The Impact of Chinese Herbal Medicine on In Vitro Fertilization Outcomes:

A Systematic Review

By

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Abstract

Many are familiar with acupuncture and its possible benefits for infertility patients. Numerous studies on IVF and acupuncture have been conducted over the last twenty-five years. In the United States fewer are aware that historically in China the specialty of women's health in Chinese medicine is almost exclusively herbal. In Vitro Fertilization has now been in use for 40 years, originally developed to help women conceive who had blocked fallopian tubes. Recent advances in freezing embryos and preimplantation genetic testing for aneuploidies (PGT-a) have helped physicians gradually increase their IVF rates of success. Pregnancy rates at some of the nation's top fertility clinics hover at approximately 65%. Physicians and patients alike continue to seek novel methods to further optimize their IVF cycles. This work seeks to explore mechanisms of action and the impact of one of the world's most ancient medical systems, Chinese medicine's Chinese herbal medicine (CHM) on the outcomes of IVF. **Methods:** This literature review and synthesis began with a search of English and Chinese databases for research which contained keywords IVF and Chinese Herbal Medicine. Data was extracted for number of eggs retrieved, fertilization rates, possible changes in egg and embryo quality, pregnancy rates and when available live birth rates, spontaneous abortions in one study which sought to reduce this rate, and any proposed CHM method of action. These results were presented in table format and discussed at length.

Results: 13 eligible studies and 2 meta-analyses in English as well as 3 meta-analyses in Chinese met the study inclusion criteria. Overall, preliminary evidence suggests a benefit to patients undergoing IVF who add CHM to their regiment in all of the above-mentioned measures. Although statistical significance was not always demonstrated in each study, there was a clear

and apparent trend towards improvement. Plausible methods of action are likely to be related to active ingredients in the medicinals, increase in blood flow to the ovaries and endometrium, and changes in the follicular fluid and endometrial environment.

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Chapter 1: Introduction

As the cost of medical care continues to increase and many women are delaying childbearing until later in life it is important to utilize a patient's treatment dollars and time wisely(Macaluso et al, 2019). Currently in the United States the cost of IVF is approximately $12400 (ASRM, n.d.), this figure does not include costly medications estimated between $3000-7000 (FertilityIQ, n.d.) or PGT-a genetic testing approximately $5000 (FertilityIQ, n.d.) of the embryo which is routinely recommended if the woman is over thirty-five years old. In vitro fertilization is one method couples may elect and has been used for 40 years. Patients and physicians alike continue to look for safe and efficacious methods to increase their pregnancy success rates. Reproductive endocrinologists are generally unaware of the benefits of CHM for IVF and are concerned about possible harm; this paper will help to more explicitly educate and inform our western colleagues and open a dialogue for collaborative patient care and integrative medicine research. Chinese herbal medicine's tradition of treating obstetrics and gynecology conditions can be traced back at least 1800 years to the 金匱要略 (*Jin Gui Yao Lue) Essential Prescriptions of the Golden Cabinet* (Zhang, Ji, 210 AD). There have been few attempts to compile and summarize the existing literature on the topic of CHM and IVF. This literature synthesis will serve to fill the gap of having one

comprehensive review of what is currently known about the use of CHM to benefit IVF outcomes to direct practitioners in the clinic and guide future researchers.

The purpose of this study is to investigate the trends and patterns associated with the use of Chinese herbal medicine to affect pregnancy outcomes therefore providing guidance to Chinese medical practitioners who prescribe CHM leading up to, during and immediately after their patient's In Vitro Fertilization (IVF) cycles. A review and synthesis of completed research will help practitioners know what is possible when one adds Chinese herbal medicine (CHM) to an IVF cycle. At present many reproductive endocrinologists have embraced acupuncture as a safe and perhaps efficacious means of increasing their patient's IVF outcomes, but many are reluctant to recommend their patients pursue CHM in part because of non-FDA approval, lack of understanding of mechanism of action, concern of how it may adversely impact outcomes, and unfamiliarity with the current research on the subject. Upon completion of the proposed research synthesis a bridge will be laid for both practitioners of Chinese and western medicine to enter into dialogue about collaborative patient care, and results may be used to develop a pilot clinical study.

This researcher will further attempt to analyze what single herbs and prescriptions have most commonly been used in previous studies, define the optimal period and phases that one should take CHM prior to, during and after IVF transfer as well as discuss the Chinese medical theory used to write such prescriptions, and when

available describe possible mechanism of action as has been discussed in the current literature. A generalized treatment approach will be proposed for use in the clinic and to serve as a guide for future research. Finally, an attempt will be made to make specific suggestions for particular Chinese medical differential diagnoses or particular issues such as insufficient uterine lining. If it is appropriate a discussion may be added to explore a future multi clinic pilot trial which would seek to compare IVF alone, IVF with acupuncture, and IVF with acupuncture and CHM

Chapter 2: Background (Review of Literature)

This chapter will serve as a background to introduce patients and Chinese medical practitioners who have little experience working with fertility patients to the Western definition, prevalence, diagnosis, and treatment options of infertility. It is not intended to serve as a comprehensive text covering reproductive endocrinology and infertility for physicians or other advanced practitioners. For patients, researchers and physicians a basic introduction of the fundamental concepts of Chinese medicine as they pertain to women's health, and the historical context of Chinese medical gynecology as a specialty will be covered. A brief explanation of how Chinese medical practitioners make a differential diagnosis according to the principles of Chinese medicine will be detailed. Common Chinese medical patterns for diagnosis of infertility will be reviewed. Single Chinese herbs and Chinese herbal prescriptions which are commonly used to treat infertility will be discussed exploring possible mechanism of action when available. A phasic treatment approach will be outlined for CHM and IVF. Finally, a small number of animal studies relevant to mechanism of action for IVF will be discussed briefly. This will set the stage for a more complete understanding when individual studies and meta-analyses are discussed in the following chapter and later when various topics are explored in the discussion section.

Epidemiology and Prevalence of Infertility

Infertility is defined as a disease of the female and/or male reproductive system when a couple have engaged in unprotected intercourse regularly for 12 or more months but have failed to conceive (*Infertility WHO*, 2020). Estimates are that infertility affects 48 million couples and 186 million people worldwide (WHO). In the US a reported 7.3 million, 1 in 8 (13.1%) women ages 15-49 experience impaired fecundity according to the CDC data from 2015-2017 (*FastStats Infertility*, 2020). 8.8% of women in this age are infertile and 12.7% have used infertility services. Among married women infertility increases with age, 7% by age 30, 11% by age 35, 33% by age 40 and 87% by age 45.

There has been a steady decline in both birth and fertility rates in the United States since the 1950's. In 2001 the birth rate was 14/1000 and fertility rate was 65.3/1000 and in 2019 it was 12 and 58.3 respectively (See table 2.1 below). Some of this can be attributed to availability of contraception and abortion, females entering the workplace, age due to women delaying marriage in pursuit of advanced academic degrees and career goals, and possibly known or unknown environmental factors detrimental to both male and females. The mean age at first live birth has been increasing: 1970 it was 21.4 years old, in 2000 it was 24.9, and 2018 it was 26 years old. People are having fewer children from one generation to the next, by 45 years of age women in 1957 had 3.7 children and in 1976 had 1.8 children and 1.93 in 2020.

Table 2.1 Historical Birth and Fertility Rates in the United States		
Year	Birth Rates	Fertility Rates
1790	55/1000	Unavailable
1950	24.27/1000	105.2
1990	16/1000	70.9/1000
2001	14/1000	65.3/1000
2015	12.3	62.5
2018	12	59.1
2019	12	58.3

In 2018 the CDC Fertility Clinic Success Report there were 306,197 ART cycles. An ART cycle was defined as any cycle where eggs or embryos were handled i.e., IVF; IUI and medicated timed intercourse cycles were not included. Information on these cycles collected from 456 clinics yielded 73831 live born infants. A little more than one-third of these ART cycles were cycles in which either all the eggs or resulting embryos were frozen for later use. The use of ART among Americans has almost doubled in the last 10 years and today approximately 1.9% of infants born are conceived as a result of IVF.

Diagnosis of Infertility (Gordon, 2016)

After 12 months of regular unprotected sex (or less with older patients) a thorough evaluation of both the female and male should be conducted. On day 3 of the woman's menstrual cycle FSH, Estradiol and LH are checked. An Antral Follicle Count (AFC) can be performed on cycle day 2-4. AMH, inhibin B, and thyroid levels can be checked at any time in the cycle. Progesterone levels can be checked 7-8 days past positive ovulation predictor kit. Tubal patency may be evaluated by hysterosalpingogram. A hysteroscopy or transvaginal ultrasound is carried out to further evaluate the uterine cavity for the presence of fibroid, polyps, or adhesions. A semen analysis is performed on the male which will report count, motility, morphology and liquefaction. A sperm DNA fragmentation test may be ordered for additional information. If the semen analysis is abnormal a physical examination of the testicles, scrotum is performed and FSH, LH, testosterone, TSH and prolactin will be checked.

Problems with a woman's eggs, uterus, fallopian tubes, hormonal imbalance, fallopian tube blockage, infections and genetics can all be causative factors for female infertility. Causes of infertility for the male include problems with sperm shape, motility, count, function, prostate infection, varicose veins in the testicles, and genetic issues. Roughly it is said that about 1/3 of infertility is caused solely by female factor, another 1/3 male factor alone, and the remaining 1/3 can be attributed to issues with both the male and female or remain unexplained. Thirty-five percent of cases are due to

male factor. Thirty-five percent of cases may be due to tubal factors and another 15% due to ovulatory dysfunctions such as PCOS. While the remaining 15% is either unexplained or divided into rarer and unusual issues such as blood clotting disorders, auto-immune issues, uterine malformations, and genetic conditions such as absence of vas deferens or Klinefelter syndrome in the male, Turner syndrome in women or Kallman's syndrome in both men and women.

Treatment Options for Infertility

Treatment options for the couple generally can be divided into 3 options: timed-intercourse with medications to induce ovulation, intrauterine insemination (IUI), and In Vitro Fertilization (IVF). If the tubes are open and sperm is present and in good order, it's common practice for the couple to try 2-4 cycles of time-intercourse with a medication such as Clomid or Femara, followed by 2-4 rounds of IUI prior to progressing to IVF. If the tubes are blocked then the couple will typically go directly to IVF. Chances for conception per cycle with Clomid are 5.6%, IUI 8.3-17% depending on whether gonadotropins are used or not, IVF 20.7%, IVF with freeze all cycle 40%, IVF with PGT-A genetic testing 60% and IVF with donor egg 65% (Magarelli, 2020).

IUI involves placing the sperm directly into the uterus during ovulation. Bypassing the vagina and cervix that the sperm would naturally swim through increases the number of sperm present in the uterus and therefore increases chance for conception. IUI is typically combined with an ovulation induction drug such as Clomid

or Femara with the hopes that 2-3 follicles will mature (rather than one) thus increasing chances for pregnancy over timed intercourse. If the woman has failed previous IUIs, is anovulatory or the physician wishes to time the IUI more perfectly a trigger shot such as Ovidrel may be added to insure proper timing of ovulation.

In Vitro Fertilization was developed and first performed in England over forty years ago and in 1978 Louise Brown was the first baby born via IVF. Originally developed as a curative treatment for infertile women with blocked or absent tubes it is currently used for wide number of reasons, including severe male fertility as only one sperm is needed to inject into each mature egg with a technique known as intracytoplasmic sperm injection (ICSI). In IVF the women's egg cells are combined with the man's sperm cells outside the uterus, and the resulting embryo is transferred back into the uterus.

The woman undergoes controlled ovarian hyperstimulation (COH) taking FSH or hMG injections to stimulate the growth of as many eggs as possible. Multiple eggs are retrieved from the woman's ovaries via ultrasound-guided aspiration and fertilized in a culture medium inside a petri dish. The embryos are typically grown out to blastocyst over the next 5-7 days and may be transferred back to uterus or frozen to be transferred at a later date. Many IVF protocols exist; the 3 most commonly used long agonist, short agonist, and short antagonist will be detailed below.

The long agonist (down regulation) protocol begins in the previous cycle's luteal phase or at the beginning of the new cycle with the patient taking 7-10 days of a gonadotropin releasing hormone (GnRH) agonist such as Lupron prior to the start of her stimulation regiment. In normal physiology the GnRH agonists are released in a cyclical fashion to increase FSH and LH from the pituitary gland. However, when exogenous GnRH agonists are given continuously while there is first an increase in gonadotropins, it is then followed by a down regulation or cessation of the body's normal gonadotropin production. After taking the GnRH agonist the patient will have an ultrasound and bloodwork to confirm suppression and then begin FSH injectables such as Follistim or Gonal-F for approximately 10-12 days.

The short agonist (down regulation, flare protocol) begins with the patient starting a GnRH agonist on cycle day 1 or 2 and continued until the eggs mature in order to prevent early release/ovulation. FSH or hMG shots are then begun on cycle day 3 or 4. Lower doses of FSH or hMG medication can be used because this protocol initially "flares" the body's own endogenous FSH.

The (short) antagonist protocol compared to the long agonist protocol requires fewer injections, with a shorter stimulation period, and uses a lower dose of stimulation medications and generally produces fewer side effects. After 5-6 days of gonadotropins the GnRH antagonist (for example Cetrotide or Ganirelix) will be added to similarly

prevent early release of the follicles maturing oocytes. (Lyttleton, 2013; Wu & Leonard, 2019)

Brief Historical Overview of Chinese Medical Gynecology

Note: All names of individual Chinese herbs, Chinese herbal formula names, organ names when discussed in terms of Chinese medicine (to distinguish their understanding and function from Western medicine), channel and vessel names, Blood (again to distinguish it from Western medical concept of blood) , Jing (Essence), Qi and Chinese medical diagnoses will be capitalized in the text to serve to off-set them to the reader's eyes.

Currently there is only one available English source discussion on the history of Chinese medical gynecology and obstetrics (Maciocia, 2011). The following section is an analysis, selection, and paraphrase from Giovanni Maciocia's *Obstetrics and Gynecology in Chinese Medicine*, 2nd Edition. The earliest writings on Chinese medical gynecology were recorded on bones and tortoise shells in the Shang dynasty (1500-1000 BC) and discussed problems of labor. *The Historical Annals* from the same period refers to famous physician Bian Que as "DaiXiaYi" women's doctor or doctor who treats below the belt or waist. Medicinal herbs to treat infertility were first mentioned in *Book of Mountains and Seas* from the Warring States period (476-221 BC). *The Yellow Emperor's Classic of Internal Medicine – Simple Questions* discusses women's anatomy and physiology and the diagnosis and treatment of gynecological ailments. The function of the uterus is discussed as well as it's connection with the Heart and Kidneys via the Bao Mai (Uterine Vessel) and Bao Luo (Uterine Channel). The first chapter of *Simple Questions* famously discusses changes in women's physiology in seven-year cycles resulting from waxing and waning of the Chong and Du Mai (Penetrating and Governing Vessels) in essence describing hormonal changes in a woman's life long before knowledge of the endocrine system or hormones were known. "When a girl is

14, the Tian Gui arrives, the Governing vessel is open and the Penetrating Vessel flourishes, the period arrives and she can conceive."

One of China's most famous herbal physicians Zhang Zhongjing in his book *Shang Han Lun* makes reference to a *Series of Herbs for Obstetrics* a book lost in antiquity that proves even before the Han Dynasty there were books entirely devoted to gynecology. In the other half of *Shang Han Za Bing Lu*n called *Jin Gui Yao Lue (Essential Prescriptions of the Golden Cabinet)* there are three chapters (chapters 19-21) devoted entirely to gynecology and obstetrics. These chapters discuss the treatment of disease of pregnancy, post-partum diseases, and women's miscellaneous diseases including disorders of menstruation, vaginal discharge and infertility. Wen Jing Tang, Jiao Ai Tang, and Gui Zhi Fu Ling Wan are among the most famous prescriptions discussed which are still commonly used in modern practice.

Wang Shu He of the Jin Dynasty (265-420) author of *The Pulse Classic (Mai Jing,* 280 AD) seminal work on Chinese pulse diagnosis described various pulses in relationship to labor and pregnancy, miscarriage and further detailed the relationship between the Kidneys and Uterus and their rear position of the pulse. Sun Simiao in the Tang Dynasty (618-907 AD) authored *Qian Jin Yao Fang (The Thousand Golden Ducat Prescriptions* 652 AD) included 3 chapters on gynecology which contained hundreds of herbal prescriptions covering a wide range of conditions including infertility, menstrual disorders, leukorrhea, and obstetrical disease.

China's earliest known gynecology and obstetrics department was during the Song Dynasty (960-1279) within the Imperial Medical College and gave rise to a flourishing of writings on women's health as a specialty. The most influential of this period was Chen Ziming's *Fu Ren Liang Fang Da Quan* (*Great Treatise of Useful Prescriptions for Women* , 1237).

> The book comprises 24 volumes including 20 chapters on menstrual diseases, 91 miscellaneous disease, 10 on infertility, 8 on 'fetal education', 9 on pregnancy problems, 70 on post-partum diseases, and 10 on boils and ulcers. More than 260 diseases are discussed in all with various formulae for each. This book exerted a profound influence on the development of obstetrics and gynecology in subsequent dynasties.

During the Jin and Yuan Dynasties (1115-1368) two of the most prominent practitioners were Li Dongyuan (1180-1251) and Zhu Danxi (1281-1358). Li Dongyuan known as the father of the Spleen Stomach School of Thought in Chinese medicine, placed disharmony among these two organs at the center of the foundation of disease. For treating gynecological disease, he believed tonifying the Spleen and Stomach was of utmost importance. Zhu Danxi famously stated that, "Yang is often in excess and Yin is often deficient" recommending that nourishing yin be the most important treatment principle.

Zhang Jingyue was one of the most influential physicians of the Ming Dynasty (1368-1644). In the gynecology section of *The Complete Works of Jingyue* he suggests regulating menstruation to be crucial to treating gynecological disease. To regulate the

period, he advocated strengthening the Spleen and Stomach in order to nourish Blood, and to tonify the Kidneys in order to "calm the Uterus".

During the Qing dynasty (1644-1911) many important gynecological texts were written, none were more influential than *Fu Qingzhu's Gynecology* by Fu Qingzhu (1607-1684). He stated that the Kidneys are the most important organ when it comes to menstrual function and that, in fact, they are the origin of menstrual blood. He believed menstrual blood to be different from other blood in the body and said that it was precious fluid stemming from the Kidney Essence.

Western medicine was introduced to China in the late Qing Dynasty and its practice was integrated with Chinese medicine. Tang Zonghai (1862-1918) and Zhang Xichun were two prominent physicians of the day that strongly urged this integration of the two medical systems. Tang Zonghai wrote about the importance of Blood Stasis in gynecology as a pathological etiology and taught that it was important to tonify both the Spleen and Kidney as well as to invigorate Blood when treating these diseases. The integration of Chinese and Western medicine has been strongly encouraged since 1949 and since 1956 when Chinese medical colleges were established many modern and ancient texts on treating gynecological disease continue to be printed.

Current Practice of Chinese Medicine as it Pertains to Reproductive Medicine in the United States

In the United States, patients may visit an acupuncturist's office to assist in their efforts to conceive whether they are just beginning their journey, beginning medicated cycles with a gynecologist, or undergoing advanced ART such as IUI or IVF with a fertility specialist. The acupuncturist may treat the patient with acupuncture, prescribe herbs, discuss dietary and lifestyle changes in accordance with the principles of Chinese medicine, and even teach simple movement exercises known as qigong to reduce stress. In the US acupuncture is almost always included in this whole systems approach to treating infertility with Chinese medicine. Some practitioners have studied Chinese medicinal herbs and utilize them while others may not.

Reproductive Chinese medical specialist Diane Cridennda and reproductive endocrinologist Paul Magarelli have researched the benefits of acupuncture for patients undergoing IVF for over twenty years. The Cridennnda Magarelli Acupuncture protocol (CMAP) is widely used by reproductive acupuncturists in the United States and Europe and frequently cited in the debate over whether or not acupuncture offers a benefit for IVF patients. Their chapter entitled *The Revolution of Assisted Reproductive Technologies: How Traditional Chinese Medicine Impacted Reproductive Outcomes in the Treatment of Infertile Couples* published in the book *Infertility and Assisted Reproduction* (Rizk et al., 2008) is the first entire chapter on acupuncture and IVF published in a

textbook intended for physicians pursuing their fellowship in reproductive endocrinology and infertility. The CMAP combined the work of Elisabet Stener-Victorin electric stimulation acupuncture on the back which had been shown to decrease the pulsatility index in the uterine artery thus increasing blood flow to the uterus with the work of Paulus et al. which originally was shown to increase pregnancy rates of IVF patients by 10-12% with only two acupuncture treatments performed immediately before and after embryo transfer. The work of Cridennda and Magarelli has been shown to significantly decrease ectopic pregnancies and increase birth and ongoing pregnancy rates for poor responders, decrease ectopic pregnancies and increase live births in good responders, to increase pregnancies and decrease ectopic pregnancies and multiple births in combined all IVF patients (Magarelli et al., 2009). It has been proposed that mechanistically acupuncture might be working to improve IVF outcomes by modulating neuroendocrinological factors, increasing blood flow to the uterus and ovaries, modulating immune factors especially cytokines, and reducing stress, depression and anxiety (Anderson et al., 2007).

In contrast in China, patients desiring to add Chinese medicine to their fertility efforts will visit a Chinese medicine hospital's gynecology department. In addition to a thorough medical history, bloodwork and pelvic exam may be conducted. Medication such as Clomid or progesterone may be used in combination with Chinese medicine. Patients will not be given acupuncture but instead will be prescribed Chinese herbal

medicine in dried plant form which they will return home to boil producing a liquid decoction, the hospital will cook herbs and put them in liquid filled pouches, or granules may be prescribed which are dissolved in hot water and taken orally. Acupuncture is a separate department in a Chinese medicine hospital and not commonly sought out by Chinese patients when trying to conceive.

In Chinese medicine the practitioner will prescribe an herbal prescription typically composed of 10-15 ingredients based on the patient's Chinese medical diagnosis. This diagnosis is made by conducting a detailed patient intake and further clarified by examining the tongue and taking the pulse bilaterally at the radial artery. The patient will be asked about whether they tend to run cold or hot, if they have night sweats or hot flashes, about the quality of their sleep and energy level, mood, libido, observable fertile mucus or vaginal dryness, previous pregnancy history, urination and bowel movements etc. Further information about the woman's menses and cycle will be collected at great length and would include asking about her age of menarche, length of cycle and number of days of menses, how heavy her periods are, if there are cramps, back pain or clots, or headaches, breast tenderness, irritability or depression or bloating leading up to the start of the period. Chinese medicine holds that this information about the woman's monthly cycle and periods is useful in making a diagnosis and treatment plan and often a contributing factor to the patient's infertility. The presence or absence of menstrual cramps, clots in the menses, a history of fibroids, painful periods or

endometriosis, depression or anxiety, breast distension, headache, night sweats or flashes, observable egg white cervical mucus or vaginal dryness and much more are all taken into account. Based on this information the practitioner seeks a collection of symptoms to form a pattern which is the patient's Chinese medical diagnosis. While physicians in ancient China did conduct cadaver dissection and could see blood, muscles, nerves, bones, and organs they could not yet see or understand the body at the biochemical or hormonal level. When mentioning Spleen, Liver, Kidney in Chinese medicine it is important to keep in mind this is their system of understanding how the body is put together and is not meant to be a perfect match with the biomedical understanding and function of spleen, liver, and kidneys. Table 2.1 on the following page summarizes the functions of the organ systems as they are traditionally understood in Chinese medicine.

