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Complementary and Alternative Therapy with Traditional Chinese Medicine for Infertility

Yen-Nung Liao, Wen-Long Hu and Yu-Chiang Hung

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Abstract

Infertility results in a country with a low birth rate and an aging population, and thus there is vested interest in treating this problem by using both complementary and alternative therapies, in addition to conventional western medicine. Traditional Chinese medicine (TCM) has been widely used for healthcare in the Eastern world for thousands of years. This chapter describes the evidence to support the role of TCM in the management of male and female infertility.

Keywords: complementary and alternative therapy, traditional Chinese medicine, acupuncture and moxibustion, infertility

1. Introduction

1.1. Definition

Normal fertility was previously defined as the ability to conceive within 2 years of regular unprotected sexual intercourse [1, 2]. Recently, infertility has been defined as failure to conceive within 1 year of regular unprotected sexual intercourse in women less than 35 years old, or within 6 months of unprotected sexual intercourse in women older than 35 years old [2, 3].

1.2. Epidemiology

According to a World Health Organization (WHO) report, the prevalence of infertility has increased since 1990, and the most recent data from 2010 estimated the worldwide incidence of infertile couples to be approximately 48.5 million (**Figure 1**) [4]. In the United States, the

percentage of married women aged 15–44 years old who were infertile decreased from 8.5% in 1982 (2.4 million women) to 6.0% (1.5 million) in 2006–2010 [5]. In Taiwan, the total female fertility rate decreased from 7.04 million in 1951 to 1.175 million in 2015 [6]. Taiwan has thus become one of the countries with the lowest fertility rates in the world. In China, the 1- and 2-year infertility rates in newly married couples were 12.5 and 6.6%, respectively [7]. In 2004, a WHO evaluation of Demographic and Health Surveys (DHS) data estimated that more than 186 million ever-married women of reproductive age were infertile, translating into one in every four couples [8].

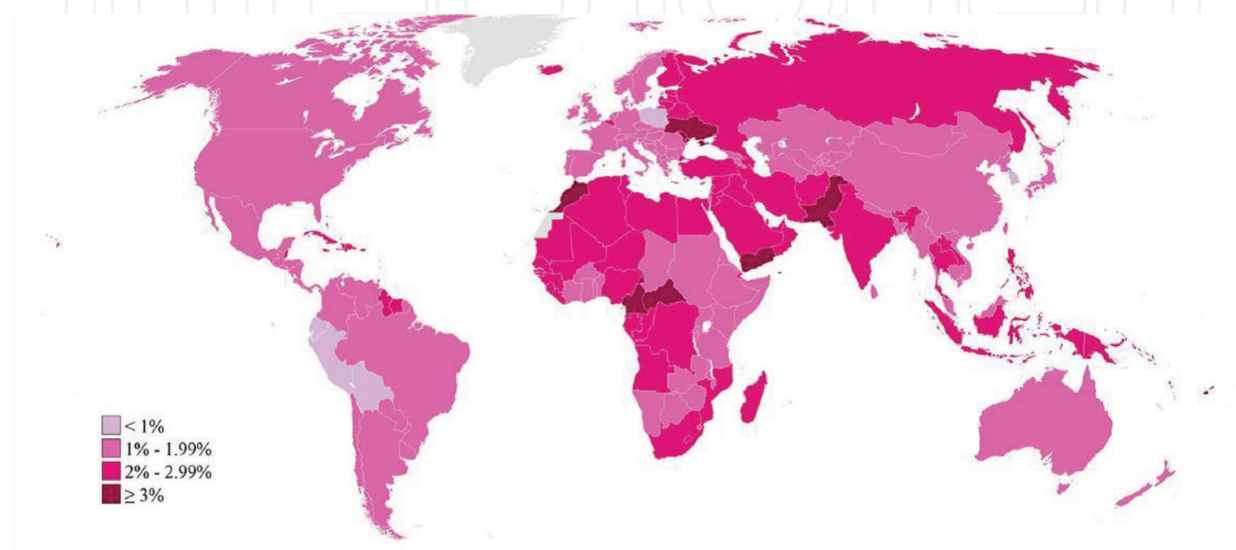


Figure 1. Worldwide prevalence of primary female infertility (2010). Infertility prevalence is indexed based on the age of the female partner; age-standardized prevalence among women aged 20–44 years old is shown here [4].

1.3. Impact

A low fertility rate results in a low birth rate and an aging country. According to the Taiwan Population Policy White Paper, the total population of Taiwan is expected to decrease after 2022 [9]. A review showed that infertility or subfertility is associated with intimate partner violence (IPV) in low- and middle-income countries (LMICs) [10]. Certain fertility treatments may increase the risk of ovarian or breast cancer [11, 12], while others have poor pharmacological efficacy in infertile women older than 40 years [13]. Around one-fifth of all subfertile couples seeking fertility treatment have clinically significant levels of depression, anxiety, and suffering, but the effects of educational and psychological interventions on mental health outcomes and pregnancy outcomes including distress, and live birth or ongoing pregnancy rates, is unclear owing to the very low quality of evidence [14].

