complementary Medicine*. DOI: 10.1089/acm.2006.6125

<sup>30</sup>Retrieved from

<http://www.pbs.org/wgbh/americanexperience/features/timeline/babies/1/>