Table 2.2, Functions of Organ Systems according to Chinese Medicine (Lewis, 2005) Reproduced with permission from author	
Organ Systems	*Functions*
Kidney	• Contains our genetic makeup • Controls the reproductive system and a woman's hormones • Connects reproductive, skeletal, neurological, and endocrine systems • Stores Essence (Jing), one of the key energies of the body
Spleen	• Governs energy production, metabolism, digestion, and elimination • Converts nutrients and Qi into Blood • Essential for healthy menstrual cycle • Affects thyroid hormone production • Sustains luteal phase
Heart	• Governs mind and spirit • Controls Blood and circulatory system • Provides Blood for Uterus
Liver	• Controls smooth flow and distribution of Blood • Responsible for all transformations in body, including ovulation • Provides Blood for menstruation • Affects expression of emotions, calms emotional energy • Stores Blood
Uterus	• "Palace of the child" • Connected with rest of body, especially the Heart and Kidneys • Source of Conception and Penetrating meridians

In addition to patient history and zang-fu organ/bowel type of diagnosis in gynecology most commonly related to the Chinese medical understanding of imbalances in the Kidney, Liver, Spleen, the herbalist is guided by 8 guiding principles which are hot/cold, interior/exterior, deficiency/excess and yin/yang. Hot and cold, is there a predominant sensation felt by the patient either tendency to feeling too cold or hot? Heat may also be thought of as an inflammatory process. Is the condition caused by interior disharmony or an external pathogen? Deficiency and excess, is there not enough of something or is there too much of something causing the problem? Is the condition primarily yin or yang in nature? Yin in the body can be generalized as cooling, moistening, nourishing, resting or storing in nature, and some have drawn parallels between yin and estrogen. While Yang is warming, moving and may be thought to be related to hormones such as testosterone and progesterone. Treatment principles are guided by the diagnosis. *The Yellow Emperors Canon on Internal Medicine* fundamentally states:

> "If there is heat, cool it;
>
> If there is cold, warm it;
>
> If there is dryness, moisten it;
>
> If there is dampness, dry it;
>
> If there is vacuity, supplement it; If there is repletion, drain it."

Common Diagnoses for infertility in Chinese Medicine

The following section is a translation and paraphrase of selected parts from *中医妇科学 (Chinese Medical Gynecology, 5th ed.)* by Shanghai Science and Technology Publishing (Y. Luo & Ceng, 1986) which was at one time the national standardized Chinese textbook on the subject for Chinese medical students in mainland China. Common Diagnoses for infertility in Chinese medicine can be divided into 4 categories Kidney Deficiency, Liver Stagnation, Phlegm Dampness and Blood Stasis. Kidney deficiency is further subdivided into Kidney Yang Deficiency, Kidney Yin Deficiency. Each diagnosis will be made if a collection of symptoms are present to form that particular pattern and will be paired with an accompanying treatment principle and representative herbal formula.

For Kidney Yang Deficiency the patient may have delayed periods (long cycles), light periods which are pale in color, or very infrequent periods, or amenorrhea. The facial complexion is dark, there may be achy lumbar pain and weakness of the legs, poor libido, long voiding of clear urine, or loose stool. The tongue coating may be pale white and the accompanying pulse may be deep and thin or deep and slow. The treatment principle would be to warm the Kidney, tonify Qi, and nourish Blood, as well as to regulate and tonify the Chong and Ren vessels. The herbal prescription Yu Lin Zhu from the *Jing Yue's Complete Compendium* (Zhang Jiebin, 1624) with additions of Zi

He Che, Dan Shen, and Xiang Fu may be given containing Ren Shen, Bai Zhu, Fu Ling, Bai Shao, Chuan Xiong, Zhi Gan Cao, Dang Gui, Shu Di, Tu Si Zi, Du Zhong, Lu Jiao Shuang, Chuan Jiao.

For Kidney Yin Deficiency there may be early periods（short menstrual cycles）, with light periods, which are red and without clots, or periods are still normal but with emaciation and weakness and soreness of the lumbar and legs, dizziness, palpitations and insomnia, rash/restless and impatient in nature, dry mouth, vexing heat in the five hearts, and low-grade afternoon fever. The tongue is slightly red, with little coating, and a thin rapid pulse. It is suitable to nourish the Yin and Blood and regulate the Chong and benefit Essence. Representative herbal formula such as Yang Jing Zhong Yu Tang from *Fu Qingzhu's Gynecology* (Fu Qingzhu, 1827) containing Dang Gui, Bai Shao, Shu Di, and Shan Zhu Yu with the additions of Nu Zhen Zi and Han Lian Cao may be prescribed.

Infertility due to Liver Depression (Stagnation) presents with irregular menstruation, menstrual cramps, inhibited menstrual flow, light in quantity and dark in color with small clots, premenstrual breast distension and pain, mental depression, vexation agitation and quick to anger. The tongue body may be normal or dark red with a thin white coating, while the pulse is wiry. The accompanying treatment principle is to soothe the Liver and resolve depression while nourishing Blood and rectifying the

Spleen. Fu Qing Zhu's Kai Yu Zhong Yu Tang is appropriate and contains Dang Gui, Bai Zhu, Bai Shao, Fu Ling, Mu Dan Pi, Xiang Fu, and Tian Hua Fen.

A diagnosis of Phlegm Dampness related infertility may be made when there is obesity, delayed menstruation, in severe cases amenorrhea, copious vaginal discharge which is sticky and thick, bright white facial complexion, dizziness of the head and palpitations, oppression in the chest with sensation of nausea, white tongue coating and slippery pulse. The correct treatment principle is to dry dampness and transform phlegm as well as rectify the Qi and regulate the menses. The experiential herbal formula Qi Gong Wan with Shi Chang Pu can be utilized which is comprised of Zhi Ban Xia, Cang Zhu, Xiang Fu, Shen Qu, Fu Ling, Chen Pi, Chuan Xiong.

When there is Blood Stasis related infertility there may be late menstruation which is light in quantity, purple black in color with clots, possibly menstrual pain, lower abdominal pain occurring outside the period, pain which is worse with pressure. The tongue appears dark and purple or the sides may have purple dots and the pulse will be thin and wiry. With Blood Stasis one would invigorate the Blood and transform stasis to regulate the menses. The representative formula to treat Blood stasis is Shao Fu Zhu Yu Tang from *Correction of Errors in Medical Classics* and contains Xiao Hui Xiang, Gan Jiang, Yan Hu Suo, Mo Yao, Dang Gui, Chuan Xiong, Rou Gui, Chi Shao, Pu Huang and Wu Ling Zhi.

Choosing the Correct Herbs Based on Temperature and Flavor (Bensky et al., 2004; J. Chen & Chen, 2004)

Individual herbs for an herbal prescription may be chosen by several means. Traditionally, the temperature and flavor of the herbs dictated the herb's function and usage. Subsequently actions were ascribed to herbs and particular herbs were believed to enter specific channels.

Chinese herbs can be divided into hot, cold, warm, cool, and neutral, acrid, sweet, bitter, sour, salty, and bland. *The Inner Classic* chapter 74 states that hot diseases must be cooled, while cold diseases must be warmed. Therapeutically cool or cold herbs might be selected to treat a person who suffers from hot flashes, night sweats, inflammation, redness, and swelling. While a person who frequently feels cold perhaps from hypothyroid or poor circulation or another condition may be treated with herbs that are warming or hot in nature.

The tastes of Chinese herbs are believed to contribute to their functions. The six tastes of flavors are acrid, sweet, bitter, sour, salty and bland. Acrid herbs are thought to disperse and move. Sweet flavor tonifies, harmonizes, and may be moistening in nature. The bitter flavor drains (removing heat downward via stool or urination) and dries dampness. Herbs which are sour are said to stabilize and bind which means to reduce and prevent the loss of fluids. Salty flavored herbs purge excess and soften hardness

and guide the herbs to the Kidney. Bland herbs with little or no taste leech out dampness and promote urination.

By combining taste and flavor, actions and indications were later added to Chinese herbal medicine. The eight therapeutic methods include promoting sweating, inducing vomiting, purging, harmonizing, warming, clearing, tonifying, and reducing. Later herbs were thought to have an affinity with or enter a particular Chinese medical organ. For example, Rou Gui enters the Kidney channel, Bai Shao enters the Spleen channel, and Chuan Xiong and Chai Hu enter the Liver channel.

Research on Single Chinese Herbs for Infertility

An animal study on PCOS comparing metformin to Rou Gui, found Rou Gui to be as effective for lowering testosterone, LH, and insulin resistance, while a pilot RCT human study of overweight PCOS women demonstrated it improved metabolic profiles of homeostasis model of insulin resistance (HOMO-IR) and quantitative insulin sensitivity check index (QUICKI). Studies on Bai Ji Li showed that it induced ovulation in polycystic ovaries, and was equivalent to Clomiphene for ovulation induction for women with oligo/anovular infertility. Gan Cao in studies have been shown in both mice and women to lower androgen levels and increase frequency of ovulation. (Arentz et al., 2014)

Tu Si Zi an herb from the tonify Kidney Yang category (herbs from this category are often used as part of an herbal formula to treat infertility); in a study on

psychologically stress induced rats, it was found to help ovarian endocrine dysfunction by increasing LH receptors expression in the ovaries, estrogen receptor expression in hippocampus, hypothalamus, and pituitaries. Yi Mu Cao from the invigorate Blood and transform stasis herbal category is commonly used in cases of Blood Stasis causing dysmenorrhea and endometriosis among infertility patients. It has been shown to increase serum progesterone, inhibit inflammation, relax uterine spasms, and decrease prostaglandin concentrations in uterine smooth muscle (Liao et al., 2017).

Research on Chinese Herbal Prescriptions for Infertility

The herbal prescription Wen Jing Tang invigorates Blood and transforms stasis, warms the meridians to dispel cold, and tonifies the Qi and Blood and has been shown to favorably reduce LH and estradiol levels in PCOS patients with ovulatory dysfunction. In anovulatory women Wen Jing Tang in combination with Clomiphene induced ovulation among women who were not ovulatory with Clomiphene alone (Liao et al., 2017). Y Chen observed a beneficial effect on women who suffered from immune-related recurrent spontaneous miscarriage of unknown cause and related benefit to T-lymphocytes who took the classic Chinese herbal formula Gu Shen An Tai Recipe (D. Jiang & Li, 2017).

In a study with ninety participants, half took progesterone alone while the treatment group took progesterone plus Gu Shen An Tai Recipe. The control group had continued pregnancies in 71.1% while the treatment group had 86.7%. CD4, CD8,

CD4/CD8 levels were observed before and after treatment and it was shown that the herbs could correct immunological disorders (D. Jiang & Li, 2017).

Animal Studies Chinese Herbal Medicine Utilized During IVF

The herbal prescription You Gui Wan (YGW) is sometimes selected to treat Kidney Yang Deficiency infertility and traditionally tonifies Kidney Yang and nourishes Essence and Blood. Research has revealed that a You Gui Wan medicated serum can significantly increase the percentage of mature oocytes and fertilized oocytes in rats. The study demonstrated an increase in concentrations of cyclic adenosine monophosphate (cAMP) and expressions of a number of signaling molecules protein kinase A (PKA), cAMP - response element binding protein (CREB), mitogen - activated protein kinases (MAPK), maturation promoting factor (MPF), protein kinase C (PKC), and a decrease in the oocyte nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) concentrations and the expression of protein kinase G (PKG). Jiang's group theorized that one possible mechanism of action of YGW might be the regulation of oocyte maturation via signaling pathways including the cAMP/PKA/MAPK pathway, the PKC-MAPK pathway, and the NO-cGMP-PKG pathway, which are similar to those induced by the body's natural FSH. They further assumed that the higher fertilization rate may be as of the result of YGW influencing oocyte maturation and perhaps egg quality. (X.-H. Jiang et al., 2014)

Controlled ovarian hyperstimulation may cause early maturation of the endometrium, leading to a glandular and stromal dyssynchrony in the uterine lining unfavorable to implantation. HOXA10 is an important marker of implantation. Normally it upregulates its target gene Integrin Beta 3 (β3) and downregulates EMX2, 2 additional markers of uterine receptivity. COH was demonstrated to downregulate both HOXA10 and Integrin Beta 3 and adversely increase expression of EMX2 which is deleterious for implantation. Gao et al demonstrated in mice that giving Zishen Yutai Pill during COH could alleviate this dyssynchrony and precocious maturation in the endometrium. Furthermore, the mechanism of action appeared to be due to it increasing HOXA10 and Integrin Beta 3 while simultaneously reducing EMX2, leading to a more favorable environment for implantation. (Q. Gao et al., 2015)

A study of seventy mice which had been given Alarelin, a gonadotropin-releasing hormone analog to create a model with reduced endometrial receptivity were randomly divided into three groups and subjected to controlled ovarian hyperstimulation (COH). The experimental treatment group was given Shoutaiwai (STW) herbs comprised of Sha Yuan Zi, Huang Qi, Sang Ji Sheng, Xu Duan, Bai Zhu, Chuan Xiong and Dang Shen. A second group was given Aspirin and a third group serving as a control was given a solution of sodium chloride. Expression levels of integrin β3 and leukemia-inhibitory factor (LIF) were analyzed in the endometrium during the window of implantation. Levels of both integrin β3 and LIF were statistically

elevated between the CHM STW treatment group and the Aspirin treated group. The Aspirin group levels of integrin β3 and LIF were statistically higher than the control group. Secreted by the endometrial glandular and luminal epitheliums post ovulation, Integrin β3 is involved in the adhesion of blastocyst implantation. LIF are secreted by natural killer cells and belong to the family of Interleukin-6 (IL-6) cytokines that are involved in the regulation of human reproduction including embryonic development, implantation, and pregnancy maintenance (X. Y. Chen et al., 2015).

Chinese Herbal Phasic Approach to Supporting IVF Patients

If Chinese herbal medicine is found to be beneficial for IVF patients, then the crucial question of when would it be most helpful to take should be discussed. Studies detailed in the following chapters vary in timing of when patients took herbs and for how long they were continued. It is helpful to have an understanding of what the goals are for Chinese medicine leading up to, during, and after the various phases of IVF. Dr. Yuning Wu, Chief Gynecologist, Professor of integrated Traditional Chinese and Western Medicine, Beijing Hospital of TCM affiliated to Capital University of Medical Science proposes 6 stages of treatment with Chinese herbal medicine to support IVF. These are Preparation: Regulating, Down-regulation: Nourishing, Menstruation: Purging, Stimulation: Promoting, Egg collection: Relaxing, Embryo transfer (and beyond) Consolidating. (Wu & Leonard, 2019)

The preparation stage may begin 1-3 months prior to starting the IVF cycle. This phase is focused on identifying and treating the patients underlying Chinese medical diagnosis according to pattern presentation. Commonly seen in clinic as mentioned above are Kidney Yin Deficiency, Kidney Yang Deficiency, Phlegm-Dampness, Liver Qi Stagnation and Blood Stagnation. Improvements in the patient's overall health including better sleep and digestion, less anxiety and stress, more energy, improvement in symptoms associated with the period such as cramps, mood swings, breast tenderness are all positive indicators. Blood Stasis in particular, Dr. Wu cautions must be addressed prior to starting IVF as left untreated may contribute to poor egg quality and lower implantation rates.

During down-regulation the patient will be taking a GnRH agonist such as Lupron or oral contraceptive pill. These medications tend to diminish reserves of Blood and Yin, worsen symptoms of deficiency heat, Blood deficiency, Qi stagnation, Liver Yang Rising and Heart and Kidney Disharmony. An herbal prescription which focuses on nourishing to counter some of the expected side effects of medication should follow the treatment principle of nourishing Blood and Jing to strengthen the Chong and Ren vessels. As the physician is down regulating the ovaries with medication to rest the ovaries, the prescribing herbalist should not use too many Kidney Yang herbs which are warming in nature nor too strong of blood moving herbs which might encourage ovulation.

The third phase of herbs is given around menstruation and is focused on purging or sloughing off the old endometrial lining ensuring a healthy environment for the transfer's implantation to occur. The prescription should be one that nourishes and invigorates blood to regulate menstruation. This may be given from 2-3 days before the period until day 3 or 4 of the cycle, or may focus solely on the first few days of the period, and may continue throughout the day before stimulation injections are to be started.

Patients will take stimulation shots on average for 10-12 days. Stimulation herbs are to be prescribed in tandem with the start of stimulation injections and continue up to 2-3 days before retrieval, 1-1.5 days before retrieval, or even up until the evening prior to the retrieval (if phase 5 herbs are not to be dispensed) depending on practitioner preference and clinical experience. The herbal prescription will follow the treatment principle of tonifying the Kidney and replenishing Jing, invigorating Blood and regulating the Chong and Ren vessel in order to promote follicular growth. This prescription may be modified on the basis of whether the patient is more Kidney Yang or Yin deficient as well as to counter stress and anxiety produced by treatment.

The fifth phase focuses on the time leading up to the egg retrieval. While Dr. Wu considers this type of prescription should be taken 2-3 days before egg collection, others may only prescribe this type of formula for 1-1.5 days or leave it out altogether. Elevated cortisol levels may impair proper development of the endometrium so at this

time Chinese medicine will always use some herbs which regulate Liver qi and calm the spirit. The treatment principle in general will tonify the Kidney and nourish Jing, invigorate blood and regulate the Chong and Ren vessel, and regulate the Qi and calm the mind.

The final stage of Chinese herbal medicine during IVF is referred to as consolidation and begins from the day of the embryo transfer and continues for 10-12 days until the pregnancy test. These herbs are safe to take during pregnancy and are similar to ones that might be prescribed for patients suffering from recurrent pregnancy loss. Some practitioners will have the patient continue taking the same or similar herbal prescription through the first trimester to secure or safeguard the pregnancy. The guiding treatment principle is to strengthen the Kidney and Spleen to consolidate the Chong and Ren vessel. The herbal prescription will contain herbs which tonify the Spleen and Kidney, nourish Blood, astringe, and may contain ingredients to calm the mind. These herbs are believed to support implantation and a healthy pregnancy in the same way that a fertility specialist may prescribe progesterone after an IVF transfer and during the early part of pregnancy.

Chapter 3: Methods

A systematic review was conducted to evaluate the impact of Chinese herbal medicine on the outcome of female patients undergoing IVF. A search of Pubmed, Google Scholar, Cochrane Library was conducted for English and CNKI (China National Knowledge Infrastructure) for Chinese language clinical trials containing the search terms : Chinese herbal medicine, Chinese herbs, Chinese medicine, In Vitro Fertilization/Fertilisation, IVF, Controlled Ovarian Hyperstimulation, COH and 体外受精 (IVF), 试管婴儿(IVF), 中医(Chinese medicine), 中药(Chinese herbs), 中西结合(Chinese/Western integrated medicine) respectively.

Inclusion criteria for articles: Women who took Chinese herbal medicine before, during or after IVF who participated in clinical trials (including meta-analyses, systematic review, randomized clinical trial, controlled clinical trial, prospective single cohort clinical trial, retrospective 3-arm controlled clinical trial with between group analysis) published between 2006-2020 which reported either of the primary or secondary fertility measures below. This study included studies published in English but also obtained and translated three meta-analyses from a list of 65 Chinese sources found.

Exclusion criteria for articles: Animal studies will be excluded but may be considered for use in introduction or discussion if novel ideas are presented not available in later

human studies. Studies on exclusively male reproductive issues are excluded from this study. Acupuncture studies that did not include herbs were excluded.

Primary measures: Live birth rate, clinical pregnancy rates, ongoing pregnancy rates, miscarriage rates.

Secondary measures: number of oocytes retrieved, number of oocytes fertilized, number of blastocysts, number of high-quality embryos, measurements which track blood flow to the uterus, endometrium thickness, amount of FSH dosages for stimulation, incidence of ovarian hyperstimulation syndrome (OHSS) and miscarriage rate.

The number of eggs retrieved and fertilized, number of blastocysts and high-quality embryos created all bare a direct correlation with improving the odds for pregnancy and live births. Increasing blood flow to the uterus may play a role in endometrial receptivity or to assist in thickening the uterine lining. An insufficient endometrial thickness will require a cancellation in a patient's IVF transfer. IVF medication is very costly, if CHM were able to reduce the necessary dose of fertility medication then it is of obvious benefit to the patient. Incidence of OHSS is important because if it can show that CHM will not increase OHSS (safety) in normal populations or if it can show reduction in OHSS in a population expected to overstimulate, such as PCOS patients (benefit).

Data Collection Procedures, Data Analysis and Reporting: Data was organized into tables and charts. Articles were reviewed by 2 researchers and graded utilizing the modified twelve question Jadad Scale (Jadad et al., 1996) in an attempt to gauge the current quality of research on this subject. An article abstraction table was created to show sample design, population size, isolate which of the primary and secondary measures each study tracked and to highlight additional pertinent information including timing and duration of taking herbs, which herbs were included, if modification of base prescription was recommended, and if Chinese medical differentiation was used. Conclusions were also presented in the abstraction form, as well as if a study had any unique attributes which stood out from the other studies. Various tables were constructed to help visualize how results in primary and secondary measures manifested across the studies collected. Another table highlights the synopsis of data in the five meta-analyses.

Assessment and Scoring Process:

The two researchers scored the 13 articles independently of one another. As they read the articles, the answers to the twelve-question modified Jadad Scoring were entered into an excel spread sheet. The questions can be seen below in Table 3.1. Each question answered in the affirmative was given one point. Questions 1 and 2 were awarded an additional one point each if the method of randomization and method of double-blinding was reported. The maximum score possible for the twelve questions

plus the additional two "bonus points" for description of randomization and double-blinding was fourteen points. After scoring the studies independently, the researchers conferred online via Zoom to agree or disagree on the individual points awarded for each question for all studies. If the authors could not come to an agreement, a third reviewer would serve as a tie breaker. No disagreements arose and the third reviewer was not required. Upon completion of the review process a final point value was tallied for all studies. Prior to grading the articles, the researchers agreed to the following quality scoring:

14 to 11 points = Highest Quality
10 to 7 points = Moderate Quality
6 to 0 Points = Low Quality

Table 3.1, Twelve-Question Modified Jadad Scoring

1. Was the study described as randomized?
2. Was the study described as double-blind?
3. Was there a description of withdrawals and drop outs?
4. Were the objectives of the study defined?
5. Were the outcome measures defined clearly?
6a. Was there a clear description of the inclusion and exclusion criteria?
6b. Were the comparison groups reported as similar at baseline?
7. Was the sample size justified (e.g., power calculation)?
8. Was there a clear description of the interventions?
9. Was there at least one control (comparison) group?
10. Was the method used to assess adverse effects described?
11. Were the methods of statistical analysis described?

Chapter 4: Results

Upon conducting the search, 65 articles were found in Chinese and 19 in English. Due to limitations in time and budget for professional translation, all Chinese articles with the exception of 3 meta-analyses were excluded. The meta-analyses were included as they were believed to be the strongest representative overview for what was available in Chinese research. Among the English studies, two animal studies, one male study, two case study reports, one retrospective cohort study were excluded. The retrospective cohort study was excluded because the effect of CHM was not able to be determined in a whole systems approach as the author did not report separately who in her study did or did not use CHM.

This study included a total of 13 studies and 5 meta-analyses (3 translated from Chinese and 2 in English). This chapter will identify and summarize the primary and secondary measures outlined in the methods inclusion section for all studies and meta-analyses including: biochemical pregnancy rates, clinical pregnancy rates, ongoing pregnancy rates, live birth rate, abortion rate (miscarriage), number of oocytes retrieved , fertilization rate, number of blastocysts, high-quality embryos rate, endometrial thickness, increased blood flow to the uterus, amount of FSH dosages for stimulation, incidence of ovarian hyperstimulation syndrome (OHSS). The herbs used, form of herbs prescribed, modifications, and timing of when the herbs were taken will be covered.

The Chinese medical or Western medical diagnosis inclusion for each relevant study will be broken down. Studies which required participants to have previously failed IVF will also be separately discussed. Pregnancy outcomes and improvements in egg and/or embryo quality in both the individual studies and meta-analyses will be summarized and tabulated.

Study results which attempted to discover plausible mechanisms of action will also be detailed. An in-depth synopsis of each of the studies and meta-analyses will follow which attempts to organize the studies in a fashion that would be of practical use for a clinical practitioner. For example, studies which had a Chinese medical differential diagnosis as an inclusion criteria such as Kidney Yin Deficiency, Liver Qi Stagnation, or Blood Stasis will be grouped together. Studies that discussed repeated IVF failure or poor responders will be discussed near one another. Studies that focused on treating a particular western diagnosis such as endometriosis or PCOS will be placed together. Studies that had a unique focus such as reducing rates of abortion, the only study whose participants did frozen embryo transfer or underwent a low dose stimulation IVF will be placed at the end. By searching the document with "control F" or "command F" the practitioner will easily be able to find which study and herbal prescription might be helpful to thicken the endometrium, improve egg quality, increase the fertilization rate, increase blood flow to the uterus, etc.

Summary of the Types of Studies Included and Participants:

In the 13 studies included, there were 8 RCT's, 2 CCTs, 2 prospective single group cohort study, 1 retrospective 3-arm CCT with between group analysis. The number of participants in these studies ranged from 30 to 433 with a mean number of 131.46 per study and a median value of 66.

Table 4.1, Age, FSH, and BMI of Participants in Included Studies

Study	Age	FSH	BMI
(An et al., 2014)	Age Range not Specified BBR: 28.2 ± 3.8, MET: 28.7 ± 4.2, PL:28.4 ± 4.0	BBR: 5.2 ± 1.5, MET: 5.5 ± 1.2, PL: 5.0 ± 1.4	BBR: 24.6 ± 3.1 MET: 24.0 ± 3.0 PL: 24.2 ± 3.2
(Inoue et al., 2013)	Age Range not Specified 38.5 ± 0.7	Not reported	Not reported
(X. Jiang et al., 2020)	Age range: 25-45 Control: 33.6 ± 4.0 TCM: 32.7 ± 4.6	< 10 for inclusion Control: 6.62 ± 1.89 TCM: 6.74 ± 1.64	Normal 18-25 for inclusion Control: 21.0 ± 1.7 TCM: 21.1 ± 1.9
(X. Gao et al., 2013)	All patients were ≥35 Age Range not Specified Experiment: 29.1 ± 2.5 Control: 29.7 ± 2.0	< 10 for inclusion Exact numbers not reported	Not reported
(J. Guo et al., 2014)	All patients were less than 42 years old Age Range: 22-42	CHM: 7.1 ± 2.4 Control: 6.9 ± 2.1	CHM: 22.1 ± 3.4 Control: 22.1 ± 3.0

	CHM: 32.1 ± 4.3 Control: 31.6 ± 4.3		
(Lian et al., 2009)	Age range: 22-46 Treated: 31.2 ± 5.4 Control: 30.7 ± 6.7 Non-Endo: 31.9 ± 6.5	Treated: 5.21 ± 3.68 Control: 4.97 ± 3.02 Non-Endo: 4.78 ± 2.82	Not reported
(Lian et al., 2013)	Age Range: 25-40 Treatment: of 33 cases 3 were 25-30, 9 were 30-35, 21 were 35-40 Control: of 33 cases 2 were 25-30, 10 were 30-35, 21 were 35-40	Stated hormonal tests were normal for inclusion	Not reported
(Lian et al., 2014)	Age range: 25-40 Treatment: 30.33 ± 3.23 Control: 30.70 ± 3.42 Syndrome control: 30.33 ± 2.89	Stated hormonal tests were normal for inclusion	Not reported
(Y. Liu & Wu, 2006)	Age range in treatment group: 22 - 43 years, among whom 51 cases were 22 - 29 years old, accounting for 38.93 %, 62 cases were 30-35 years old, accounting for 47.33%, 14 (10.68%) 36-39 years, and4 (3.05%) of 40-43 years, with the average age in them as 31.08± 4.08 years. Age range in control group: 23 - 41 years old,	Not Reported	Not reported

	among whom 44 cases were 23 - 2 9 years old, accounting for 37.93 %, 52 cases 30-35 years old, accounting for 44.83%, 17 (14.65%) 36-39 years, and 3 (2.58%) 40-41 years, with the average age in them as 31.26 ±4.14 years.		
(Ushiroyama et al., 2012)	Age range: 31-45 38.1 ± 4.8 years	14.4 ± 3.2	Not reported
(Xu et al., 2015)	Age range 25-40 Mean age not specified	Inclusion states that hormone levels were normal	Not reported
(Xue et al., 2017)	Age range not specified Treatment: 35.10 ± 7.39 Control: 34.80 ± 7.53	Treatment: 12.63 ± 1.36 Control: 12.81 ± 1.43	Treatment: 22.97 ± 1.68 Control: 23.47 ± 1.58
(Zhang et al., 2006)	Of 262 subjects, 122 women were under 30 years old, 106 between 30-35 years and 32 over 35 years. Mean age not specified	Not reported	Not reported

Herbal Prescription Composition/Characteristics

Seventeen herbal prescriptions were used in the thirteen studies included. With the exception of (Ushiroyama et al., 2012) and (Inoue et al., 2013) there was no homogeneity among the herbal prescriptions; in the latter, 3 ingredients were added to

the former's MACH base. (An et al., 2014) was unique as it was the only study included which utilized one herbal ingredient in the treatment group. The Traditional Chinese Comprehensive Therapy (TCCT) (Xu et al., 2015) used 3 different herbal prescriptions. (J. Guo et al., 2014) used three different herbal prescriptions during stimulation injections and post embryo transfer. The remaining 11 studies used one prescription for the treatment group.

A total of sixty-eight herbs were used in seventeen Chinese herbal prescriptions. Dang Gui, Shu Di Huang, and Tu Si Zi were used 9 times with the greatest frequency. Dan Shen was used 6 times, while Bai Shao, Bai Zhu, and Gou Qi Zi were used 5 times each. Dang Shen, Du Zhong, Huang Qin, Shan Yao, and Shan Zhu Yu were used 4 times. Ba Ji Tian, Chai Hu, Fu Ling, Huang Qi, Nu Zhen Zi, and Xu Duan were used 3 times. The remaining fifty herbs were used 1-2 times and all herbs used with frequency of use have been summarized below in Table 4.2:

Table 4.2, Most Commonly used Herbs with Frequency of Use

Frequency of Use	Herb Name
9 times	Dang Gui, Shu Di Huang ,Tu Si Zi
6 times	Dan Shen
5 times	Bai Shao, Bai Zhu, Gou Qi Zi
4 times	Dang Shen, Du Zhong, Huang Qin, Shan Yao, Shan Zhu Yu
3 times	Ba Ji Tian, Chai Hu, Fu Ling, Huang Qi, Nu Zhen Zi, Xu Duan
2 times	Che Qian Zi, Chuan Xiong, Gan Cao, Hong Hua, Ji Xue Teng, Jin Yin Hua, Mu Dan Pi,

	Nan Gua Zi, Sang Ji Sheng, Sheng Di Huang, Di Huang (Tan), Xiang Fu, Yin Yang Huo, Zi He Che
1 time (37 herbs)	Ai Ye (Tan), Berberine (Huang Lian Su), Bei Sha Shen, Bai He, Bo He, Bu Gu Zhi, Chen Pi, Chi Shao, Chuan Niu Xi, Chuan Xiong, Di Yu (Tan), E Jiao, E Zhu, Gui Jia, Han Lian Cao, Hong Teng, Huang Jing, Jin Yin Hua, Lian Qiao, Lu Jiao Shuang Mai Men Dong, Mei Gui Hua, Mo Han Lian, Nan Sha Shen, Ren Shen, Rou Cong Rong, Rou Gui, San leng, Sheng Jiang, Suan Zao ren, Wu Zhu Yu, Xi Xin, Xian Mao, Xu Chang Qing, Ze Xie, Zhi Gan Cao, Zi Shi Ying

Table 4.3 below is a breakdown of the eighteen most frequently used Chinese herbs in the included studies according to the traditional categories that they belong to within Chinese herbal medicine. These herbal categories of tonics for Blood, Spleen Qi, Kidney Yang, Yin, and Essence, as well as invigorate Blood, regulating the Qi of the Liver, and clearing heat are commonly featured in herbal prescriptions which seek to help patients conceive both naturally and during IVF.

Table 4.3, Commonly Used IVF Chinese Herbs by Category	
Herbal Category	**Chinese Herb Name**
Tonify Blood	Dang Gui, Shu Di Huang, Bai Shao, Gou Qi Zi
Tonify Kidney Yang	Tu Si Zi, Du Zhong, Ba Ji Tian, Xu Duan

Invigorate Blood (which cools and eliminates irritability)	Dan Shen
Clear Heat (calms the fetus during signs of threatened miscarriage)	Huang Qin
Tonify the Qi (often incl. to assist the Spleen)	Dang Shen, Huang Qi, Bai Zhu, Shan Yao, Fu Ling (assists these herbs to drain dampness and prevent cloying nature of Qi tonic herbs)
Tonify Kidney Yin, Yang and Essence	Shan Zhu Yu
Tonify Kidney Yin	Nu Zhen Zi
Regulate/Sooth the Qi (as it pertains to Liver Qi Stagnation)	Chai Hu

As can be seen in the use of these herbs tonifying Blood, Kidney Yang and Yin, and tonifying the Spleen are of utmost importance when treating female infertility. Supplementing the primary ingredients with herbs that sooth Liver Qi (reduce stress), invigorate blood (increase blood flow or break up blood stasis), and clear heat (reduce markers of inflammation) is a common approach when composing a comprehensive herbal formula.

Four of the herbs most commonly used in these studies were from the tonify Kidney Yang category. Interestingly, animal studies have been done on mice in China that demonstrated that herbs from this category enhance mitochondrial and ATP production in tissue and that they increase antioxidant defenses at the cellular level (Lyttleton, 2013). Listed in descending order of effectiveness in increasing ATP they are: Tu Si Zi, Du Zhong, Ba Ji Tian, and Xu Duan. In her book *It Starts with the Egg* (Fett,

2019) Rebecca Fett in trying to explain how without sufficient energy the maturing egg or embryo may stop developing she sites Toronto RE Dr. Robert Casper:

> "the ageing female reproductive system is like a forgotten flashlight on the top shelf of a closet. When you stumble across it a few years later and try to switch it on, it won't work, not because there's anything wrong with the flashlight but because the batteries inside it have died."

In her book, Jane Lyttleton suggests adding some of the herbs from the Kidney Yang category during the time of ovarian stimulation to in essence help the battery (mitochondria) of eggs and embryos so they might continue to develop particularly in older patients whose mitochondria might be tiring.

The discussion of which form of Chinese herbal medicine is the strongest and/ or most appropriate for research is beyond the scope of this paper, however generally speaking CHM can be given in dried raw (loose) herbs, granules, pills and in more recent years tinctures. Clinically, it is commonly held that the traditional dried raw herbs which are to be decocted at home by the patient or cooked at the hospital in a Chinese setting are the strongest way to dispense CHM. Two of the included studies used a pill or tablet. Five studies used decoction, one of these also included rectal drops. Four studies used water soluble granules. Two did not specify the method of herbal preparation, but from the dosage of ingredients this author believes one was likely a decoction. The summary is provided in Table 4.4

Table 4.4, The Form of Herbs Dispensed in Included Studies	
Herbal Form	**Studies Which Used this Form**
Decoction	(Q. Gao et al., 2015), (J. Guo et al., 2014), (Xu et al., 2015), (Xue et al., 2017), (Zhang et al., 2006)
Granules	(Lian et al., 2009), (Lian et al., 2013), (Lian et al., 2014), (Ushiroyama et al., 2012)
Pill/Tablet	(An et al., 2014) - Tablet (Inoue et al., 2013) - Pill
Rectal Drops	(Xu et al., 2015)
Unspecified	(X. Jiang et al., 2020) - Not Specified (Y. Liu & Wu, 2006) - Not Specified (assumed decoction by dosage)

Modifications to Chinese herbal prescriptions

Eleven of the thirteen studies included were given a fixed ingredient herbal prescription with no modifications. Only two of the studies (J. Guo et al., 2014) and (Y. Liu & Wu, 2006) offered relevant modifications. E Jiao, Ai Ye Tan, Di Yu Tan and Di Huang Tan were added if there was vaginal bleeding, and if a patient's tongue was red with a thick yellow coating Huang Qin was added to the decoction (Y. Liu & Wu, 2006). In the first phase of stimulation injections, if there was Spleen Qi Deficient diarrhea present Bai Shao was removed and Bai Zhu was added, Huang Qi was added for Qi Deficiency, and Huang Qin and Sheng Di Huang were added if excessive heat and dry mouth were present. Later during stimulation, Bai Zhu, Sheng Di Huang and Bei Sha

Shen were added for dry throat and constipation, while Huang Qin was added if excessive heat with red tongue and yellow coating was present. Furthermore, if there was anxiety, nervousness, and insomnia Xiang Fu and Suan Zao Ren were added. After the first five days post transfer Dan Shen was removed from the base prescription (J. Guo et al., 2014).

Duration and Timing that Chinese Herbal Medicine was Taken During IVF

Table 4.5 is a detailed synopsis of when and for how long participants took CHM in all 13 studies. The time periods which participants took CHM were divided into 4 categories: before IVF, during ovarian stimulation injectable mediations, after the embryo transfer, and during pregnancy. "---" indicates that Chinese herbal medicine was not taken during that time period of the IVF cycle.

Table 4.5, Duration and Time During the IVF Cycle that Chinese Herbal Medicine was Taken

Author Name	Before IVF	During Ovarian Stimulation (Stim) Injectable Medications	After Transfer	Pregnancy
(An et al., 2014)	3 cycles prior to IVF	---	---	---
(X. Gao et al., 2013)	---	During stim up until the day of hCG trigger shot	---	---
(J. Guo et al., 2014)	---	With stim Cd 3-7, then another formula from cd 8 until hCG trigger shot	Another set of herbs from day of transfer for 12-15 days	---
(Inoue et al., 2013)	---	CD1 to retrieval	---	---

(X. Jiang et al., 2020)	---	During stim drugs	---	---
(Lian et al., 2009)	"From the day of cessation of menstruation or withdrawl bleeding for 20 successive days every month"	---	---	---
(Lian et al., 2013)	3 menstrual cycles prior to the scheduled IVF. From cd 3-16, for a total of 3 menstrual periods. The third is the month of the retrieval	During stim until trigger shot	---	---
(Lian et al., 2014)	3 menstrual cycles prior to IVF. Same as Lian 2013 above	During stim until trigger shot	---	---
(Y. Liu & Wu, 2006)	---	---	(A) from day of transfer (B)14 days post-embryo transfer (ET)	Taken continuously to the 12th week post ET
(Ushiroyama et al., 2012)	---	From Cd 1 of IVF cycle	Through approx 7 days past transfer (~20 days)	---
(Xu et al., 2015)	3 cycles prior to IVF	continued	continued	If pregnant, continued to 70 days past the transfer
(Xue et al., 2017)	3 cycles prior to IVF from cd 7-21	---	---	---
(Zhang et al., 2006)	---	Cd 4-9 of FET, no stim shots	---	---

--- indicates that no Chinese herbal medicine was taken at this time period

Chinese Medicine Diagnosis as part of Inclusion Criteria:

Five studies, (X. Gao et al., 2013), (Lian et al., 2009), (Lian et al., 2013), (Lian et al., 2014), and (Xu et al., 2015) had a Chinese medical diagnosis as one of their inclusion criteria, Liver Qi Stagnation, Blood Stasis with Toxic Stagnancy, Kidney Yin Deficiency, Kidney Yin Deficiency, and Kidney Deficiency + Liver Stagnation + Blood stasis (KLB) respectively. Three of the studies (Lian et al., 2013), (Lian et al., 2014), and (Xu et al., 2015) tracked and reported statistical improvement in the symptoms associated with their Chinese medical diagnosis ($P<0.05$).

Western Medical Diagnosis as Inclusion Criteria:

Three studies required the patients to have a particular Western diagnosis as an inclusion criteria. (An et al., 2014) patients all had a diagnosis of PCOS. (Lian et al., 2009) patients in the treatment and one of the control groups had been diagnosed with endometriosis. The patients in the (Xue et al., 2017) study were diagnosed with poor ovarian response (POR).

Previously Failed IVF as Inclusion Criteria:

Four studies (Inoue et al., 2013), (Ushiroyama et al., 2012), (Xu et al., 2015), and (Xue et al., 2017) required that its participants had already failed previous IVF attempt(s). Prior to entering the study the (Inoue et al., 2013) participants had previously undergone 7.9±1.5 retrievals. (Ushiroyama et al., 2012) inclusion required

low rates of developing good quality cleaved embryos and who had not become pregnant in at least 3 previous IVF attempts.

Summary of Pregnancy Outcomes for Included Studies:

In the thirteen studies included, 4 showed significant improvements in biochemical pregnancy rate. Additionally, (Inoue et al., 2013) demonstrated significant improvement for biochemical pregnancies among frozen embryo transfers but not fresh embryo transfers. Ushiroyama et al., 2012) reported, "33.3% pregnancy rate compared to same group of women for whom 0 had become pregnant after 3 or more previous cycles", however the author did not report this as meeting statistical significance. Eight demonstrated improvement in clinical pregnancy rate, of which 6 were statistically significant. Three revealed improvements in live birth rates, of which 1 (An et al., 2014) was significant. Another of the 3 (Inoue et al., 2013) was significant $p=0.01111$ for combined fresh and frozen embryo transfers (but not for fresh or frozen independently). (J. Guo et al., 2014) revealed an improvement in live births but it did not reach clinical significance $p>0.05$. A 4th study, (Y. Liu & Wu, 2006), showed significantly fewer abortions in the treatment group but it is unclear from the author's discussion of the results if this led to improvements in live birth rates, which favored the treatment group 86.4 % vs 76.1%. It is this author's "assumption" that it may have impacted birth rates, that fewer abortions would inevitably translate to a higher number of births, but this cannot be proven from the available data reported. In the 5 meta-analyses all showed statistical

improvements in at least one type of pregnancy rate. One reported improvement in biochemical pregnancy rate, all 5 had improvements for clinical pregnancy rates, 1 in ongoing pregnancy rate, and one 1 in live birth rates. See Tables 4.6 below:

Table 4.6: Pregnancy Outcomes for Included Studies				
Author Name	Biochemical Pregnancy	Clinical Pregnancy	Ongoing Pregnancy	Live Birth
(An et al., 2014)	x	x	---	x
(X. Gao et al., 2013)	x	---	---	---
(J. Guo et al., 2014)	x	x	---	^
(Inoue et al., 2013)	x for pregnancies from frozen embryo transfer p=0.0399 , but not from fresh embryo transfers	---	---	x for combined fresh and frozen p=0.0111, but did not reach significance separately for either fresh or frozen transfer
(X. Jiang et al., 2020)	---	^	---	---
(Lian et al., 2009)	---	^	---	---
(Lian et al., 2013)	---	x	---	---
(Lian et al., 2014)	---	x	---	---
(Y. Liu & Wu, 2006)	---	---	---	Statistically lower abortion rate may have improved live birth rate (86.4 %vs 76.1%) but this cannot be

				directly concluded from the study's results section.
(Ushiroyama et al., 2012)	^ 33.3% pregnancy rate compared to same group of women for whom 0 had become pregnant after 3 or more previous cycles.	---	---	---
(Xu et al., 2015)	---	x	---	---
(Xue et al., 2017)	---	x	---	---
(Zhang et al., 2006)	x	---	---	---

X = statistical significance was found
^ = increase but non-significant
--- = no improvement reported

Summary of Pregnancy Outcomes for Meta-analyses Included:

All of the meta-analyses reviewed demonstrated statistical difference and improvement in at least one measure of pregnancy outcome. Three of the 5 meta-analyses demonstrated significant improvement in 2 pregnancy outcomes. (He & Li, 2014) showed an increase in biochemical pregnancies. All 5 meta-analyses showed significant improvement in clinical pregnancy rates. While (Cao et al., 2013) revealed an increase in ongoing pregnancy rates and (Kwon et al., 2020) an increase in live birth rates. See Tables 4.7 below:

Table 4.7: Pregnancy Outcomes for 5 Meta-analyses				
Author Name	Biochemical Pregnancy	Clinical Pregnancy	Ongoing Pregnancy	Live Birth
(Cao et al., 2013)	---	x	x	---
(He & Li, 2014)	x	x	---	---
(Kwon et al., 2020)	---	x	---	x
(H. Liu et al., 2016)	---	x	---	---
(Tan et al., 2015)	---	x	---	---

X = statistical significance was found
^ = increase but non-significant
--- = no improvement reported

Summary of Measures of Egg and/or Embryo Quality Improvement:

At present there is no test for egg quality. One could try to define egg quality by saying the egg is good if it has a normal number of chromosomes and abnormal if it has too many or two few. Once an egg has been retrieved the only way to know if it was good is it to fertilize it and follow-up with genetic testing of the resulting embryo. Researchers and medical providers alike must be cautious not to promise something that cannot be quantified or proven to a vulnerable population of patients. Chinese herbal medicine may be able to improve egg quality. Since egg quality is not always clearly definable, this researcher has decided to group results which reported increase in number of oocytes retrieved, high-quality oocyte rate, high-quality embryo rate, and

blastocyst rate together. Naturally, if extended they might lead to higher birth rates. These results would be of particular value for any patient that had low ovarian reserves or had failed previous attempts at IVF. Two studies showed statistical improvement in the number of eggs retrieved and two showed nonsignificant improvement. Three studies reported significant improvements in high-quality oocyte rate. Four studies revealed a significant improve in fertilization rates, while one showed a higher tendency which did not reach statistical significance. Five studies demonstrated an increase in the high-quality embryo rate (non-blastocyst, day 3), among which (X. Jiang et al., 2020) further reported an increase in number of embryos. Furthermore, (Xu et al., 2015) found a significant improvement in the number of ovum fertilized (embryo) in the group that used CHM, but did not specify that they were of high-quality. The two studies which used Macrophage Activating Chinese Herbs (MACH) (Ushiroyama et al., 2012) and (Inoue et al., 2013) demonstrated a higher blastocyst rate. See Table 4.8 below.

The (Tan et al., 2015) meta-analysis reported significant improvements in the number of eggs retrieved and for the rates of fertilization and high-quality embryos among those who utilized CHM during IVF. The (H. Liu et al., 2016) meta-analysis showed significant improvements in fertilization rates and high-quality embryo rates of development.

Table 4.8: Improvements in the Number or Quality of Eggs Retrieved or Embryos					
Author Name	# of Eggs Retrieved	High Quality Oocyte Rate	Fertilization Rate	High Quality Embryo Rate	Blastocyst
(Lian et al., 2009)	x	---	x	---	---
(Lian et al., 2013)	---	x	^	x	---
(Lian et al., 2014)	---	x	---	x (Blastomere)	---
(X. Gao et al., 2013)	---	---	---	x	---
(J. Guo et al., 2014)	---	---	x	x	---
(Inoue et al., 2013)	^In some individual patients but cumulatively not statistically significant	---	---	---	x
(X. Jiang et al., 2020)	^	---	x	x (# of embryos & # of high qlty embryos	---
(Ushiroyama et al., 2012)	---	---	---	x	x
(Xu et al., 2015)	---	---	x	x - # of embryos was increased, but high quality was not specified	---
(Xue et al., 2017)	x	x	---	---	---

x = statistical significance was found
^ = increase but non-significant
--- = No improvement reported

Increases/Improvements in Uterine Blood Flow:

A possible correlation may exist between increased blood flow to the uterus and uterine receptivity and endometrial thickness. (X. Jiang et al., 2020)'s study reported lower pulsatility index and resistance index in the CHM treatment group ($P<0.05$). Previously a meta-analysis (Tan et al., 2015) had stated that CHM, "was superior in increasing the mean of uterine blood flow pulsatility index" and that the CHM was, "better than that of the control group in reducing the uterine blood flow resistance index". However, upon closer examination of the forest plot in the meta-analysis, 4 of the 5 trees/blobs representing the studies fell on the left side (labeled "Favours [control]) of the line of null effect indicating the control group actually had increased blood flow over the CHM group. The 5th study fell on the right side (labeled "Favours [experimental]) but this study had the fewest participants, least weight 5%, and it crossed over the line of null effect indicating that the results were not statistically significant. While it is possible the authors of this meta-analysis may have accidently mislabeled the two sides of the forest plot, the two largest studies with combined weight of 83.6% had only the slightest effect between the control and experimental group, the mean difference of each was -0.08. As the data from the forest plot contradicts the author's write up in the results section, we can draw no conclusion of CHM impact.

Endometrial Thickness:

An adequate endometrium is necessary for implantation and insufficient endometrial thickness may lead to an IVF transfer being cancelled. Endometrial thickness was reported in 3 of the studies. While the thickness increased in (X. Jiang et al., 2020) it was not statistically significant. In (X. Gao et al., 2013) the difference in endometrial thickness was found to be significant over the experiment group 9.7 ± 1.4 and 8.8 ± 0.6, P=0.004. (J. Guo et al., 2014) also reported a significant improvement of endometrial thickness between the 2 groups, the average endometrial thickness in the CHM was (10.84 ± 1.75) mm and (10.52 ± 1.50) mm in the control group, (P<0.05).

(He & Li, 2014) mention that two of their studies showed improvement in endometrial thickness and one did not, but meta-analysis could not be conducted on the results of these studies. Among 4 studies the (Tan et al., 2015) group conducted meta-analysis on the difference in endometrial thickness which was significant and favored the CHM treatments groups. (H. Liu et al., 2016) meta-analysis of 11 studies concluded that CHM could improve endometrial thickness in IVF patients.

Adverse Events:

Question 10 of this researcher's modified Jadad scoring asked "Was the method used to assess adverse effects described?". If the study stated that there were no adverse events or described them in detail, they were awarded the point for this question. However, only (J. Guo et al., 2014; Lian et al., 2013, 2014) actually described the methods

utilized to assess adverse effects. (J. Guo et al., 2014) stated there were abdominal distension, nausea, mild diarrhea, and increased frequency of bowel movements among five patients, and that blood and urine including hepatic and renal function tests showed no abnormalities 2 weeks after participants ceased intake of CHM. (Lian et al., 2013) stated that patients were observed and queried for adverse reactions during the treatment period and that clinical laboratory tests (routing urine, stool, and blood tests) and electrocardiograms were performed on the day of enrollment (pre-treatment) and the day after the transfer (post-treatment) with no adverse events reported. Similarly, (Lian et al., 2014) stated that patients were observed for adverse reactions during treatment and that routine tests of blood, urine, stool, and liver and kidney function remained unchanged after treatment and that there were no adverse events. (An et al., 2014) reported diarrhea and nausea in a small number of test subjects, with fewer experienced by those taking CHM than in the Metformin group. (X. Gao et al., 2013; X. Jiang et al., 2020; Lian et al., 2009; Xue et al., 2017) contained no discussion of adverse events. Among the non-RCT studies, (Inoue et al., 2013; Y. Liu & Wu, 2006; Ushiroyama et al., 2012) stated there were no adverse events but with no discussion of how they were tracked. The remaining two studies (Xu et al., 2015; Zhang et al., 2006) made no mention of adverse events. No serious side effects were seen in any of the participants taking CHM, with gastrointestinal complaints being the only adverse events reported.

Abortion/Miscarriage Rates:

For many studies on this topic live birth rates are not reported (but would be considered the gold standard of success), however a reduction of miscarriages might be useful to extrapolate possible higher birth rates. Furthermore, showing that more miscarriages did not occur as a result of taking CHM during IVF would contribute towards establishing safety.

Effect of Gutai Decoction on the Abortion Rate of in vitro Fertilization (Y. Liu & Wu, 2006) was unique among the papers reviewed in that it specifically sought to determine CHM's effect on IVF miscarriage rates. They reported that the treatments groups A and B had abortion rates of 12.84% and 13.64% respectively compared to 23.28% in the control group, the difference between the treatment and control groups was significant ($P<0.05$). Three studies (X. Gao et al., 2013), (J. Guo et al., 2014), and (X. Jiang et al., 2020) reported non-significant differences in abortion rates among study participants. The (Inoue et al., 2013) study mentions that prior to taking CHM, when pregnancies occurred gestational sac were present but fetal heart beats were absent. However, after taking CHM when the same group of women fell pregnant both gestational sacs and heartbeats were present, but the authors did not mention if this was significant or not.

Among the meta-analyses there were conflicting reports. (Kwon et al., 2020) concluded that there was no significant benefit for taking CHM with regards to abortion rate (8 studies: RR 0.82, 95 % CI 0.49–1.36, $I2 = 0\%$. While (H. Liu et al., 2016) determined

that those participants who took CHM did have significantly lower abortion rates, OR=0.30, 95%CI: 0.13-0.69. After comparing biochemical and clinical pregnancy rates in six studies (He & Li, 2014) found that the abortion rate in the CHM groups was 5% while in the control groups was 19.05% demonstrating statistical difference, OR=0.17 [0.07,0.41].

Incidence of Ovarian Hyperstimulation Syndrome (OHSS):

The occurrence of OHSS can range from a mild to serious life-threatening complication of IVF. Individual studies by (X. Gao et al., 2013) and (J. Guo et al., 2014) as well as meta-analyses by (Cao et al., 2013) and (Kwon et al., 2020) all concluded that CHM offered no benefit in reducing the occurrence of OHSS in IVF patients. In contrast, meta-analysis by (H. Liu et al., 2016) demonstrated a reduction in the rate of OHSS in the CHM group participants (OR=0.35, 95%CI: 0.17~0.73), however this conclusion could not be confirmed due to small sample sizes. Interestingly in a population of PCOS patients who are most at risk of OHSS, patients who took CHM had lower rates of severe OHSS requiring hospitalization than did the control group ($P<0.05$).

Reduction in Gonadotropin (r-FSH & hMG) Dosage:

The r-FSH and hMG stimulation medications that are used during controlled ovarian hyperstimulation are expensive and most insurance policies in the United States will not pay for them. Three studies including, (An et al., 2014), (Lian et al., 2013),

and (X. Gao et al., 2013) demonstrated that those in the CHM treatment groups required significantly lower dosage of gonadotropin medication than the control group ($P<0.05$). The (H. Liu et al., 2016) meta-analysis of 11 studies concurred with the aforementioned individual studies (SMD=-0.69, 95%CI: -0.96~ -0.42).

High FSH, Low AMH Patient Benefits of CHM

Patients who have low AMH and high FSH levels are likely to be poor responders during IVF. When TGYL was taken by women who previously had poor ovarian response during IVF, FSH levels were significantly lower after treatment, while AMH and AFC were increased (all $P<0.05$) (Xue et al., 2017). FSH serum levels were significantly reduced after MACH herbs from 14.4 ± 3.2 mIU/ml to 10.5 ± 2.4 mIU/ml (Ushiroyama et al., 2012).

Proposed Method of Action for CHM's Benefits for IVF Outcomes:

Ten of the studies included study measures or proposed theories to try to better understand the mechanism of action of CHM and how it might be impacting study outcomes. The collected studies suggested a variety of possible mechanisms of action ranging from active ingredients in the medicinals themselves or hormone regulation, to exploring complex methods of measuring inflammatory and immune response markers in serum, follicular fluid, and endometrium. (Y. Liu & Wu, 2006) suggested that it was high amounts of vitamin E and zinc contained in the herbs that might help to prevent miscarriage. (Ushiroyama et al., 2012) and (Inoue et al., 2013) research focused on a

group of 4 macrophage activating Chinese herbs (MACH) believing that their enhancement of the immune system might have played a role in higher quality embryos and a greater percentage of blastocyst production. Greater number of live births among PCOS patients were reported once CHM had been taken and successfully lowered various androgen and glucose/insulin measures (An et al., 2014). One group found that taking CHM lowered blood flow impedance indices thus increasing blood flow to the uterus and possibly helping with implantation rates. Furthermore, vascular endothelial growth factor (VEGF) gene expression levels were increased and which are related to the formation of blood vessels (X. Jiang et al., 2020). (Xue et al., 2017) found that TGYL CHM increases follicular fluid levels of GDF-9, TGF-β1 and VEGF as well as endometrial levels of integrin αVβ3, TGF-β1 and VEGF in patients with POR. The roles of these will be detailed further in the discussion chapter. GDF-9, important in oocyte maturation was again found to be increased in the (X. Gao et al., 2013) experimental CHM group. Among the three studies completed by Dr. Lian Fang and her group, two of them focused on looking in the follicular fluid and one in the endometrium itself for clues as to how CHM medicine may be working. (Lian et al., 2013) found increased levels of DNMT1 in the endometrium, believed to play a role in endometrial receptivity, and which were higher in the pregnant patients in the study. (Lian et al., 2014) observed changes in follicular fluid protein expression concentrations of retinol binding protein 4, transthyretin, apolipoprotein, and C4-B which may be correlated to Kidney Yin

Deficiency infertility. Another study showed that CHM reduced levels of 2 inflammatory markers TNF-α and IL-6 in the follicular fluid of endometriosis patients undergoing IVF (Lian et al., 2009). Synopsis below in Table 4.9

Table 4.9, Studies with Purposed CHM Method of Action

Study / Herbal Prescription(s)	CHM Proposed Method of Action
(Y. Liu & Wu, 2006) / Gutai Decoction	High amounts of vitamin E and zinc contained in the herbs might help to prevent spontaneous abortion (miscarriage)
(Ushiroyama et al., 2012) and (Inoue et al., 2013) / MACH Herbs	Macrophage activating Chinese herb's (MACH) enhancement of the immune system and favorable impact on the endocrine system might play a role in higher quality embryos and a greater percentage of blastocyst production
(An et al., 2014) / Berberine Tablet	Berberine's ability to help lower BMI, reduce various androgen and glucose / insulin markers may have contributed to a greater number of live births among PCOS patients
(X. Jiang et al., 2020) / Bushen Yutai Recipe	CHM Increases blood flow to the uterus by lowering blood flow impedance and increases formation of blood vessels via increasing vascular endothelial growth factor (VEGF) gene expression levels, both which may aid in implantation
(Xue et al., 2017) / Tiaogeng Yijing Decoction	CHM increases follicular fluid levels of GDF-9, TGF-β1 and VEGF as well as endometrial levels of integrin $\alpha V\beta 3$, TGF-β1 and VEGF in patients with POR
(X. Gao et al., 2013) / Xiao Yao San	CHM increases follicular fluid levels of GDF-9 which is important in oocyte maturation in patients with Liver Qi Stagnation.

(Lian et al., 2013) / Erzhi Tiangui Granules	CHM given to patients diagnosed with Kidney Yin Deficiency increases levels of DNMT1 (believed to play a role in endometrial receptivity) in the endometrium, and was found to be higher in the pregnant patients in this study.
(Lian et al., 2014) / Liu Wei Di Huang Wan	Among infertility patients diagnosed with Kidney Yin Deficiency changes were observed in follicular fluid protein expression concentrations of retinol binding protein 4, transthyretin, apolipoprotein, and C4-B after taking CHM.
(Lian et al., 2009) / Quyu Jiedu Granules	CHM reduced levels of TNF-α and IL-6 (2 inflammatory markers) in the follicular fluid of endometriosis patients undergoing IVF

Quality of the CHM for IVF Studies Included:

Of the thirteen included studies 8 were RCTs and 5 were of a quasi-experimental research design. The quasi-experimental design like the RCT attempts to establish causal relationship and show differences between a control and a treatment group. However, because it does not offer random assignment as a true RCT would, it is subject to internal bias, i.e., selection bias. In the accompanying table 4.10 this researcher separates out the results for the RCTs and non-RCT (quasi-experimental). After scoring all thirteen studies with the 12 question (14 point) modified Jadad instrument, 5 of the 8 RCT studies were categorized as high quality (scoring 11-14 points), 3 of the 8 RCTs were of moderate quality (scoring 7-10 points), and the remaining 5 non-RCTs were of low quality (scoring 0-6 points).

(J. Guo et al., 2014) was the only study reviewed which reported power calculation in order to justify sample size. A point was deducted from (Lian et al., 2009),(Xu et al., 2015), and (Xue et al., 2017) total scores because although it is possible to see in a table that all participants did complete the study, there was no discussion of withdrawals. (Lian et al., 2014), although a point was rewarded for withdrawals because it states that 23 participants withdrew, no discussion of why they dropped out was included; this does not meet fundamental best-quality research practices. Many additional examples of idiosyncrasies, poor study design, and varying degrees of possible bias can be seen by carefully examining the notes in the Modified-Jadad Methodological Quality instrument included in the appendix. The score of each of the included thirteen studies can be see below in table 4.10a and b.

Table 4.10a: RCT Score for the Included Studies with the 12 question (14 point) Modified Jadad Instrument

Quality Level of the Study:	**Study Author with Score:**
High Quality: 14-11	(An et al., 2014) – 13 points (J. Guo et al., 2014) – 12 points (X. Gao et al., 2013) – 11 points (Lian et al., 2013) -11 points (Lian et al., 2014) – 11 points
Moderate Quality: 10-7	(X. Jiang et al., 2020) – 10 points (Lian et al., 2009) – 9 points (Xue et al., 2017) – 8 points
Low Quality: 6-0	None of the RCTs scored low quality

Table 4.10b: Quasi-Experimental Design Score for the Included Studies with the 12 question (14 point) Modified Jadad Instrument	
Quality Level of the Study	Study Author with Score
High Quality: 14-11	None of the Quasi-experimental studies scored high quality
Moderate Quality: 10-7	(Y. Liu & Wu, 2006) – 7 points (Ushiroyama et al., 2012) – 7 points
Low Quality: 6-0	(Xu et al., 2015) – 6 points (Zhang et al., 2006) – 6 points (Inoue et al., 2013) – 5 points

Detailed Synopsis of the Included Studies and Meta-Analyses:

Ushiroyama's study evaluated the effects of a blend of Macrophage-Activating Chinese Herbs (MACH) on embryo quality in 30 women who had experienced long-term infertility and had failed to become pregnant after 3 or more cycles of IVF (Ushiroyama et al., 2012). This was a single group prospective cohort study. The age of these women was 31- 45 with a mean of 38.1±4.8 years old. In 1981 Kojima Y., after screening 200 Chinese herb to find which ones produced an interferon producing effect via a macrophage activation assay, combined Nan Gua Zi, Che Qian Zi, Hong Hua and Jin Yin Hua with *Bifidobacterium longum* and lactulose to form a proprietary immune strengthening blend. The Ushiroyama study gave a daily dose of 6g MACH granules (without lactulose) to women for approximately twenty days from the first day of menses until seventh day after embryo transfer. Embryo quality was assessed by calculating the percentage of good quality day 3 embryos (Good quality defined by

Veeck's classification of grade 1 or 2 in 6 cell embryos on day 3 of culture. The percentage was calculated by dividing the number of good D3 embryos by the total number of oocytes retrieved) and the percentage of embryos that continued on to blastocyst stage. Prior to the participating in the study the women had undergone retrieval 5.4 ± 4.8 times/person and the rate of good quality day 3 embryos was 18.7 ± 16.2%. After taking the MACH herbal blend this value increase to 36.1± 27.1% (1.9-fold increase, $p < 0.01$). In 19 women who desired late-stage blastocyst transfer, prior to MACH herbal treatment the rate of late-stage blastocysts was 14.8 ± 11.2% increasing with MACH to 21.1 ± 23.1% (1.4-fold increase, $p < 0.05$). All patient's rate of good day 3 embryos increased and 10 of 19 (52.6%) of patients saw an increase in development of embryos to blastocyst. Furthermore, in the women with FSH over 10, serum levels of FSH on the day of retrieval decreased from 14.4 ± 3.2 to 10.5 ±2.4 mIU/ml ($p < 0.05$). Ten of 30 participants (33%) of patients achieved pregnancy. No adverse events were reported and no patients dropped out of the study. By increasing the percentage of embryos that develop to day 3 and blastocyst, the percent of women who fall pregnant may increase.

In a single group retrospective cohort study of 31 women who had repeatedly failed to conceive with ICSI-IVF, T. Inoue's group attempted to improve oocyte quality and ovarian function with the use of 7 Chinese herbs (Inoue et al., 2013). The average age of the patients was 38.5 ± 0.7 years. As the author was aware that increasing blood

flow with acupuncture and low reactive-level laser therapy (LLLT) had been shown to increase pregnancy rates, Dang Gui, Shu Di Huang, and Ren Shen were added to the above-mentioned MACH herbs (Nan Gua Zi, Che Qian Zi, Hong Hua, Jin Yin Hua) and were taken twice daily in pill form from cycle day one of the period during the oocyte retrieval cycle up until the retrieval. The number of retrieved and mature oocytes, their morphology and physical qualities, as well as the rates of fertilization, oocyte development, and pregnancy was compared before and after intake of Chinese herbs. The retrieved and mature oocyte numbers, oocyte morphology and physical qualities, and fertilization rate were not significantly different before and after herbal treatment. However, the oocyte development rate (the number of fertilized eggs that developed into blastocysts) was significantly higher 58.0% (47 blastocysts/81 fertilized eggs) after taking Chinese herbs than before 32.5% (40/123); $p = 0.0003$. Furthermore, the successful pregnancy rate was significantly higher after herbal usage than before 6.9% (5 successful pregnancies/72 embryo transfers) versus 0% (0/90); $p = 0.0111$) Five babies were born and were healthy at 2 and 4 weeks after birth. While fresh embryo transfer pregnancy rates were not improved, FET pregnancy rates were higher after taking herbs (4 successful pregnancies/30 embryo transfers (13.3%) versus 0/30 (0%); $p = 0.0562$). Retrieved oocyte number was similar before (3.5 ± 3 oocytes) and after (3.3 ± 2.3 oocytes) the intake of herbal medicine. However, when the individual patient data were examined, ovarian function improvement was marked in some cases. In 1 patient, the

average retrieved oocytes was 4.5 before herbs and 8 after; in another, the average retrieved oocytes was 1 before taking herbs and 3.5 after. This reveals the effect of herbal medicine varies between person to person. This statistically non-significant improvement along with the higher percentage of oocytes that made it to blastocysts may serve some patients to increase their conceptions rates.

Xue et al.'s randomized control trial of 40 women with poor ovarian response (POR) gave Tiaogeng Yijing decoction (TGYJ) to study its therapeutic effects during in vitro fertilization-embryo transfer (IVF-ET), and possible molecular mechanisms of action of these effects (Xue et al., 2017). Patient mean age was 35.10 ± 7.39 and 34.80 ± 7.53 years in the treatment and control groups, respectively. Inclusion criteria required that the patients had undergone at least one failed embryo transfer. Patients in the treatment group took TGYL decoction twice daily for 2 weeks from cycle day 7-21 for 3 cycles leading up to IVF with microstimulation. Clomiphene 50mg was given from cycle day 2-6 and was followed by low dose gonadotropin 100-150 IU/day from cycle day 8. The patients in the control group underwent the same IVF protocol without any prior treatment. TGYL is comprised of Shu Di Huang 15, Ba Ji Tian 12, Shan Yao (stir-baked) 18, Du Zhong (stir-baked with salt solution) 12, Dang Gui (alcohol-processed) 15, Bai Shao (stir-baked) 15, Dan Shen (alcohol-processed) 15, Ji Xue Teng 15, Chai Hu 9, Chuan Niu Xi 15, Xiang Fu (vinegar-prepared) 12, Tu Si Zi 18, Huang Jing (alcohol processed)12, Dang Shen 12 and Bai Zhu (stir-fried with wheat bran) 12. The following

were measured after treatment: Serum levels of sex hormones, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) and anti-mullerian hormone (AMH); follicular fluid levels of cytokines, including growth differentiation factor (GDF)-9, transforming growth factor (TGF)-β1, leukemia inhibitory factor (LIF), granulocyte-colony stimulating factor (G-CSF) and vascular endothelial growth factor (VEGF); and endometrial levels of cytokines, including integrin αVβ3, TGF-β1, LIF, G-CSF and VEGF. In addition, the antral follicle count (AFC), mean ovarian diameter (MOD), number of oocytes retrieved, percentage of high-quality oocytes and embryos, and pregnancy rates were measured. The women in the treatment group showed decreased serum levels of FSH and E2, and significantly increased serum AMH levels, the AFC, follicular fluid levels of GDF-9, TGF-β1 and VEGF, and endometrial levels of integrin αVβ3, TGF-β1 and VEGF, in addition to pregnancy outcomes (all $P<0.05$ vs. the control group). In addition to an increase in clinical pregnancy rates ($P=0.024$), the number of oocytes retrieved ($P=0.002$) and high-quality oocytes ($P=0.004$) was significantly increased when compared against the control group.

In this randomized controlled trial with 219 patients between the ages of 25-45 were divided into two groups in order to determine how Bushen Yutai (BSYT) recipe might effect patients undergoing a low dose stimulation protocol and to explore possible mechanism of action including the level of VEGF gene expression (X. Jiang et

al., 2020). Participants were normal responders and had normal FSH below 10 IU/mL. Bushen Yutai Recipe was prescribed to those in the herbal treatment group during mild ovarian stimulation and the ingredients were Shu Di Huang 15, Nu Zhen Zi 6, Tu Si Zi 6, Bu Gu Zhi 9, Mai Men Dong 6, Huang Qi 15, Dang Shen 9, Dang Gui 9, Chuan Xiong 6, Dan Shen 6. Mild ovarian stimulation began for both groups on cycle day 3 and consisted of Clomiphene Citrate (CC) 25mg daily together with 150 IU of hMG. Embryos were examined at the cleavage stage on the third day after retrieval. Fresh transfer was considered a desirable outcome and patients received a fresh transfer if their linings were above 8mm, endometrium morphology pattern A or B with endometrial blood flow confirmed by positive ultrasound, there were more than 2 high-quality day 3 embryos, and patients had no risk of OHSS. On the seventh day of stimulation and on hCG trigger day endometrial receptivity indicators and sex hormone levels were observed. Based on these measures, a decision was made to go ahead to fresh transfer or not. On the day of fresh ET, endometrial receptivity indicator, embryo receptivity indicators, embryo quality, and endometrial receptivity genes were observed. Pregnancy outcomes including fresh embryo transfer rates, implantation rates, clinical pregnancy rates, and ongoing pregnancy rates were documented as well. There was a non-significant increase in the number of oocytes retrieved from the treatment group 6.2 ± 3.1 vs 5.4 ± 3.4. The fertilization rate in the BSYT herbal treated group was significantly higher than in the control, as was the number of embryos 5.1 ±

2.8 vs 3.8 ± 2.6 (P<0.01 in both cases). Furthermore, the number of high-quality embryos 4.2 ± 2.2 in the treatment group was significantly higher than 3.0 ± 2.0 (P<0.01). Estradiol levels in the experimental group were significantly higher than in the control 2510.8 ± 1135.5 pg/mL vs 2098.6 ± 1215.5 (P<0.01). On the day of hCG trigger the endometrium was thicker than in the control but not significantly. The difference in endometrial morphology was also insignificant. However more patients in the treatment group had positive endometrium blood flow via ultrasound 49.5 vs 38.7, P<0.01. In the treatment group the authors report that the "proactive inhibition" (PI) and "retroactive inhibition" (RI), which are related to endometrial blood flow were significantly higher in the control groups, PI= 1.4 ± 0.7 and RI=0.7 ± 0.2 vs PI =1.1 ± 0.8 and RI=0.6 ± 0.5 in the experimental group (P<0.05). This was demonstrated again 3 days later at embryo transfer. It is this researcher's view that proactive and retroactive were likely English errors and that Jiang et al. were attempting to report improvements in blood flow as changes in pulsatility index (PI) and resistance index (RI). VEGF gene expression was significantly higher in the BSYT group (0.8 ± 0.8), vs (2.1 ± 1.9) in the control group ($P < 0.05$). The fresh embryo transfer rate was higher in the BYST group 45.7% vs 33.0% ($P < 0.05$). The clinical pregnancy rate 40.0% vs 35.3% (this value is from table 8, (12/34) however the results section reports 38.2%) was higher in the herbal group but was not statistically significant (P=0.4). There were two pregnancy losses in the control group but none in the group that received BYST.

Traditional Chinese comprehensive therapy (TCCT) was given by Xu Xiaojuan et al to patients that had previously failed IVF and had the Chinese medical diagnosis of Kidney Deficiency, Liver Stagnation, and Blood Stasis (KLB)(Xu et al., 2015). Sixty-seven patients between 25-40 years old with normal levels of basal hormones were divided into two groups, 35 in the trial group and 32 in the control group in this controlled clinical trial. TCCT was composed of auricular acupuncture, oral herbal decoction (one formula given before ET and a second after ET), and herbal enema. TCCT was given to the treatment group for 3 months after the previous failed IVF-ET attempt and the control group waited for 3 months with no additional treatment. Both groups were free to try to conceive naturally during the 3 month wait and agreed to undergo IVF long protocol. During the 1st stage (from the failure of IVF-ET to the next IVF-ET down regulation day) TCM II prescription + ear point + the TCM rectum drops were given. Drops were taken rectally via enema from after the period until 7 days after a rise in BBT. During the 2nd stage (from down regulation to the ET day) patients took TCM II prescription + ear point + the TCM rectum drops +normal down regulation, and ovulation induction. In the 3rd stage (from the ET day to 14 days after the ET day) TCM of miscarriage prevention + ear point + normal luteal support was provided. Finally, in the 4th stage (from diagnosis of pregnancy to 70 days after ET) TCM of miscarriage prevention + ear point + normal luteal support were used. TCM II prescription contained Tu Si Zi, Gou Qi Zi, Chai Hu, Bai He. TCM prescription for

miscarriage prevention was composed of Tu Si Zi, Chuan Xu Duan, Nan Sha Shen, and Chen Pi. TCM rectum drops were composed of Dan Shen, San Leng, and E Zhu . auricular acupuncture points: Gan (CO12), Pi (CO13), Shen (SC6), Shenmen (TF4), Neifenmi (CO18), Xin (IC5), Zigong (TF2), and Jiaogan (AH4). Points were massaged gently for 1-2 minutes each time, 4 to 6 times per day. The ear points were stimulated for 4-5 days. Natural conception occurred in 7 of the women in the treatment group but 0 in the control group (P=0.012). The trial group also showed a significant increase in ova fertilization rate (P=0.047). Clinical pregnancy rates between the two groups were significant (P=0.044). Symptoms of Kidney Deficiency, Liver Stagnation, and Blood Stasis were significantly improved in the treatment group but not in the control group.

In Chinese medicine, infertility and stress are commonly associated with the pattern of Liver Qi Stagnation and one of the most commonly prescribed herbal prescriptions used in clinic today is Xiao Yao San. Gao, Xing et al. randomized controlled trial sought to explore the effect of the Chinese medical treatment principle "soothing the Liver" with Xiao Yao Powder in women undergoing IVF and its possible mechanism of action (X. Gao et al., 2013). Fifty-eight women who all fit the diagnostic criteria for Liver Stagnation syndrome and who were ≥ 35 years old (experimental group had a mean age of 29.1 ± 2.5 years versus 29.7 ± 2.0 years for the control group) were randomly divided into two groups. Thirty women in the experimental group were given Xiao Yao Powder (XYS) with a long GnRH downregulation protocol and day 3

embryo transfer (ET) while the 28 in the control group underwent controlled ovarian hyperstimulation with ET alone. In the experimental group women took XYS herbs with ovarian stimulation medications until the day of hCG trigger injection. XYS contains Chai Hu 15, Bai Shao 15, Dang Gui 15, Fu Ling 15, Bai Zhu 15, Gan Cao 6, Sheng Jiang 6, and Bo He 6 and patients took a boiled decoction of this prescription twice daily. The total gonadotropin (Gn) doses required, antral follicle count (AFC), endometrial thickness, oocyte numbers, high quality embryo production rate, pregnancy rate, and pregnancy complications of the two groups were observed and compared. Growth differentiation factor-9 (GDF-9) concentration in follicular fluid was detected by western blotting and the expression of GDF-9 mRNA in granulosa cells was measured using reverse transcription-polymerase chain reaction amplification. In the experimental group there was a significant reduction in gonadotropin dose compared to the control group (P=0.023). In the article's abstract result section it says that significant difference were found in high-quality embryo rates and pregnancy rates. However, later in the paper's results section the author states, "...the high-quality embryo and pregnancy rates had higher tendencies than in the control group, albeit not significantly", however this does not agree with table 3 which shows 74.1% vs 61.7%, P=0.004, or 70% vs 42.8% P=0.037 respectively, which demonstrates there was statistical significance in these two areas. In the experimental group, the GDF-9 content was 1.31 ± 0.90, greater than 0.94 ± 0.19 in the control group and the difference was significant (*P*<

0.05). The granulosa cell expression levels of GDF-9 mRNA in the experimental group (0.78 ± 0.10) was significantly higher than in the control group (0.59 ± 0.04) (P<0.05). Endometrial thickness was significantly thicker in the experiment group 9.7 ± 1.4 and 8.8 ± 0.6, P=0.004. There was one miscarriage in the experimental group and one case of miscarriage as well as one case of ovarian hyperstimulation syndrome (OHSS) in the control group. These complications were not found to be statistically significant.

The following two studies like the previous by Gao, Xing also required a Chinese medical diagnosis for inclusion and are by the same author Dr. Lian, Fang, Integrative Medicine Research Centre of Reproduction and Heredity, Affiliated Hospital of Shandong University of TCM. Dr. Lian is the single most published author in the field of research on CHM and IVF. The vast majority of her studies remain untranslated; she appears as primary or secondary author in 8 of the 65 Chinese studies identified.

Lian, Fang's group conducted a randomized, double-blinded placebo controlled study to explore the effects of giving Erzhi Tiangui (EZTG) granules on the levels of DNA methyltransferases (DNMT) 1 protein expression in the endometrium of women with Kidney Yin Deficiency who were undergoing long protocol IVF (Lian et al., 2013). Sixty-six women aged 25-40 were randomly assigned to either receive EZTG granules or placebo granules (control group). The scores of the Kidney-yin Deficiency syndrome were assessed. Outcome measures included the dosage and duration of Gn, the number

of retrieved oocytes, the rate of high-quality oocytes, the rate of high-quality embryos, the fertilization rate, and the clinical pregnancy rate as well as a Kidney Yin Deficiency scoring assessment. The EZTG granules were made from the boiling and concentration of dried herbal ingredients Nu Zhen Zi 15, Han Lian Cao 15, Gou Qi Zi 15, Tu Si Zi 15, Dang Gui 12, Bai Shao 12, Chuan Xiong 9, Shu Di Huang 12, and Zhi Gan Cao 6. Treatment began 3 months leading up to the IVF, 6g of EZTG granules were taken 3 times a day from cycle 3 to 16 in the treatment group and 6g of the placebo granules were taken by the control group. The third cycle, when the COH and IVF actually occurred, the patients discontinued taking the granules on the day of trigger shot. Two to three high-quality day 3 embryos were transferred. Significant improvements in Kidney Yin Deficiency syndromes scores were seen in the EZTG treatment group, both when the same group was compared to itself before and after treatment and when it was compared with the other placebo group. The Gn dosage was both significantly lower and for fewer days in the treatment group ($P<0.05$). Both the high-quality oocyte rate and high-quality embryo rate were significantly higher in the EZTG group than the control. Fertilization rate though higher in the treatment group, was not significant. The treated groups biochemical and clinical pregnancy rates both 54.55% (18/33) were higher than in the control group 36.6% (12/33) and 30.30% (10/33) respectively, $P<0.05$. Endometrial histological examination in the treatment group revealed a typical decidual endometrium with synchronous growth of stroma and glands and that the glandular

epithelium had normal secretion. In contrast, the endometrium from the control group displayed asynchronous growth of stroma and glands, and reduced gland secretion. The endometrial DNMT1 expression among the pregnant patients in the two groups demonstrated increased expression in the treated group compared with the control group. Statistically, the H-score of the immunohistochemical image for endometrial DNMT1 expression in the treatment group (3.31 ± 0.46, $n = 33$) was significantly higher than that in the control group (2.97 ± 0.49, $n = 33$, $p > 0.05$).

A year later Dr. Lian's group published an additional study involving Kidney Yin Deficiency diagnosed patients, a randomized placebo-controlled trial which gave Liu Wei Di Huang (LWDH) granules to a group of women aged 25-40 to study its effects on IVF outcomes and to observe differences in proteome expression in the follicular fluid as a clue to possible mechanism of action (Lian et al., 2014). Ninety-nine participants were in the study, all who would undergo long protocol COH and IVF with 2-3 embryos transferred on day 3 after fertilization. Sixty-six patients with Kidney Yin Deficiency were randomly assigned to a treatment or control group, while an additional thirty-three subjects without Kidney Yin Deficiency were taken as a syndrome-control group. The patients in the first two groups were diagnosed with Kidney Yin Deficiency and were given a syndrome score in the same fashion as the previous mentioned study. Patients in the treatment group were given 6g of LWDH three times daily, while the patients in the two control groups were given placebo

granules in the same quantity and frequency. Granules were taken for 3 menstrual cycles leading up to the IVF. Again, all participants took the granules from cycle day 3 continuously for 14 days or up until the day of trigger shot. LWDH is the quintessential Chinese herbal formula to treat patterns of Kidney Yin Deficiency and contains Shu Di Huang, Shan Zhu Yu, Shan Yao, Mu Dan Pi, Ze Xie, and Fu Ling. Measures included the number of retrieved oocytes, rates of high-quality oocytes and embryos, fertility rate and clinical pregnancy rate. Further, the follicular fluid was collected on the day of egg retrieval, the differential protein expression was detected using 2D gel electrophoresis, and followed by matrix assisted laser desorption ionization time-of flight mass spectrometry (MALDI-TOF-MS) to identify the proteins. Kidney Yin Deficiency syndrome scores significantly improved in the treatment group when compared to before treatment from 16.09 ± 2.58 to 8.67 ± 2.13 and were also significant when comparison was made between the groups ($P<0.05$). The high-quality rates of oocytes and embryos and clinical pregnancy rate were all significantly improved in the treatment group vs the control group (82.29% vs 78.08%, 76.76% vs 68.79%, 63.64% vs 36.36%, all $P<0.05$). Approximately 400 protein expressions were obtained in each of the 3 groups. The follicular fluid protein expression map showed that compared with the control group, 33 differential protein expressions were found in the syndrome-control group, among which 18 were down-regulated, and 15 up-regulated; in the treatment group 28 differential protein expressions were shown, among which 15 were down-

regulated, and 13 up-regulated. It's unclear as to what differential protein expressions were found in the control group. Through MALDI-TOF-MS, 14 proteins were identified ($P<0.05$), including 5 which changed among the 3 groups, retinol binding protein 4, transthyretin, apolipoprotein A-I, apolipoprotein E, complement C4-B. When compared to the syndrome control group, the expressions of retinol binding protein 4, transthyretin, and apolipoprotein increased, while complement C4-B decreased in the control group; in the treatment group, all the 3 increased expressions were lower, and the complement C4-B was higher than in the control group.

Lian et al. in a randomized control trial gave Quyu Jiedu (QYJD) Granules to a group of women 22-46 years old diagnosed with infertility, endometriosis, and met the Chinese medical diagnostic criteria for Blood Stasis with Toxic Stagnancy syndrome who were undergoing long protocol of IVF to observe its effect on IVF outcomes and the micro-environment of ova (Lian et al., 2009). Twenty women were randomly assigned to either receive CHM or go directly into the IVF cycle. Of the 10 women in the treatment group and 10 in the control group, there were 8 and 7 cases of endometrioma respectively. An additional 20 women (non-endometriosis group) were selected at random and included in the study who did not have endometriosis but instead were doing IVF due to tubal factors. The dosage of gonadotropin medication, the number of eggs retrieved, fertilization rate and clinical pregnancy rate were all recorded, and the levels of tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) in follicular fluid as

well as their mRNA expressions in ovarian granular cells were detected by reverse transcription polymerase chain reaction (RT-PCR) on the day of oocyte retrieval. 1-2 high-quality day 3 embryos were transferred. The women in treatment group took 1 pack per day of 71 grams of water-soluble granule extract comprised of Hong Teng 15, Mei Gui Hua 6, Jin Yin Hua 10, Lian Qiao 10, Dan Shen 10, Chi Shao 10, Mu Dan Pi 10. In the treatment section of this study it says, "starting from the day of cessation of menstruation or withdrawal of bleeding… 20 successive days ***every month***" This researcher believes this is an English error and therefore it is difficult to tell when the patients in the study took the herbs. Is that 20 days after the period stopped in the cycle immediately prior to the start of the IVF cycle, perhaps partially overlapped with GnRH agonist drug in the luteal phase of said previous cycle? Or were the herbs meant to be taken for X amount of months for 20 days each month prior to initiating the IVF process? The dosage of required gonadotrophin injectables used in patients with endometriosis was 33.40 ± 9.48 ampoules for the treated group and 35.80 ± 8.87 ampoules for the control group, both significantly higher than that used in patients with tubal factor infertility (26.67±4.46 ampoules). The number of eggs retrieved (13.80 ± 6.87) and fertilization rate (0.69 ± 0.31) in the treated group were both significantly higher than in the control group (9.80 ± 5.32 and 0.47 ± 0.22) respectively. The amounts of TNF-α and IL-6 present in the follicular fluid in the treated group were 1.38 ± 0.21 ng/mL and 130.56 ± 12.81 pg/mL, respectively, which were significantly lower than those in the

control group (1.98 ± 0.34 ng/mL and 146.83 ± 17.65 pg/mL). The patients who had taken QYJD still had higher levels of TNF-α and IL-6 in the follicular fluid when compared to those in the non-endometriosis group, but these levels were no longer statistically significant. Further, the treated group showed significantly lower mRNA expressions of TNF-α and IL-6 in ovarian granular cells when compared to the control ($P<0.05$) but again were only insignificantly higher than the non-endometriosis group. The clinical pregnancy rate in the QYJD group was 30% (3/10), which was higher than (albeit insignificantly so) in the control group (10%, 1/10, $P>0.05$). This may have failed to demonstrate statistical significance due to the small sample size. The pregnancy rate in the treated group was closer to that of the non-endometriosis group (40%, 8/20, $P>0.05$).

Patients with polycystic ovarian syndrome (PCOS) present a unique clinical challenge as due to high AMH and AFC they are more likely to suffer ovarian hyperstimulation syndrome (OHSS) and because elevated circulating androgen levels may be a detriment to their egg quality. Berberine is a type of isoquinoline derivative alkaloid extracted from Huang Lian, Huang Bai and other medicinal herbs. It is widely used in China to treat bacterial food poisoning and has been well-researched to demonstrate its ability as an effective insulin desensitizer on par with the drug Metformin. Researchers from Harbin Medical University sought to evaluate the possible benefits to IVF patients with PCOS by studying the clinical, metabolic and endocrine effects of berberine vs Metformin (An et al., 2014). In this prospective

randomized placebo-controlled double-blinded clinical trial, 150 women who met the PCOS criteria set by the Rotterdam consensus were randomly divided into 3 groups, Berberine (BBR), Metformin (MET), or control. All the women were advised to increase their exercise levels and to follow a diet that would be suitable for type 2 diabetic patients. Patients took either 500 mg of berberine three times daily, three placebo pills, or metformin for ≥ 12 weeks prior to COH. No more than 2 two-to-three-day embryos were transferred after COH, which started FSH stimulation at 150IU per day and were adjusted per estrogen levels and follicle growth upon ultrasound examination. BMI and hip to waist ratio were calculated. During the early follicular phase, fasting blood levels were taken for LH, FSH, PRL, fasting insulin, total testosterone (TT) and steroid hormone–binding globulin (SHBG). Fasting plasma glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), were measured as well. HOMA-IR [fasting insulin (mIU/ml) x fasting glucose (mmol/l)/22•5] was calculated to determine the severity of insulin resistance (IR). All of these were recalculated after the subject underwent 3 months of pre-IVF treatment. The number of oocytes retrieved and number of embryos transferred per cycle were recorded. The number of clinical pregnancies and spontaneous abortions were recorded as well. 22 patients were excluded or withdrew either because of incomplete data, voluntary drop out, were lost to follow up, transient gastrointestinal complaints. A total of 128 of 150 subjects (85%) completed the first 3 months of the

study, with final numbers of subjects from the three groups similar, BBR 44, MET 41 and placebo 43. After 3 months of pretreatment, two women in the BBR group, three in the MET group and one in the placebo group became pregnant naturally. Thus, 122 women started stimulation shots. An additional 13 women were either excluded or dropped out due to poor ovarian response, OHSS or lack of good quality embryos. The remaining 109 participants had an embryo transfer, 37 in the BBR group, 38 in the MET group and 34 in the placebo group. Following treatment, BMI, waist circumference and waist/hip ratio decreased significantly in all three groups. A significantly greater reduction in BMI was seen in the BBR group than in either the MET or placebo groups. Greater reductions in waist circumference and waist/hip ratio were observed in the BBR and the MET groups than in the placebo group. After 3 months of treatment, statistically significant decreases were shown in total testosterone, free androgen index (FAI), and increases in SHBG, in the BBR and the MET groups which were similar to one another. Compared with placebo, berberine and metformin exerted equal and significant benefits on fasting glucose, fasting insulin and HOMA-IR. The BBR group demonstrated a significant decrease in total cholesterol and LDL cholesterol. The BBR group used significantly lower total FSH dosages for ovarian stimulation than in the MET and placebo groups (P = 0001). However, the serum E2 level on HCG day was significantly lower in the BBR and MET groups than in the placebo group. The bio-chemical and clinical pregnancy rates were significantly higher in the BBR and MET

groups than in those who received placebo. The live birth rate was higher for subjects taking berberine, BBR 48.6% vs MET 36.8% (P = 0.047). Furthermore, both berberine and metformin equally reduced the incidence of severe OHSS requiring hospitalization.

Unique among this collection of studies is a controlled clinical trial to study the effect of Gutai Decoction(GTD) on the rates of spontaneous abortion in women who had undergone IVF (Y. Liu & Wu, 2006). Among 280 women aged 22-43, 154 volunteered to be in the CHM group while the remaining 126 were allocated to the control group. From this original number, 23 women stopped CHM for various reasons and 10 in the control group turned to CHM when they experienced symptoms of threatened miscarriage. Of the remaining 247 participants, there were in 131 treatment and 116 in the control group. Both groups received the usual care of progesterone 20-80mg started from 2 days prior to the fresh or frozen transfer and if deemed appropriate estrogen. Patients were tapered off the progesterone starting at 9 weeks. The treatment group was divided into Group A (109) and Group B (22), with the first group beginning GTD the day after the transfer, and Group B starting GTD with confirmation of + beta-hCG (β-hCG) test > 25 IU/L, 14 days after the transfer. Women in Group A who fell pregnant and Group B continued GTD through 12 weeks of pregnancy. Dang Shen 15, Shu Di Huang 20-30, Bai Zhu 30(?), Shan Yao 30, Shan Zhu Yu 15, Xu Duan 15, Du Zhong 15, Tu Si Zi 30, Gou Qi Zi 15, Bai Shao 15, Gan Cao 6, Sang Ji Sheng 15 comprised one day's herbs divided into two doses. An error in the ingredients listed in the study exists,

listing Bai Shao twice. It is this authors belief that the first mention of Bai Shao is actually Bai Zhu 30, this conclusion stems from the fact that it is listed near Dang Shen and Shan Yao from the same category and that the composition of GTD from Chinese sources includes both Bai Zhu and Bai Shao. Bai Shao is likely correctly listed next to a similar ingredient Gou Qi Zi which also nourishes the blood. If a patient's tongue was red with a thick yellow coating, Huang Qin 10 was added to the decoction. If there was vaginal bleeding E Jiao 10, Ai Ye (Tan) 10, Di Yu (Tan) 20, Di Huang (Tan) 10 were added to the GTD. In the control group, if there were signs of threatened miscarriage the hemostatic Turinal 5mg BID, Vitamin E 50mg, folic acid 0.4 mg were prescribed to protect the fetus. β-hCG, E2 and P4 were checked 14 and 16 days after the transfer and in the fifth week or pregnancy. Ultrasounds were carried out during the 5^{th}, 9^{th}, and 12^{th} week of pregnancy. Symptoms such as bleeding and abdominal pain were noted. Among the 131 cases in the treatment group there were 6 ectopic pregnancies and 17 abortions. When the ectopics were subtracted out, 108/125=86.4% live birth rate, and an abortion rate of 13.6%. In the control group there were 3 ectopic pregnancies and 27 abortions, 86/113=76.1% live birth rate, and an abortion rate of 23.89%. The difference in abortions rates between the treatment groups and non-treatment group was significant ($P<0.05$). There was no statistical difference between the abortion rates of Group A and Group B. When twin pregnancies were excluded, there was a tendency which was non-significant for the β-hCG levels to be higher in the treatment group. The percentage of

those whose β-hCG levels doubled from 14 to 16 days after the transfer was statistically higher in the treatment group 90.84% vs 78.45% ($P<0.05$ by χ^2-test). In order to know if there might be any adverse effect from taking CHM during pregnancy, Liver and Kidney function tests were taken on 30 subjects from the treatment group once they had ceased taking GTD. No abnormalities were revealed. There were no birth defects with the exception of one infant with harelip from the control group. The study was designed to explore whether CHM could help to reduce the miscarriage rate. This is important because it both demonstrates safety and may lead directly to increased live birth rates. Other studies that tracked and revealed no change, or an increase or decrease in miscarriage rates would support possible safety or harm of using CHM with IVF.

In a randomized control trial of 433 women Dr. Guo's group divided women aged 22-42 into two groups to determine the effects of using CHM during assisted reproductive technology (ART)(J. Guo et al., 2014). Inclusion required women to have an FSH of less than 15, LH/FSH < 3.6, and a bilateral AFC of ≥ 5. 216 Women in the intervention group and 217 in the control group received one of four conventional IVF protocols according to their ovarian reserve function. The intervention group received "Kidney nourishing and cycle-regulating" herbs during the stimulation phase of their IVF and a different set of herbs from after the transfer until the pregnancy test. The herbs were cooked for patients and were provided in sealed pouches of which the

patient took 200ml in the morning and the evening. During controlled ovarian hyperstimulation, the combination of a modified Erzhi pill and Siwu decoction were taken during cd 3-7, consisting of Nu Zhen Zi 15 g, Mo Han Lian 12 g, Gou Qi Zi 15 Tu Si Zi 20 g, Shu Di Huang 20 g, Shan Zhu Yu 15 g, Dang Gui 10 g, Bai Shao 12 g, Zi He Che 15 g and Shan Yao 20 g. If there was Spleen Deficiency and loose stools Bai Shao was removed and Bai Zhu 15 g added. Huang Qi 15 g was added for Qi Deficiency. If there was excessive heat and dry mouth Huang Qin 10 g and Sheng Di Huang 15 g were added. From cd 8 until the day before the hCG trigger shot modified Erxianchuyun decoction and Siwu decoction, consisting of Xian Mao 10 g, Yin Yang Huo 15 g, Ba Ji Tian 15 g, Tu Si Zi 20 g, Zi Shi Ying 15 g, Shu Di Huang 20 g, Dang Gui 15 g and Chuan Xiong 10. Bai Zhu 20 g, Di Huang 15 g and Bei Sha Shen 15 g were added for dry throat and constipation. If there was red tongue, yellow tongue coating and excessive heat Huang qin 12 g were added. For nervousness, anxiety, insomnia and vagueness Xiang Fu 10 g and stir-fryed Suan Zao Ren 30 g were added. From the day of the transfer Wen Shen An Tai (WSAT) Decoction was taken: Shu Di Huang 15 g, Tu Si Zi 20 g, Xu Duan 15 g, stir-frying Du Zhong 15 g, Sang Ji Sheng 20 g, Ba Ji Tian 15 g, Gou Qi Zi 15 g, Dan Shen 15 g, Huang Qin 10 g, Huang Qi 15 g and Dang Gui 10 g. After taking WSAT for 5 days, Dan Shen was removed and the decoction was continued for an additional 7-10 days. Endometrial thickness and quality, number of acquired eggs, and rates of normal fertilization and high-quality embryos, biochemical and

clinical pregnancy of participants were recorded in both groups. Normal fertilization rate was calculated: number of normally fertilized eggs/total number of eggs retrieved. Once the embryos had divided into 4-8 cells, they were morphologically evaluated, with grade I and II regarded as high-quality. High-quality embryo rate was calculated by number of high-quality embryos/ number of "spontaneously splitting embryos". The rate of cycle cancellation and OHSS were also recorded. On the day of hCG injection, the average endometrial thickness in the CHM group was (10.84 ± 1.75) mm and (10.52 ± 1.50) mm in the control group, the difference being statistically significant ($P<0.05$). The fertilization rate was significantly higher 58.5% in the intervention group and 54.7%, $P=0.003$. The high-quality rate was significantly higher 52.1% (from the results section, however was noted as 51.9% in both the abstract and table 2) vs 48.7%, $P=0.036$. The bio-chemical pregnancy rate was statistically better in the intervention group 51% vs 38.9%, $P=0.019$, as was the clinical pregnancy rate 44.2% vs 34.8%, respectively $P=0.043$. Live birth rate was higher in the intervention group but not significantly so, $P=0.664$. There were no statistical differences in the rates of early abortion, or OHSS between the two groups. Figure 1 of the study gave a detailed explanation of drop outs, from an original 440 participants, 206 from the CHM group and 198 from the control group completed the trial, the drop-out rate was approximately 8%. No abnormalities in the CHM group were detected upon examination of urine and bloodwork which screened for hepatic and renal function 2 weeks post treatment cycle. A detailed

discussion of side effects was also presented in the study ranging from mild gastrointestinal discomfort, vaginal bleeding (side effect of hormone regiment), painful swollen breasts (side effect of hormone regiment, as it was not abated by cessation of the herbs), one instance of diarrhea and one of vomiting due to irregular diet and not produced by the herbs.

A retrospective controlled clinical trial (3 arm study with group comparison) was carried out to determine Bushen Wengong Decoction's (BSWGD) effect on the implantation (IR) and pregnancy rates (PR) in women undergoing frozen embryo transfer (FET) with a low dose hMG (Zhang et al., 2006). 85 participants who ovulated naturally were placed in Group A and received no pretreatment. The remaining 177 subjects who did not have normal ovulation were assigned to Group B but subdivided into 3 groups depending on what treatment they received. Group B1 received BSWGD cd 4-9, Group B2 received hMG 150 IU every other day from cd 5-13 or 5-11 totaling 600IU, and Group B3 received both BSWGD and hMG 150 once on cd 11 and once on cd 12 totaling 300IU. Trigger shots were given to Groups B2 and B3. Bushen Wengong Decoction: Dang Shen 15, Bai Zhu 12, Fu Ling 12, Wu Zhu Yu 4.5, Rou Gui 6, Lu Jiao Shuang 12, Yin Yang Huo 12, Rou Cong Rong 12, Shan Zhu Yu 9, Du Zhong 12, Gui Jia 12, Xi Xin 2.5, Dang Gui 9, Dan Shen 30, Ji Xue Teng 30, Xu Chang Qing 12 added to the decoction after cooking for several minutes, and 2 grams of Zi He Che was added to the decoction. When compared to Group A, IR and PR were significantly higher in Group

B1 in ages 30-35 and >35 years old and in all age 3 age groups (<30, 30-35, >35 years old) from B2 and B3 ($P<0.05$). No significant difference was found for IR and PR for Groups B2 and B3. However, comparisons between Group B1 and B2 were not offered in the study.

The first meta-analysis on Chinese herbal medicine and IVF published in English searched 8 databases, included 20 RCTs with 1721 women with an average of 43 participants per study group. (Cao et al., 2013) Their objective was to evaluate the effectiveness of CHM used in conjunction with IVF against those receiving IVF alone, as well as its safety. Included RCTs had to report at least one of the following outcomes: clinical pregnancy, ongoing pregnancy, or live birth. Only one of the trials was on frozen embryo transfers. 4 of the trials used CHM 2-3 months prior to IVF, and none of them were individualized according to syndrome differentiation. In nine trials CHM was used during IVF, including 6 on the first day of GnRh-a injections and 3 which all used Lian Fang's EZTG on the first day of FSH injections. Three trials used CHM after egg retrieval or after transfer. Three trials utilized CHM during and after IVF, and the remaining one was the only to use CHM before, during, after IVF. The most commonly used herbs were Shu Di Huang (16 trials), Dang Gui (15 trials), Bai Shao (12 trials). Clinical pregnancy rates were reported in all trials, while ongoing pregnancy or implantation rates were reported less frequently. Adverse events such as OHSS and miscarriage were reported in 1/3 of the cases. Meta-analysis showed use of CHM

significantly increased the clinical pregnancy (OR 2.04, 95%CI 1.67 to 2.49, p=0.00001, 20 trials, I^2 = 0%) and in the four trials that reported the ongoing pregnancy rate it significantly improved ongoing pregnancies (OR 1.91, 95%CI 1.17 to 3.10, p=0.009, 4 trials, I^2=0%). CHM significantly increased the implantation rate (OR 1.64, 95%CI 1.33 to 2.01, p,0.00001, 6 trials, I^2 = 0%). Only one trial used CHM after IVF with the intent of protecting the fetus (safeguarding the pregnancy). Of 81 women in the trial, 5 in the CHM group and 9 in the control group experienced miscarriage revealing that the use of CHM after transfer was significantly beneficial in reducing the abortion rate (OR 0.29, 95%CI 0.09 to 0.97, p = 0.04. Four of the six trials that mentioned OHSS reported an OHSS rate and meta-analysis showed no difference between the treatment and control groups. (OR 0.39, 95%CI 0.14 to 1.11, p = 0.08, 4 trials, I^2 = 0%). The potential clinical pregnancy rate of the women who used CHM with their IVF was 53.2% (95%CI 47.7%–59.0%) compared to IVF alone (36.2%, as the median risk across studies). Women who combined CHM with their IVF treatment had 44.2% ongoing pregnancy rate (95%CI 32.5%–60.2%) vs the control group without CHM (30.1% as the median risk across studies)

Seven years later, Kwon CK et al.'s English meta-analysis on this subject was published; it searched in 13 databases and included Japanese and Korean databases as well as English and Chinese. Korean, Japanese, and Kampo were added to the search

term list (Kwon et al., 2020). All 43 RCTs included were conducted in China and the average sample size in the studies was 100.4 (range: 20-433). Included RCTs had to report at least one of the following outcomes: clinical pregnancy, ongoing pregnancy, or live birth. Additionally, adverse events (AEs), including miscarriage, ectopic pregnancy, fetal abnormalities, or ovarian hyperstimulation syndrome (OHSS) were included as secondary outcome measures. CHM was consistently more likely to increase the LBR (RR 1.34, 95 % CI 1.05–1.72) and CPR (RR 1.38, 95 % CI 1.29–1.49) than those not receiving herbal treatment. The CPR in the CHM treatment group was also increased when compared to the placebo group (RR 1.85, 95 % CI 1.42–2.42). Trials that compared the efficacy of CHM administrated immediately before, during and/or after IVF with a placebo, no treatment, or other active treatments were included. Among the included trials there were 4 focusing on PCOS, 5 on diminished ovarian reserve, 3 with a history of failed IVF failure and 2 on endometriosis. Twenty studies utilized pattern identification as a condition for inclusion, including Kidney Deficiencies (n = 16), Damp-Phlegm (n = 3), Blood Stasis (n = 2), and Stagnation of the Liver (n = 3). All but four of the studies were fresh IVF-ET rather than FET. Among the 39 RCTs, HM was prescribed before IVF (n = 12), during IVF (n = 16), after IVF (n = 4), before to during IVF (n = 3), during to after IVF (n = 3), and before to after IVF (n = 1), respectively. In total, 61 HM prescriptions were used in 43 included trials. Various HM prescriptions were used in the included studies. In particular, Erzhi Tiangui granule was most frequently

used in 7 studies, and Bushen Tiaojing formula was also used in 3 studies. Regarding HM dosage form, decoction was the most commonly used in 34 HM prescriptions, followed by granule (n = 22), capsules (n = 3), and pills (n = 2). The number of herbs used in the HM prescriptions was 92. The most commonly used herbs in the different herbal formulae included Tu Si Zi (in 43 prescriptions), Shu Di Huang(in 39 prescriptions), Dang Gui (in 38 prescriptions), Bai Shao (in 28 prescriptions), Gou Qi Zi (in 26 prescriptions), Xiang Fu (in 24 prescriptions), Chuan Xiong (in 20 prescriptions), Nu Zhen Zi (in 20 prescriptions), Shan Yao (in 19 prescriptions), Bai Zhu (in 19 prescriptions), Gan Cao (in 18 prescriptions), Fu Ling (in 17 prescriptions), and Shan Zhu Yu (in 17 prescriptions).

Three meta-analyses were found in Chinese, published in 2014, 2015, and 2016 and translated by Chinese medical physicians who had professional experience translating for a large medical publishing house in China. The first meta-analysis on combining CHM with IVF-ET was conducted by the First Affiliated Hospital of Zhejiang University Medical College (He & Li, 2014). The group searched 8 databases, and included 10 RCT and Quasi-RCTs with 1000 subjects aged 24-45. All studies included either the rate of high-quality embryos, chemical pregnancies, or clinical pregnancies. Meta-analysis was conducted on 7 studies which included biochemical pregnancy rate for 797 patients. The CHM group's biochemical rate was 49.11%, the control group was 37.31%, OR=1.70 [1.27, 2.27]. The results showed that the biochemical

pregnancy rate for the Chinese medicine intervention group for IVF-ET was higher than the control group. Meta-analysis was conducted on 9 Studies which included clinical pregnancy rate for 930 patients. The clinical pregnancy rate of CHM group was 45.39%, and the control group was 30.38%, OR=2.01 [1.53,2.65]. The results showed that the clinical pregnancy rate of the Chinese medicine intervention in IVF-ET was higher than the control group. Meta-analysis was done on the high-quality embryo rate in 6 studies. The high-quality embryo rate of CHM group was 60.57%, while the control group was 50.12%, OR=1.55[1.39,1.72]. The results showed that the high-quality embryo rate of the Chinese medicine intervention group in IVF-ET was higher than the control group, $P<0.01$, the difference being statistically significant. 4 studies examined changes in the endometrium but meta-analysis could not be performed as the measure varied between the studies. 2 showed improvement in endometrial thickness, 1 did not, and one showed that it could reduce endometrial vascular resistance thus increasing endometrial blood flow.

The Third Affiliated Hospital of Guangzhou Medical University conducted a meta-analysis to observe the mechanism of Bushen herbal medicine (Bu Shen means Tonify the Kidney) on the effect on ovarian reserve and endometrial receptivity in IVF-ET (Tan et al., 2015). CNKI and Wanfang database were searched, finding 12 RCT studies with 795 participants which met their criteria for inclusion which included patients must have a Chinese medical diagnosis of Liver and Kidney Deficiency. Chinese herbs such as

Dang Gui, Shan Yao, Bai Shao, Shu Di Huang, and Tu Si Zi were used in treatment. To calculate significance of the number of eggs retrieved a mean difference analysis was used from ten eligible studies, MD=0.94, 95%CI is [0.10, 1.78]>0. According to analysis results, the number of eggs retrieved in the experimental group compared to the control group was statistically significant (P=0.03). For 3 studies which calculated fertilization rate, a mean difference analysis was performed, MD=0.07, 95% CI is [0.03, 0.10] >0. According to these results, there was significant difference in fertilization rate between the experimental group and the control group ($P < 0.0001$). High-quality embryo rates were given in 5 studies, mean difference analysis was performed, MD = -0.07, 95% CI is 0.04, 0.11 > 0. Accordingly, there was statistical significance between the experimental group and the control group in the rate of high-quality embryos ($P < 0.0001$). When mean difference analysis was done for the 4 studies which reported endometrial thickness, MD = 0.88, 95% CI is 0.48, 1.28 > 0, the difference between the experimental group and the control group was found to have statistical significance ($P < 0.0001$). Five studies reported uterine blood flow pulsation index and resistance index. Both stated that there were significant differences between blood flow to the uterus for these indices in favor of the experimental group. However, in contrast the data represented in the forest plot shows the opposite, that the control group had higher values for these indices. Therefore, no conclusion can be drawn from this data point with regards to whether CHM does or does not improve blood flow. Clinical pregnancy rate was

discussed in 9 studies. In clinical pregnancy rate analysis, using odds ratio fixed effect model, OR = 2.12, 95% CI is [1.54, 2.91] > 0. According to this analysis, the clinical pregnancy rate of the experimental group and the control group has statistical significance (P < 0.00001). The results showed that the clinical pregnancy rate of IVF patients in the experimental group was higher than that in the control group

In order to assess the effects and safety of CHM in IVF-ET, based on current evidence, Hunan University of Chinese Medicine conducted a meta-analysis searching 10 databases as well as several journals (H. Liu et al., 2016). All RCTs trials of Chinese traditional medicine in IVF-ET, with patients either receiving CHM vs placebo or no additional treatment beyond the required IVF medications that both groups received were included. 2385 patients from thirty trials were included. All of the studies included clinical pregnancy rates. Data was divided into 3 groups according to when the patients took herbs: during down-regulation, before and after ovulation promotion, and prior to beginning IVF. Meta-analysis revealed that CHM taken during the down regulating phase could increase clinical pregnancy rates (CPR)(Relative Risk, Risk Ratio RR=1.55, 95% CI: 1.31~1.84). CHM taken before and after promotion of ovulation could increase CPR (RR=1.38, 95% CI: 1.23~1.55) CHM taken prior to IVF could similarly increase CPR (RR=1.54, 95% CI: 1.22~1.95). The aggregate/summary result further demonstrated an improvement in the CPR (RR=1.45, 95%CI: 1.33-1.59). This meta-analysis broke down results for all the three groups and then gave aggregate results for

each type of result for CPR, Gn dosage, and fertilization rates. For the Gn dosage and fertilization rate results, this researcher will provide solely the aggregate numbers. The fertilization rate from 11 studies (RR=1.12, 95%CI: 1.08-1.15), the implantation rate from 5 studies (RR=1.36, 95%CI: 1.17~1.58), the high-quality embryo rate from 10 studies (RR=1.16, 95%CI: 1.06-1.26) all demonstrated positive impact of CHM. 11 studies included endometrial thickness measurements taken on the day of hCG trigger shot and showed that CHM was able to thicken the endometrium (MD=0.77, 95%CI: 0.1-81.37) Based on 11 studies, CHM reduced the dosage of Gn necessary during IVF (SMD= -0.69, 95%CI: -0.96~-0.42). As for complications occurring during IVF, 8 studies reported rates of abortion and 7 studies reported OHSS rates which upon meta-analysis, (OR=0.30, 95%CI: 0.13-0.69) and (OR=0.35, 95%CI: 0.17-0.73) respectively indicated that CHM may help reduce these risks. However, due to small sample size this conclusion could not be confirmed for abortion and OHSS rates.

Chapter 5: Discussion

Summary of Findings:

This literature review did find evidence from the reviewed studies and meta-analyses to support that the inclusion of CHM may be beneficial to women undergoing IVF. All the studies and meta-analyses did show improvement in at least one pregnancy/birth outcome. Ten studies demonstrated improvement in at least one measure of egg and/or embryo quality, as did the (Tan et al., 2015) and (H. Liu et al., 2016) meta-analyses. Some of the studies included showed evidence that like acupuncture CHM may be helpful to increase blood flow to the uterus and aid in implantation. Three of the studies showed normalization of crucial hormones related to fertility such as AMH, FSH, or increase of AFC. Possible mechanisms of actions were illuminated, including active constituents of CHM, macrophage activating properties of some CHM, as well as changes in the follicular fluid and endometrium involving GDF-9, TGF-β1, VEGF, integrin αVβ3, GDF-9, TNF-α, IL-6, DNMT1 and other proteome expressions. There was not an increase of abortions or incidence of OHSS reported in the literature suggesting safety in use of CHM during IVF.

Implications for Theory: Western Biomedical Possible Mechanisms of Action

Cytokines are a set of immunoregulatory proteins that are secreted by cells which allow for intracellular communication which have been found to serve an important role in human implantation (Chimote et al., 2010) . In essence for successful invasion of the blastocyst into the endometrium there must be the right combination of cytokines, chemokines, growth factors and adhesion molecules present in the local environment. A delicate balance of pro and anti-inflammation must be present for this life-sustaining "handshake" to take place so that the embryo is not rejected as a foreign object by the would-be mother's immune system (Mourik et al., 2009). "The cytokines most often associated with changes in endocrine function are IL-l, IL-2, IL-6, and tumor necrosis factor-alpha (TNF-α)." For example, the protein IL-6, this enhances anterior pituitary hormone secretion and is produced within the anterior pituitary gland (Spangelo, 1997). TGF-β1, VEGF, Gdf-9, IL-6 and TNF-α are all cytokines and whose individual significance will be discussed below.

Earlier studies in animals of Kojima's MACH immune strengthening herbal blend of four interferon inducing natural medicinals (galenicals) had been shown to increase macrophage phagocytosis (Ushiroyama et al., 2012). Previous studies by Ushiroyama in 2004 demonstrated that MACH could alleviate menopausal symptoms and improve symptoms of premenstrual discomfort and decrease the presence of a

certain cytokine in the blood, GM-CSF. While it was not specifically proven, on the basis of the reduction of menopausal symptoms in a previous study and reduction in FSH in patients with elevated levels in the 2012 study, it is assumed that MACH has some type of estrogenic activity. Ushiroyama et al. theorized that the benefits of MACH may stem from the known herbal properties of its ingredients which play a regulatory role on the immune system and exert an influence on local inflammation via activation of phagocytic cells. Improvement of embryonic quality may therefore be from immunostimulation and suppression of microinflammation. MACH was able to improve outcomes of some patients who had repeatedly failed IVF due to poor embryo quality and who had elevated FSH.

After taking Bushen Yutai CHM during IVF vascular endothelial growth factor (VEGF) was elevated and pulsatility and resistance indices (PI) and (RI) were lower in the treatment group (X. Jiang et al., 2020). Acupuncture with electric stimulation was found to lower PI thus reducing uterine artery blood flow impedance (Stener-Victorin et al., 1996)(Ho et al., 2009). A reduction in the PI is believed to be indicative of a reduction in impedance distal to the point of sampling (Rizk et al., 2008). Lower impedance equates to increased blood flow. A study utilizing uterine artery doppler has found higher RI & PI in a group of women with unexplained infertility when compared to women with normal fertility (Ali zarad et al., 2021). CHM which increases blood flow

locally and angiogenesis (new blood vessel formation) via increaseing levels of VEGF may aid in implantation.

The development of oocytes takes place in the very important microenviroment of the follicular fluid. The follicular fluid is formed from combinations of the products from the secretory activity of the thecal and granulosa cells with products that cross the blood follicular barrier (Revelli et al., 2009). The surrounding follicular fluid may contain substances that reflect metabolism, steroid synthesis and play active roles in oocyte quality and futhermore increase the potential for fertilization and embryo development. Growth factors and cytokines are associated with endometrial receptivity and implantation (Xue et al., 2017). Folliular fluid was collected and analyzed in 4 of the studies: (Xue et al., 2017), (X. Gao et al., 2013),(Lian et al., 2014), and(Lian et al., 2009).

TGYL CHM significantly increased levels of TGF-β1 and VEGF in both the follicular fluid and endometrium. TGF-β1 is cytokine which can promote extracellular matrix formation, regulates cell growth and differentiation, as well as benefit angiogenesis and immune function. TGF-β1 has been shown to enhance the sensitivity of granulosa cells to FSH stimulation, which increased sex hormone production. Together with sex hormones, TGF-β1 regulates the growth of follicles and maturation of oocytes. Therefore, it serves as an important precursor element to fertilization and embryonic development. VEGF serves an essential role in angiogenesis and has been reported to be related to the regulation of intrafollicular oxygen levels (Xue et al., 2017).

Below figures 1 and 2 illustrate the role of VEGF in the interaction between the endometrium and embryo, as well as its role in the development of oocytes and embryos.

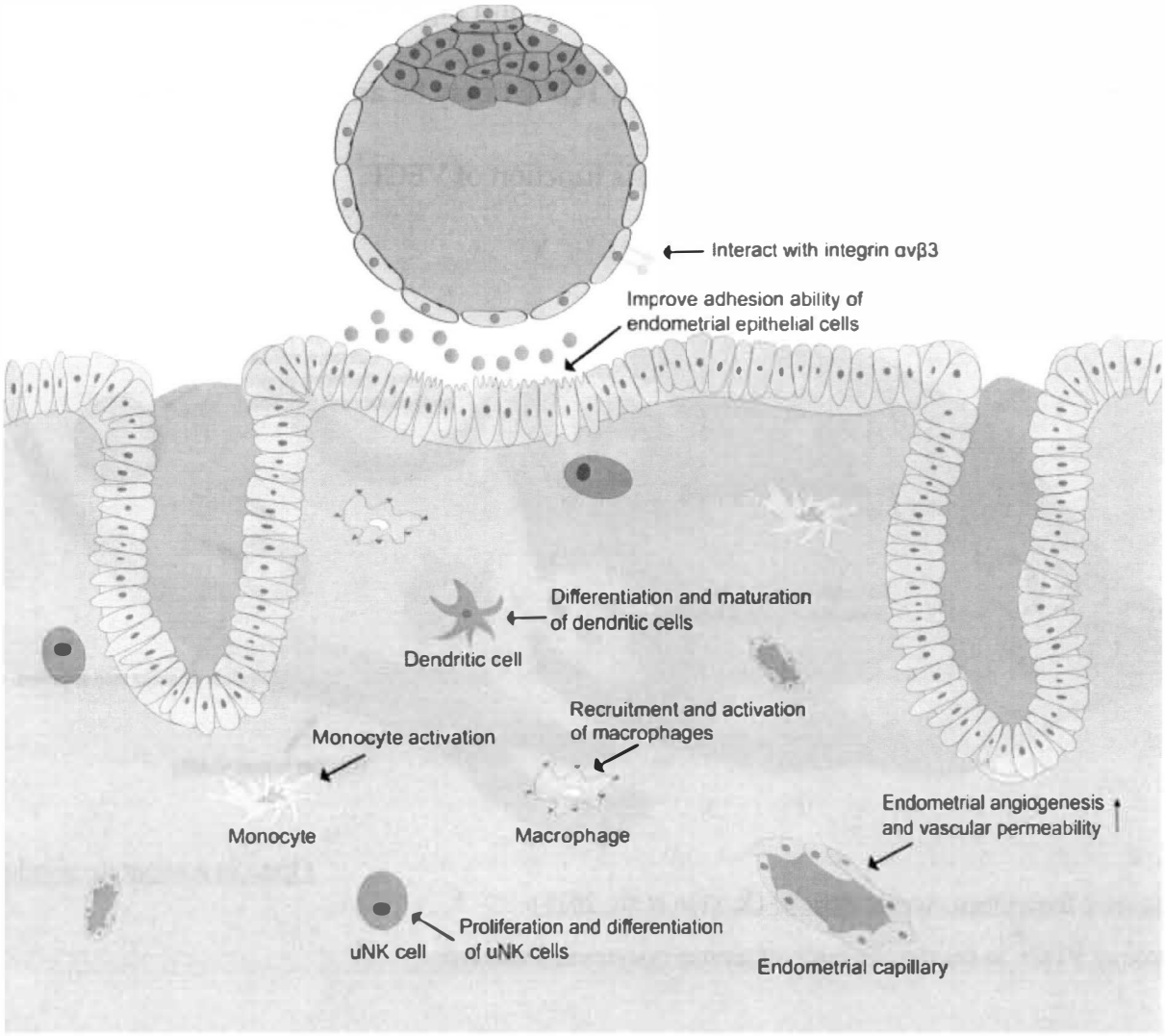

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Figure 1 from Open Access Article: (X. Guo et al., 2021)

Role of vascular endothelial growth factor (VEGF) in the human endometrium and interaction between endometrium and embryo.

The development and growth of follicles is dependent on sufficient blood flow assuring nutrients and oxygen. Follicular fluid levels which contain higher concentrations of VEGF in the follicular fluid are correlated with increased perifollicular vascularity, higher fertilization rates, better embryo quality, and higher pregnancy rates (X. Guo et al., 2021). (Xue et al., 2017) concluded that TGF-β1 may be an upstream cytokine which is involved in regulating the angiogenesis function of VEGF.

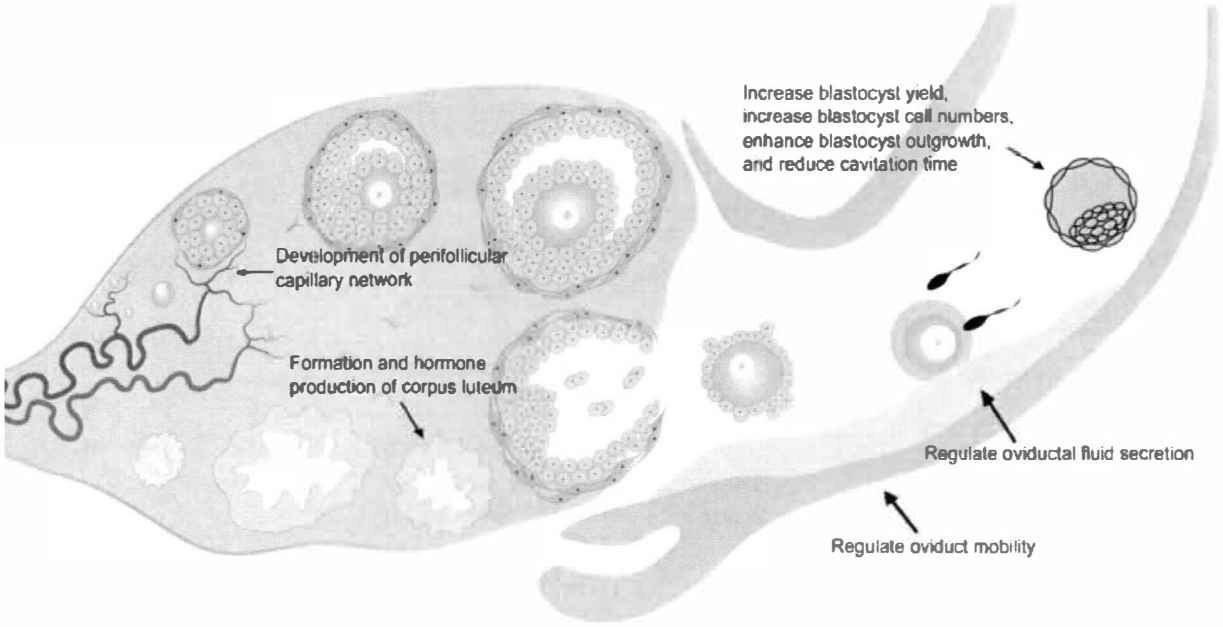

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Figure 2 from Open Access Article: (X. Guo et al., 2021)

Role of VEGF in the development of human oocytes and embryo.

Integrins are cell surface receptors that facilitate cell to cell and cell to extracellular matrix (ECM) adhesion (Hynes, 2002). Perhaps it is helpful to think of integrin as a sort of glue that helps the embryo bind to the endometrium. Alpha v Beta 3 ($\alpha v\beta_3$) Integrin

has been correlated with implantation defect and unexplained infertility. One study demonstrated women with unexplained infertility had lower levels of Integrin $\alpha v\beta_3$ in the endometrium and interestingly also had significantly higher subendometrial flow RI and thinner endometrial thickness (Elnaggar et al., 2017). TGYL CHM was shown to significantly increase Integrin $\alpha v\beta_3$ levels in the endometrium and was perhaps in part involved in increasing clinical pregnancy rates.

GDF-9, is an important oocyte-secreted factor (OSF) cytokine and member of the TGF-β superfamily crucial for oocyte maturation which is found in oocytes and the granulosa cells. GDF-9 is essential in folliculogenesis; it promotes oocyte growth and differentiation and further serves to regulate the microenvironment of the entire follicle via its effect on the granulosa cells. Furthermore GDF-9 is associated with oocyte and embryo quality (Gao et al., 2013). In patients without PCOS, serum GDF-9 concentration was associated with oocyte number retrieved and concentrations were lower in poor responders (Riepsamen et al., 2019). Another study correlated lower GDF-9 among poor ovarian responders with age. Groups under 40 with higher GDF-9 levels had higher number of oocytes, embryos, and clinical pregnancies than did older women with lower GDF-9 amounts in the follicular fluid and granulosa cells (Gong et al., 2021). XYS and TGYL CHM were both found to significantly increase GDF-9 levels in the follicular fluid.

Ovarian exudate produced by developing follicles and corpus luteum makes up much of the peritoneal fluid housed in the peritoneal cavity. Among patients suffering from endometriosis a major cause for infertility is that the peroneal cavity is in a state of chronic inflammation. Endometriomas and Endometriotic implants secrete progesterone, estradiol, transforming growth factor (TGF)-β, vascular endothelial growth factor (VEGF), and proinflammatory cytokines such as interleukin IL-6, and tumor necrosis factor alpha (TNF-α), among others. The development and progression of endometriosis is enhanced by this cocktail of secretions in the peritoneal fluid which promotes a proliferative and angiogenic environment . (Lin et al., 2018). IL-6 and TNF-α are two proinflammatory cytokines which are present as markers of inflammation in the follicular fluid and peritoneal cavity of women with endometriosis.

TNF-α is secreted by Th1 cells which are a part of the immune system that create inflammation which kill bacteria and viruses as well being involved in autoimmune responses. Interleukins are another type of cytokine which are involved in intercellular communication. They are known to regulate cell growth and differentiation. They are especially important in inflammatory immune responses (Lotha, 2019). IL-6 plays an important role in host tissue injury, and is closely related to the genesis of many diseases. When IL-6 is secreted or expressed in excessive levels, cascade may result in disease formation. Research has revealed that IL-6 and TNF-α are involved in the regulation of reproductive processes such as ovulation, implantation and embryo

development. By down-regulating the activity of aromatizing enzymes TNF-α may inhibit the production of estrogen and progesterone which could further affect the development of follicles. Inhibition of these two sex hormones in the granulosa cells might suppress the response of the ovary to gonadotrophic hormone (Lian et al., 2009). QYJD CHM was shown to reduce expressions of IL-6 and TNF-α in both the follicular fluid and granulosa cells which may have played a key role in egg quality improvement, more eggs retrieved and a higher fertilization rate. A wide range of inflammatory markers can be seen in the peritoneal cavity, ovary and fallopian tubes, and the uterine cavity in endometriosis below in Figure 3.

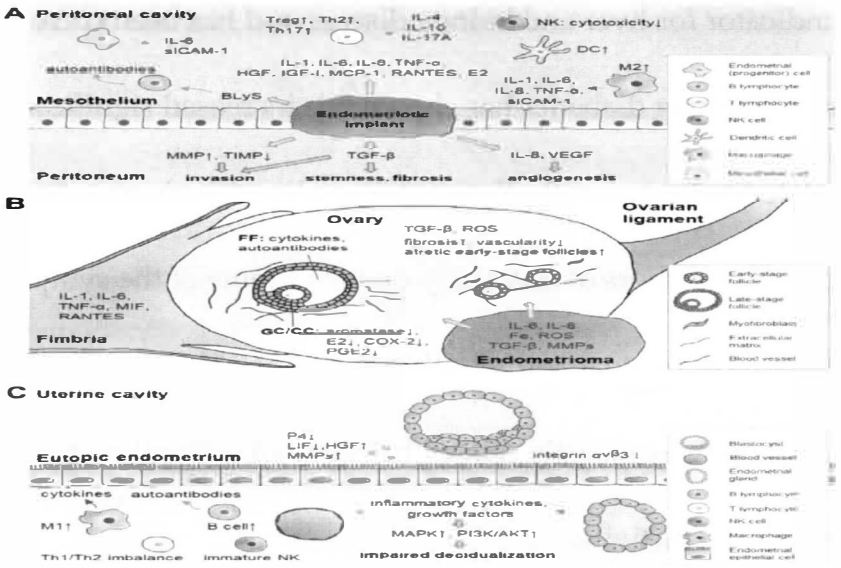

Figure 3: from Open Access Article: (Lin et al., 2018)

Different inflammatory niche in (A) peritoneal cavity, (B) ovary, and (C) eutopic endometrium in endometriosis. The population of each immune cell type, the level of cytokine/hormone/protein expression, and the activation of cellular pathways are depicted by an up arrow or a down arrow to represent an increase or a decrease, respectively.

Follicular Fluid contains many proteins which are secreted both by granulosa and thecal cells or are derived from blood plasma. Identified proteins could eventually

be employed as diagnostic markers of follicle and/or oocyte maturation and thus oocyte quality (Revelli et al., 2009). As more complex means of analysis continue to develop such as 2D gel electrophoretic separation and MALDI-TOF-MS the budding field of "proteomics" may provide exciting insights into oocyte quality in the future. (Lian et al., 2014) found an astounding approximately 400 protein expression spots in the follicular fluid of patients in their study. Of the 14 proteins that were identified 5 in particular stood out: Transthyretin (TTR), Retinol-binding protein 4 (RPB4), Apolipoprotein (Apo) A-I, Apo E, and Complement 4-B (C4-B). TTR is involved in thyroxine (the main hormone secreted by your thyroid into your blood) transport. RPB4 is a diagnostic indicator for liver and kidney disease and has been correlated to insulin resistance. Research among diabetics has shown it is increased significantly and is negatively correlated to high density lipoprotein and positively correlated to triglyceride levels. The authors of this study deduced some of the symptoms of Kidney Yin deficiency such as dry throat and mouth, sensations of heat and hot flashes, red cheeks and emaciation were directly related to hypothalamic-pituitary-thyroid (HPT) axis and lower insulin sensitivity.

Apo A-I is important in cholesterol reverse transport, has shown antiviral action, and may downregulate neutrophil functions. Apo E levels in human follicular fluid are negatively correlated to serum estrogen. In rat ovarian thecal cells Apo E has been reported as autocrine regulator, which via apoptosis may inhibit androgen secretion for

thecal follicular-interstitial cells, which subsequently led to a decrease in estrogen secretion.

The complement system is comprised of a variety of plasma proteins that react with one another to opsonize (to tag for phagocytosis) pathogens and initiate a series of inflammatory responses that help to fight infection (Janeway et al., 2001). C4-B is one of the primary components in both the classic and lectin pathways of the complement system and is essential for activation of the system itself. (Lian et al., 2014) found lower levels of C4-B in the follicular fluid among women with Kidney Yin deficiency indicating a diminished function of the complement system in this particular subset of infertility patients, and which increased in the LWDHW CHM treatment group. In summary both types of Apo, TTR, RBP4, were decreased post treatment with CHM while C4-B was increased.

The endometrium was given a closer look in Kidney Yin deficient patients in (Lian et al., 2013) to again attempt to discover a mechanism of action for EZTG enhancing endometrial receptivity which highlighted yet another case of improvement of CHM clinical pregnancy rates. The author sites 2 animal studies which reported taking CHM to tonify the Kidney led to increased uterus weight by increasing the thickness of the endometrium and the number of endometrial glands. These changes were as a result of upregulated expression of estrogen and progesterone receptors. Among rats and mice these herbs were found to promote blood circulation of the reproductive organs.

Furthermore, these class of CHM were shown to promote blood circulation of reproductive organs.

Implantation is a complex process involving synchronous action of extracellular hormonal changes, interaction between embryo and endometrium, and cellular remodeling of the endometrium. Endometrial receptivity of the embryo is likely the result of the actions and expressions of certain genes which have yet to be fully discovered/understood. DNA methylation may in part epigenetically control the transcription regulation of these genes. A higher degree of methylation is associated with a lower level of gene expression. DNA methyltransferases (DNMTs) are the principal enzymes to establish and maintain DNA methylation. In somatic cells, DNMT1 is the most abundant methytransferase. DNMT1 levels reflect the status of the genetic methylation in the body. DNA methylation plays a critical role in the migration and invasion of chorionic villus cells into the decidua of the uterus. Yamagata, Yoshiaki reported that DNMT1, DNMT3a, and DNMT3b were expressed in the nuclei of endometrial epithelial cells and stromal cells during menstruation. The study revealed that their expression was downregulated in the luteal phase of the cycle and after administration of Provera (medroxyprogesterone acetate). This suggests that DNMTs have regulatory functions in gene expression that is associated with decidualization involved in embryonic implantation(Yamagata et al., 2009). DNMT1 protein expression levels in the endometrium were increased after patients took EZTG.

As an insight to why some of the ingredients may have been chosen for Dr. Lian's EZTG she further discusses research relevant to 4 of the its principal ingredients. One of the active ingredients in Nu Zhen Zi, oleanolic acid, according to numerous pharmacological studies may increase levels of estradiol, superoxide dismutase, and glutathione peroxidase, decrease MDA levels, (the latter 3 being either assistants in breaking down free radicals or markers of oxidative stress) and improve the function and morphology of the adrenal gland and ovary among menopausal rats. The total antioxidant flavonoids from Han Lian Cao significantly eliminate reactive oxygen which are involved in free radical damage. This restrictive action on lipid peroxidation which occurs as a result of lipids breaking down and having their electrons "stolen" by free radicals of lecithin (an essential fat found in the cells of the body), could lead to a reduction of DNA oxidative damage. The flavonoids contained within Tu Si Zi were shown to increase the weight of the anterior pituitary, ovary, and uterus in adult rats, elevate the functions of gonadotropin/ luteinizing hormone receptor and the pituitary glands reactivity to gonadotropin-releasing hormone, and improve secretion of villus which play a role in implantation. Tu Si Zi water extract may improve vaginal epithelial cell cornification which is important during implantation. Gou Qi Zi which is well known to be high in antioxidants, and further has been demonstrated to possess anti-aging and anti-fatigue effects, has been reported to be beneficial to female infertility (Lian et al., 2013).

Implications for Theory: Chinese Medical Theoretical Discussion

The above western medical possible mechanisms of action while interesting to some is only part of the "how does it work". This chapter would be incomplete without delving into how Chinese herbal medicine does what it does to help fertility patients undergoing IVF according to Chinese medicine's own unique theoretical perspective. Seven of the articles included commentary on Chinese medical theory on how CHM was able to improve study outcomes.

According to Chinese medicine poor ovarian response (POR) belong to categories such as infertility, scanty periods, amenorrhea (Bi Jing) and "Blood depletion". Chinese medicine considers POR to be directly related to Kidney Qi and Essence deficiency. *Fu Qingzhu's Gynecology* states that the basic physiological processes of women are associated with the Kidneys. Furthermore, Liver Qi Stagnation is thought to play a role in POR. This researcher believes there is likely to be a correlation with elevated cortisol levels, stress, the diagnosis of Liver Qi Stagnation and POR infertility. Tiaogeng Yijing decoction (TGYL) is actually based on Fu Qingzhu's Yijing Decoction in which Ren Shen, Suan Zao Ren, Mu Dan Pi, and Sha Shen were removed and Dang Shen, Ji Xue Teng, Dan Shen, Chuan Niu Xi, Tu Si Zi, Ba Ji Tian, Huang Jing, and Xiang Fu were added. The original Yijing decoction was his suggested prescription for premature menopause aka premature ovarian failure or premature ovarian insufficiency. The authors of (Xue et al., 2017) believed that nourishing the Liver and Kidney according to

Chinese medicine might improve POR, their TGYL tonifies the Kidney, invigorates Blood, sooths the Liver and strengthens the Spleen.

Xiao Yao San (XYS) one of the most commonly prescribed herbal prescriptions in the West often prescribed for premenstrual syndrome and/or depression resulting from the Chinese medical pattern of Liver Qi Stagnation. As a treatment for infertility, it soothes the Liver, dispels stagnant heat (especially when Mu Dan Pi and Zhi Zi are added), nourishes and invigorates Blood to restore normal functions of the Liver, strengthens the Spleen, and regulates the Chong and Ren Vessels. (X. Gao et al., 2013) sites previous research that XYS can improve pregnancy outcomes by alleviating anxiety and depression of patients undergoing IVF and that is able to regulate hormone levels, improve ovarian function and promote ovulation. When taken during COH, Liver Qi stagnation was relieved in the patient and Qi and Blood in the Chong and Ren vessels was unimpeded thus enhancing oocyte maturation, fertilization rate and high-quality embryo rate. Furthermore, according to Chinese medicine XYS improves the store of Blood, while the flow of the Chong and Ren vessels will be ample to increase endometrial thickness and the rate of implantation.

One of the four major Chinese medical patterns responsible for infertility is Blood stasis. Although historically in Chinese medicine there is no disease that perfectly matches endometriosis, even today laparoscopy is the only definitive means of confirming its presence or absence, it is widely agreed upon that its primary etiology is

Blood stasis. Its chronic, stubborn unrelenting nature, with a high rate of recurrency are all characteristic of Blood stasis. After examining reports in China as well as abroad about the disease, the authors believe that the pathomechanism for endometriosis is Blood Stasis and Toxin Stagnancy which has damaged the collaterals and led to disorders and imbalance in the Qi-Blood and Yin-Yang of the patient (Lian et al., 2009). The group continues to state, "The disease is mostly caused by blood-stasis, with evil-blood stagnating in Chong-Ren Meridians and uterine vessels, which becomes toxic after a long time and induces blood stasis with toxic stagnation." Therefore, accordingly the treatment should begin with eliminating the stasis and toxin like substances. They believed that the presentation of antibodies in multiple organ and non-organ sites in patient peripheral blood and abdominal fluid, as well as high expressions of cytokines such as TNF-α and IL-6 in the follicular fluid and granulosa cells could be considered as a type of metabolic induced endogenous toxin that leads to infertility. The herbal prescription QYJD works by following the Chinese medical principles of removing stasis and toxic substances, and has the functions of removing Blood stasis, detoxifying, dredging the collaterals and relieving pain.

Blood stasis in Chinese medicine could cause painful periods, endometriosis, or uterine fibroids, or amenorrhea. None of the studies reviewed involved patients with uterine fibroids as the primary inclusion factor however as some of the same inflammatory markers such as IL-6 are present (Orciani et al., 2018) it's reasonable to

assume treatment with CHM designed to treat blood stasis for one cause may be beneficial for blood stasis which leads to another pathogenesis.

Liu Wei Di Huang Wan is the representative Chinese herbal tonic prescription for Liver and Kidney Yin Deficiency and has been widely used since the Qing Dynasty. Studies have shown that Liu Wei Di Huang Wan has immunoregulative, estrogen-like and reproductive improving effects. Chinese herbal medicine for nourishing Kidney such as Er Zhi Tian Gui (EZTG) has been shown to significantly improve the oocyte and embryo quality, as well as clinical pregnancy rates in IVF. As Chinese medicine existed before western knowledge of the HPO axis and the endocrine system, Chinese medicine has traditionally stated that the Kidney controls reproduction and is responsible for storing Essence. Essence and Blood share the same source (the Kidney) and can be thought to be interchangeable. When the Kidney Essence is sufficient there will be adequate Blood to nourish the uterus, creating a hospitable environment for implantation. Kidney deficiency leads to a malnourished uterus incapable of supporting life. A further modern interpretation by Chinese medicine is that follicular fluid belongs to Kidney Yin. Sufficient Kidney Yin and Kidney Jing (Essence) are the foundational basis of reproduction. Patients may suffer from infertility when there is Kidney Yin Deficiency syndrome due to reduced reproductive function. Parallels may be drawn to Kidney Jing that it may influence the potential of a developing embryo, embryo quality, and even the resulting child's constitution(Lian et al., 2013)(Lian et al., 2014). Kidney

Essence could be argued to be the ancient Chinese best attempt on understanding modern day genetics and epigenetics.

(J. Guo et al., 2013) herbal protocol was based on contemporary/modern Chinese medical gynecology master 夏桂成 Guicheng Xia's "Nourishing the Kidney and regulating the cycle method". There is a close association of the natural changes in Qi, Blood, Yin, and Yang in the internal organs with the monthly development and growth of follicles. Cycle day 3-8 is physiologically characterized by the growth of Yin, therefore it is suitable to take medicinal herbs which nourish the Kidney especially the Yin aspect, enrich the Blood, and which promote the circulation of Blood. A decoction containing medicinal agents with these characteristics can boost development and maturity of the follicles while simultaneously reinforcing Kidney Essence in order to enrich the Blood and benefit the growth of the endometrium. The waxing and waning of cyclic estrogen (as well as LH and FSH) and progesterone may be thought to occur like the rhythmic ebbing and flowing of Yin and Yang. After the 8th day of the cycle as suitable follicle(s) are developing it is appropriate to add Yang assisting herbs to the prescription to promote proper transformation of Yin to Yang aiding the follicle(s) to further mature and prepare for ovulation. Whether a natural cycle of timed intercourse or a cycle of controlled ovarian hyperstimulation, Dr. Xia's theory may similarly be applied. After preliminarily nourishing Yin, (J. Guo et al., 2013) appropriately modified the herbal composition to include such well-known Kidney Yang tonics as Xian Mao,

Xian Ling Pi (aka Yin Yang Huo), Ba Ji Tian, Tu Si Zi, and Zi Shi Ying during r-FSH follicular stimulation. In this study upon completion of the transfer, patients took WenShenAnTai Yin (Warm the Kidneys and Calm the Fetus decoction) to aid in implantation and to preevent miscarriage. The prescription focuses on nourishing the Kidney, tonifying Qi and gently promoting Blood circulation. While in this phase the skilled REI will supplement progesterone, the experienced Chinese medical practitioner will continue to supplement the Kidney Yang and strengthen the Spleen. The author sites animal experiments which demonstrated that CHM designed to prevent miscarriage, "can regulate the expression of endometrial heparin-binding epidermal growth factor and its receptor, facilitate development of endometrial superficial pinosomes and promote generation of endometrial blood vessels…", all of which assist in embryonic implantation.

In addition to WenShenAnTai for safeguarding the fetus or use during post embryo transplantation phase, Gu Tai Decoction (Consolidate/Secure the Fetus Decoction) was shown to reduce abortion rates among IVF patients (Y. Liu & Wu, 2006). GTD is an award winning and time-tested herbal formula for the treatment of habitual abortion. Composed by veteran Chinese medical physician 刘云鹏 Yunpeng Liu; it has been both pharmacologically clinically studied winning the Scientific and Technical Progression Award grade III of Hubei Province in 1995. As Chinese medicine holds that the fetus' foundation, growth, and development rests upon the Spleen and Kidney, then

it follows logically that if the Spleen and Kidney should weaken abortion would inevitably follow. GTD concentrates its attention on simultaneously tonifying the Spleen and the Kidney and consolidating the Chong and Ren (Penetrating and Conception) vessels. Dang Shen and Bai Zhu strengthen the Spleen Qi to supplement the Post-natal Qi to counter the underlying deficiency. Shu Di Huang, Shan Zhu Yu, and Gou Qi Zi nourish blood and Essence to tonify Pre-heavenly Qi. Tu Si Zi tonifies the Kidney while Bai Shao nourishes the Blood and alleviate uterine spasms to stop abdominal pain. In summary the herbal formula regulates and supports both the Pre-heavenly essence and Post-heavenly Acquired Essence to strengthen the Spleen and Kidney to secure the pregnancy. Stepping away from purely Chinese medical-speak the authors state that pharmacological studies previous conducted proved that, "GTD could inhibit the contraction of uterine smooth muscles, antagonize contraction induced by pitocin and pituitrin, and lead to an increasing trend of estradiol, progesterone and luteinizing hormone.". A small footnote but worthwhile mention, the authors of this study apparently could not resist the urge to replace an ingredient from the original Dr. Yunpeng Liu prescription (Chao) Bian Dou which gently tonifies the Qi which a much used and studied gynecological herb Tu Si Zi which tonifies Kidney Yang, yin and secures the essence. As previously mentioned both Bai Shao and Bai Zhu should be in this formula but in the study, Bai Shao is mentioned twice and Bai Zhu was omitted.

Implications for Practice:

All studies as well as 5 meta-analyses that were reviewed were found to be helpful in at least one parameter of pregnancy outcomes and 10 of 13 studies found that egg quality may have been improved with CHM. Familiarization with this paper and the studies contained within would provide an excellent knowledge base for Chinese medical practitioners to speak with reproductive endocrinologists (RE), patients, and insurance companies.

Whether the Chinese medical practitioner is an experienced fellow of the American Board of Chinese Reproductive Medicine (ABORM) or an aspiring Chinese medical gynecology specialist, the ability to speak to an RE in terms that s/he can comprehend and without coming across as strangely esoteric is an important skill set. As Chinese medicine is not the dominant medical paradigm, our profession must learn the western medical jargon for infertility. It is unrealistic for one to initially expect a physician to comprehend aspects of Chinese medical diagnostic such as Qi, Yin, Yang, and Shen (spirit). Doctors understand improvement in clinical pregnancy rates, reductions in PI and RI, cytokines and inflammatory markers. For the new practitioner or person wishing to specialize in gynecology one needs to learn to promote themselves by speaking to our RE counterparts and when given the opportunity their patients in potential new patient seminars that fertility centers regularly hold. An acupuncturist will inevitably get two questions, "does it hurt and how does it work?". Further the

information gleaned from this paper will be helpful for the practitioner who wishes to organize research in the area of Chinese medicine and IVF. It should be shared with other advanced practitioners of Chinese medical gynecology such as ABORM and added to the growing body of evidence that is required learning for those seeking doctoral level of training in the 3 U.S. institutions which include gynecology as an area of focus.

Having access to this paper's data may help Chinese medicine practitioners candidly answer both the simple and complex questions that patients may pose. Physicians frequently ask their patients to abstain from taking Chinese herbs during an IVF cycle siting that CHM is not FDA approved, there is no research which demonstrates their efficacy and safety, while others are concerned that it may interfere with their medication or reduce the success of their clinic's IVF success rates. Ethically if a patient comes to an acupuncturist's door for help it is a medical provider's duty to know the extent of what they may or may not be able to do for the patient. It is incumbent upon the practitioner who seeks to specialize in this field to seek out and read studies that pertain to their patient's needs. The provider's responsibility is to know and share this knowledge with patients regardless of the physician's desires; all patients have the fundamental right to autonomy where making decisions regarding their own health are concerned.

The majority of companies do not currently offer their employees insurance coverage that pay for the expenses associated with IVF. This is gradually changing as large companies seek to offer the best packages to attract and retain highly skilled talent. Insurance companies routinely deny acupuncture reimbursement for coverage stating, "acupuncture for infertility is currently considered experimental or there is no evidence to indicate its efficacy". Many providers unethically code there treatment as back pain rather than infertility, a potential bane to our profession. This paper may serve Chinese medicine to dialogue with insurance companies about possible reimbursement for Chinese medicinal herbs. The expense of eight hundred to one thousand six hundred dollars for CHM (3 months leading up to IVF through the first trimester of pregnancy) and one to two thousand dollars to cover reproductive acupuncture costs might be of interest to an insurance company if it could save them twenty thousand on fees for an additional IVF cycle. If insurance companies are not moved to make this change themselves then the information here may be useful for state Chinese medical associations to push legislators to require insurance companies to cover supplemental IVF costs which include Chinese medical treatment!

Western medicine has made great strides in the development and gradual refinement of IVF over the last 40 years; prior to this innovation couples with blocked tubes would have had no other recourse for children but to adopt. However even with IVF, there are still subgroups within infertility patients for whom western medicine has

not achieved a high degree of success, namely diminished ovarian reserve (DOR) and poor ovarian response (POR). In a study on DOR patients who underwent IVF the clinical pregnancy rate was 11.5% per cycle, and the total cancellation rate was 34.4% (Yun et al., 2017) . Among POR patients receiving IVF the overall CPR was 18.7%, LBR/ET was 11.5%, and LBR/OPU was 8.3%. The cycle cancellation rate due to zero available oocytes or embryos was 4.9% and 18.6%, respectively (Yang et al., 2015). Two studies concluded that the severity of endometriosis is negatively correlated with success rates of IVF (Kuivasaari et al., 2005), (AlKudmani et al., 2018). The research of (Ushiroyama et al., 2012) and (Inoue et al., 2013) which included women who had repeatedly failed IVF, (Xue et al., 2017) on women with POR and (Lian et al., 2009) endometriosis patients all indicate possible benefit from adding CHM to IVF. For PCOS, patients may have a great number of oocytes retrieved but due to high circulating androgens some end up with few high-quality embryos. The work of (An et al., 2014) showed statistical reduction in total testosterone levels for women with PCOS who were pursuing IVF. Furthermore, this study showed a reduced incidence of severe ovarian hyperstimulation syndrome (OHSS), and was one of 4 studies (the others being: X. Gao et al., 2013; Lian et al., 2009, 2013) that showed CHM helped to reduce the dosage of stimulation medication which directly reduces the patient cost of IVF.

While one approach might to be to approach western RE colleagues in hopes to elucidate how Chinese herbal medicine may be able to help them with their most

difficult cases, there is a more practical end goal that should be kept on the horizon for future Chinese-Western integrative collaboration. All of the studies included showed an improvement in at least one type of birth outcome. At the end of looking at one study or one hundred studies, with an "N" of 60, 400, 1000 or 10000, the goal for all medical practitioners is the same, to serve and meet our patients dreams of extending their family. In so far as the current level of studies and meta-analyses have concluded that CHM may be beneficial and unlikely to pose harm to patients, should the goal of collaboration not be to include Chinese medical care in every patient rather than merely those with poorest prognoses? At the end of all the well or poorly designed studies and well-intended statistical analysis each person is an "N" of one, should not everything that may be beneficial (and which has been proven to be harmless) be offered to try to tip the scale of odds in the favor of the patient. At day's end she is either 100% pregnant or 100% not.

On the Issue of Chinese Herbal Medicine Safety: Adverse Events, OHSS, and Abortion

While not all studies included adverse events reporting, those that did either reported no side effects or only mild to moderate gastrointestinal complaints among a small portion of participants, with no severe or life-threatening incidents. As mentioned in the above results section, 2 individual studies and 2 meta-analyses concluded that CHM offered no benefit in reducing occurrence of OHSS. While the meta-analysis by (H. Liu et al., 2016) demonstrated a reduction in the rate of OHSS in the CHM group

participants this conclusion could not be confirmed due to small sample sizes. Finally in a study involving only PCOS patients (a group who would be most likely to overstimulate), those who took CHM had lower rates of severe OHSS requiring hospitalization than did the control group ($P<0.05$). Equally or perhaps more important, none of the studies demonstrated an increased risk of OHSS when taking CHM during IVF. As for abortion rates, *Effect of Gutai Decoction on the Abortion Rate of in vitro Fertilization (Y. Liu & Wu, 2006)* concluded that taking CHM during the first trimester of pregnancy significantly decreased the rates of abortion among IVF patients. Three additional studies revealed no significant difference between abortion rates between control and experimental groups. Among the three meta-analyses which tracked abortion rates, 2 demonstrated significant reductions in abortions for those taking CHM, while the 3rd showed no significant difference between groups. While further larger and more rigorously designed studies need to be carried out here in the West, with regards to adverse events, OHSS, and abortion rates, on the whole it seems apparent CHM included in IVF does not pose a risk for harm.

Limitations of the Current Study:

While there were several limitations to this study, one that stands out by far as the single greatest impediment is the vast majority of studies on the topic are only available in Chinese language. Sixty-five potential articles were found in Chinese databases after

excluding research done for doctoral and master's thesis. Until these studies are translated into English it remains to be seen what other parameters and methods of actions have already been explored in China. Due to time and budget constraints of this research and program length, only the 3 meta-analyses were chosen for professional translation, believing that they would show an overall best representation of the current studies in China and carry the strongest weight.

Only one English study could be found that was conducted outside of China (Hullender Rubin et al., 2015) but it was excluded because the author did not specify which participants did and did not receive CHM as part of her whole systems approach, therefore no conclusions could be drawn about the single impact of CHM from this study. However, the study *Impact of Whole Systems Traditional Chinese Medicine on In Vitro Fertilization Outcomes* is noteworthy and should be considered by others in this field of research because its practice model which sometimes including acupuncture, CHM, diet and lifestyle recommendations is more in keeping with the way Chinese medicine is actually practiced outside of China. Published in the same year (Xu et al., 2015) from China also combined acupuncture and CHM to explore possible benefits for IVF patients.

Finding the studies in English themselves was challenging because though most of them included IVF in the title, most did not include "Chinese herbal medicine". Sometimes the name of the herbal prescription being tested was in the title instead of

the word "herb". One study had "berberine" in the title which is an English name for an active ingredient in 2 commonly used Chinese herbs. Some of the titles had neither CHM or IVF in the title. Some used "embryo transfer" or "controlled ovarian hyperstimulation" instead of IVF. It is possible that if the proper keywords were not associated with the studies that there may be additional studies that were not discovered.

Over the last 5-10 years there has been a shifting towards preference to freeze all embryos and if the woman is over 35 years old to recommend PGT-a genetic screening of the embryos prior to transfer (Pereira et al., 2019). Whether genetic testing is done or not some believe this to yield higher pregnancy rates over fresh embryo transfer (CCRM, 2021). Only one study looked directly at using CHM during FET and did not report whether PGT-a testing was done. The lack of studies done with CHM and FET and/or PGT-a testing raises the question would similar benefits with regards to higher pregnancy rates be conferred upon FET and embryos which had undergone genetic screening.

An Additional Word about Quality of Studies included and Issues with Choosing Jadad-based Grading Criteria for Systematic Reviews which Include both RCTs and QEDs:

The quality of the studies included has already been discussed in results and methods chapters. However, it seems imperative to cover a few additional issues with regards to quality. Questions 1 and 2 of the Jadad scale concerning whether a study

was randomized and blinded and which awarded a further point for both if the randomization and blinding was adequately discussed presented an obvious bias towards RCT studies. Perhaps it was an error by this researcher to have chosen a Jadad-based scoring system to judge the quality of all included studies. There were so few studies available in English, this researcher chose not to exclude non-RCTs. It is this researchers hope that others who may conduct systematic reviews involving both RCTs and quasi-experimental (non- randomized, non-blinded) design (QED) studies consider the research of (Singh et al., 2007) who conducted an systematic review of herbal treatments for asthma and included both RCTs and QEDs and quality assessment tools based on both Jadad for the RCTs and non-Jadad for the QEDs. Below is their quality scale form for QED studies:

TABLE 5.1.—Singh quasi-experimental design quality scale form (originally from Singh et al., 2007 pg. 687 Table 3)

Background/significance or literature review:
A Demonstrates adequate knowledge of disease/Condition?
A1 Demonstrates adequate knowledge of treatment?
Adequacy of treatment:
B Optimum/standard dose [number, duration, etc.] used?
B1 Dose [number, duration, etc.] used justified?
Power calculation:
C Number needed reported?
C1 Sufficient number recruited?
Description of product/procedure:
D Sufficient for replication of study?
Description of sample selected:
E Demographics?
E1 Diagnosis related information?
Outcome measures:
F Clearly Stated?
F1 Validity and reliability established of primary?

Data reported:
G Reported consistent with data tables, etc.
H Attention paid to possible biases in design: No control.
I No significant biases/flaws in operationalization of design.
J Comparison of **dropouts vs. completers**
K If findings are not consistent with similar studies, is there an adequate explanation of different findings?

This researcher believes it would be a mistake to discount or dismiss the validity of included studies such as the five QED (Inoue et al., 2013; Y. Liu & Wu, 2006; Ushiroyama et al., 2012; Xu et al., 2015; Zhang et al., 2006) as inconsequential simply because they were not RCTs. These studies will automatically start with an assumed lower-power benefit because in part the wrong questions were asked to evaluate their relative strength. Future researchers and clinicians might still try to utilize some of the results from these studies and might even repeat the treatment from these studies in a more stringent redesigned controlled fashion.

While perhaps the RCT is the status quo gold standard of the pharmaceutical drug industry it bears little resemblance to the actual clinical practice of Chinese medicine particularly in the United States where CHM is prescribed alongside of acupuncture and other components broadly comprising the whole-systems approach known as Chinese medicine. Though the focus of this paper was to evaluate the efficacy of adding CHM to IVF rather than evaluating the strength of whole-systems Chinese medicine, this researcher would still refer others to the work (Verhoef et al., 2005) to look beyond the limitations of RCTs when evaluating whole-systems of medicine such as Chinese medicine. The paper's premise is that RCTs may not be best way to design studies to

test treatments which are often grouped together with multiple modalities such as in Chinese medicine ie CHM, acupuncture, dietary advice, movement and spiritual practices such as meditation or qigong. Many suggestions are contained within on integrating qualitative methods into rigorous quantitative studies, individualizing treatment options even within the confines of RCTs, and offering means of study design that test model validity (Verhoef et al., 2005).

Recommendations for Future Research:

This researcher believes the first step in moving forward in research is redoing the Chinese databases search to find additional studies which incorporated CHM in IVF cycles. Western researchers should not waste time operating in a vacuum attempting to recreate the proverbial wheel. After repeat search, all CCT and RCT should be translated. It may not be necessary to translate the entirety of each study. As in this paper the data should be extracted and quality of the study should be assessed. Tables should be generated to summarize when CHM was taken in each study. Special note should be taken of improvements to pregnancy rates, birth outcomes, improvements in egg and embryo quality, and additional mechanism of actions should be sought beyond those already discussed in the English published studies discussed here. A group of Chinese reproductive medical practitioners and Western-trained reproductive endocrinologists should come together to analyze and discuss the existing literature.

This group of reproductive medical peers should try to come to agreement on which studies were of the highest quality. This researcher would suggest working on a study that explored the possible benefits of CHM for women undergoing IVF who suffered either from DOR or POR, as they are the group most in need of improving current outcomes. Also, being able to help a more difficult group lends itself to generalizing that CHM could help less complex cases.

It might be prudent prior to attempting an original CHM composition, to attempt to recreate and validate results from Chinese studies here in a Western clinical setting. Studies with shorter duration of treatment might be done first to establish initial benefit and longer phased treatment studies might be gradually developed and trialed. For example, the first study might only have patients take herbs during the 10-12 days of stimulation medication. The next study might add that patients would take herbs after transfer for 10-12 days after the transfer until the first pregnancy test. A third study would add an additional prescription to be taken during the down regulating phase of the IVF protocol. A final trial might add 2-3 months of CHM leading up to the IVF cycle to the previous 3 phases. Although costly the trial outcomes need to be tracked to calculate live birth rates. A power calculation needs to be done to determine the appropriate number of participants to show statistical differences for multiple variables but especially for live birth rates.

It is this researcher's personal suggestion that we continue to strive to produce

well-designed randomized controlled trials, however I would recommend eliminating blinding requirements. If one is to take Chinese herbal medicine in its arguably strongest traditional fashion dried-herb produced decoction it is difficult to produce a similar appearing, smelling and tasting alternative to serve as a control. Furthermore, if one were eventually to combine treatment modalities with acupuncture, sham acupuncture or placebo needles still stimulate the body's nervous system and do not offer an inert or fair shake control. Simply put, compare the outcome in the treatment group against a population of patients who either solely received IVF or retrospectively against patient's charts who were of similar baseline characteristics but received no Chinese medical treatment.

Initially a preference to focus research primarily on clinical outcomes prior to delving deeply into confirming proposed laboratory mechanisms of action is recommended. However, AFC, FSH, AMH, would be tracked before and after treatment in addition to common outcomes such as eggs retrieved, fertilization rate, quality and number of blastocysts, chemical pregnancy rate, clinical pregnancy rates, ongoing and live birth rates. The discussion needs to be had with China-based peers why studies have not been carried out with FET and PGT-a and consider further assessing is the CHM able to help patents generate a greater number of euploid embryos.

It is widely believed that the strongest method of taking Chinese herbal medicine is

to take herbs by traditional decoction rather than by teapill, tablet, capsule, or granule. (H. Luo et al., 2012) tried to compare effectiveness between decoction and granule but due to the poor quality of studies available was unable to reach a conclusion if one were superior over the other. Their group proposed favoring granules as they were perhaps easier to standardize and could be manufactured by well-regulated pharmaceutical companies. While (Flower et al., 2012) sited research done earlier in 2006 and 2009 suggesting chromatographic evidence that the level of known active compounds was reduced in the manufacturing process of granules. He therefore advocated for firstly using decoctions in CHM research whenever plausible. This researcher would strongly suggest that the traditional decoction method be maintained in modern research as it has been used clinically for well over two millennium. There are also conflicting beliefs whether it matters if individual granule ingredients were mixed post production or if it is better to create the formulas prescription by cooking all ingredients together and then creating the resulting granules. If another method such as granule or tablet were used and the results were unfavorable to CHM, Chinese medical clinicians might wonder about the potency of these less traditional methods and question the validity of the results. If granules are to be used for convenience a higher dose than what is currently prescribed in the United States should be utilized in order to better approximate the potency of decoction. American practitioners of Chinese medicine routinely dose 9-10 grams a day while in Taiwan and Japan they may dose 12-18 grams. Nine to ten grams

may be ineffective to bring about a therapeutic effect.

While designing a CHM study, a sceptic of Chinese medicine may debate whether it is necessary to use Chinese medical diagnostic techniques. This researcher's view is that (M. Jiang et al., 2012)'s discussion about the importance of 辨證論治 "Bian Zheng Lun Zhi", treatment based on syndrome differentiation , is the paramount truth when the author states that, "Correct TCM syndrome differentiation is the most important principle that guides the prescribing of Chinese herbal formulae". As two different Chinese medical diagnoses for the same Western disease name may necessitate different treatment principles and correspondingly different medicinal agents, a proper diagnosis is essential. Failing to use proper Chinese medical syndrome/pattern differentiation may lead to less satisfactory results for patients and equal or worse may lead our Western counterparts to conclude that CHM is ineffective. Modern Chinese medical research must remain true to its roots if it is to give its best to the world. Prescribing herbs without utilizing CHM diagnostic methods is on par with a western trained physician indiscriminately prescribing drugs for one condition without first completing her own diagnostic assessment. Neither practitioner would do this in their own clinical setting and so research should parallel true medical practice. Chinese medicine must not be watered down to solely seeking active ingredients and investigating -omics. This researcher suggests that prior to designing a study on CHM a thorough review should be made of the two articles, *Guidelines for randomised controlled*

trials investigating Chinese herbal medicine (Flower et al., 2012) and *Syndrome differentiation in modern research of traditional Chinese medicine* (M. Jiang et al., 2012).

This researcher would suggest including Chinese medical diagnoses as possible inclusion criteria for the patients which would serve to guide the treatment principle of the herbal prescriptions. Furthermore, while Chinese medicine traditionally writes a prescription for the unique patient, this will likely not be possible in a trial setting. Rather a compromise could be that the research carried out uses fixed base herbal prescriptions for various phases of pretreatment, IVF, and post transfer but allows for 1-2 ingredients to be added as per the patients individualized diagnosis. For instance, everyone in the study might have underlying diagnosis of Kidney Yang Deficiency, but if Liver Qi Stagnation and anxiety were present Chai Hu and Suan Zao Ren might be added, Kidney Yin Deficiency add Nu Zhen Zi and Han Lian Cao, Spleen Qi Deficiency Bai Zhu, Dang Shen are added, Blood Stasis Chuan Xiong and Dan Shen would be added and so on.

This research suggestion will require several years and to follow up until live birth for a sufficiently large size will be expensive. Recruiting sufficient number of patients to enroll in the trials who would consent not to receive acupuncture will also be a challenge in the U.S. where acupuncture is the better known of two Chinese medical modalities. This researcher suggests reaching out to Chinese herbal manufacturers and distributers, Chinese medical schools with doctoral programs which concentrate on

women's health, to the Board as well as members of the American Board of Chinese Reproductive Medicine (ABCRM), as well as universities which have programs in reproductive endocrinology as possible sources of financial backing. A multicenter study would be able to more quickly pull numbers of eligible patients together than a single center study. It would be advisable to contact some of the larger chains of fertility centers such as Shady Grove, CCRM, and CNY to inquire if they would be interested in contributing to funding as well as becoming a participating trial center.

The practice of Chinese medicine in the West is truly a multi-faceted approach which often includes both acupuncture and herbal medicine. Once a systematic study is made of which herbal prescriptions and modifications are most beneficial for patients undergoing IVF it would be logical to repeat the process in trying to determine which acupuncture is best. Eventually trials could be carried out that attempt to use best practices for CHM + acupuncture to perhaps synergistically improve outcomes in a way that might be superior to if only one were used. An end goal could be a 4-arm study in which all patients receive IVF and are randomized into one of 4 treatment groups: CHM + IVF, Acupuncture + IVF, CHM + Acupuncture +IVF, IVF with no supplemental Chinese medical treatment. Ideally, the final study would allow for some individualization of treatment strategy based on Chinese medicine's paradigm of suiting the treatment to Chinese medical differential diagnosis.

Conclusion:

The efficacy and safety of Chinese herbal medicine on key outcomes in women undergoing IVF is statistically significant, or at times falling short demonstrates a trend towards significance. As the level of most evidence was low by international standards, further large-scale, RCTs and other high-quality quasi-experimental designed studies with rigorous methodologies are needed to confirm this conclusion. The quality of studies scored ranged from low, moderate, to high and can be read above in Chapter 4 Results under the heading "Quality of the CHM for IVF Studies Included". This researcher recommends that such research be carried out collaboratively with those who have backgrounds in Western reproductive medicine and Chinese reproductive medicine. Furthermore, in keeping with long standing historical usage and modern clinical practice, such research whenever possible should include the inclusion of Chinese medical differential diagnoses as well as modifications of prescriptions which suit an individual's symptoms or pattern presentation.

Although the overall quality of available studies on the topic of CHM and IVF is poor, the results seem to consistently demonstrate benefit and therefore merit further exploration. Overall, the studies showed improvements in the quality of egg and embryos, fertilization rates, pregnancy rates, one study showed statistically fewer miscarriages, and various mechanisms of action were explored. Risks assumed by some such as increasing the incidence of OHSS or abortion rate do not seem to be supported by the available evidence. Patients and fertility clinics are continually in search of tools

to improve their outcomes. Chinese medicine has a long history of helping women conceive which in itself demonstrates both efficacy and safety. This work may serve as starting point for Chinese medical providers to discern which herbal approach to take and what time is required. The paper will help the Chinese medical practitioner in outreach to potential Western partnerships for both clinical and research endeavors. It is this researcher's hope that practitioners of both Western and Chinese reproductive medicine will come together to review this work and see that there is great promise in combining to two systems of medicine. With patience and collaboration, over time the wisdom of how Chinese medicine works may be discovered and further refined so that more patients may find success on their long and often difficult journey.

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