2. Etiology

Around 15% of couples have difficulty conceiving [15]. The etiology of infertility can be broadly classified into female- and male-related factors. Among distinguishable female fac-

tors, which are responsible for 81% of female infertility, the most common are ovulatory disorders (25%), endometriosis (15%), pelvic adhesions (12%), tubal blockage (11%), other tubal abnormalities (11%), and hyperprolactinemia (7%) [16]. Male factor infertility affects around 30–55% of all couples and is the most difficult form of infertility to treat [17]. The causes of male infertility include environmental disruptors, genetic defects, physiological and endocrine failure, and testicular pathologies [18].

According to the theory of traditional Chinese medicine, syndromes of female infertility can be classified as the following: kidney deficiency, stagnation of liver qi, static blood blocking in uterine, and accumulation of phlegm-wetness in the body. Constitution has a great effect on the syndrome patterns of many diseases including infertility. A report showed that the constitution ratio of yang deficiency, phlegm damp, and yin deficiency was 29.5, 20.0, and 21.0%, respectively, in sterility patients [19]. This report also pointed that kidney deficiency syndrome was positively correlated with yin deficiency and yang deficiency constitution, blood stasis syndrome was positively associated with blood stasis and yang deficiency constitution, and liver stagnation syndrome was positively correlated with phlegm damp and damp heat constitution.

2.1. Ovulatory disorders

A history of regular menses with molimina (breast tenderness, bloating, cramping, mood changes) is suggestive of ovulation in the majority (95%) of women [20]. Anovulation and oligo-ovulation lead to infertility because an oocyte is not available every month for fertilization. A woman's fecundability reaches a peak in her late-twenties and decreases with advancing age, with a more rapid decline after her mid-thirties [21]. Ovarian ageing causes a progressive loss of the finite pool of primordial follicles and a decrease in the quality of oocytes, mainly because of the accumulation of chromosomal abnormalities [22]. Polycystic ovarian syndrome (PCOS) is a common ovulatory disorder, and patients with this diagnosis are often obese and oligomenorrheic. They tend to have difficulty conceiving owing to ovulatory dysfunction as well as poor oocyte quality and endometrial receptivity [23]. However, the results of epidemiologic data obtained mainly from comparative studies and cohorts, have concluded that the role and size (<6 cm) of ovary cysts in infertility is controversial [24].

2.2. Endometriosis

The rate of infertility among women with endometriosis ranges from 30 to 50%, and dysfunction is due to various mechanisms including pelvic adhesions, abnormal tubal transport, implantation defects, and intraperitoneal inflammation, which can decrease oocyte quality or oocyte-sperm interactions [25].

2.3. Pelvic adhesions

Most adhesions occur after surgical procedures, but can also occur following infection, ischemia, endometriosis, or reaction to a foreign body, and these cause infertility by distorting pelvic anatomy and by blocking the fallopian tubes [26]. Peritubal adhesions negatively affect ovum transportation, while periovarian adhesions inhibit ovum release and ovulatory function [27, 28].

2.4. Tubal blockage and other tubal abnormalities

Tubal anomalies that contribute to infertility include congenital absence and major diverticula, duplication of the tubes, tubal occlusion, and hydrosalpinx [29, 30]. Other causes of tubal infertility include endometriosis, intrauterine contraceptive devices, infections (gonorrhea, chlamydia trachomatis, and genital tuberculosis), and postoperative complications of abdominal surgery [31].

2.5. Hyperprolactinemia

Symptoms of hyperprolactinemia include amenorrhea, oligomenorrhea, infertility, decreased sexual desire, and habitual abortion. Women may also have signs of chronic hyperandrogenism such as acne and hirsutism, which may be related to increasing dehydroepiandrosterone sulfate (DHEAS) secretion from the adrenal glands [32].

3. Diagnosis

History taking and physical examination are paramount to understanding the etiology of the infertility, and should be undertaken in both partners after 1 year of trying to conceive. In certain cases, investigation is indicated after 6 months of unprotected intercourse, such as when the female partner is over 35 years old or has a history of oligomenorrhea or amenorrhea, known or suspected endometriosis or tubal disorders, a past history of chemotherapy or radiation therapy, and in couples in which the male partner is known to be subfertile.

3.1. History taking

A menstrual history (menstrual interval and characteristics) should be elicited in all female patients in order to understand their ovulatory cycles. For instance, regular monthly cycles with premenstrual symptoms (breast tenderness, ovulatory pain, bloating) suggest that the patient is ovulating, whereas severe dysmenorrhea may indicate endometriosis.

A personal and lifestyle history should also be obtained from all infertile couples, including details about occupations; ages; stressors; levels of exercise; diets; and consumption of alcohol, tobacco, and other substances which can influence fertility [33]. It is also important to take a sexual history, including an evaluation of the frequency of intercourse and of underlying problems such as sexual dysfunction. Infrequent or inappropriately timed sexual intercourse can result in infertility.

Clinicians should elicit a full medical, surgical, and obstetric history including information about the number of previous pregnancies, type and number of deliveries, and number of abortions (including spontaneous and induced) [32]. A gynecological history should evaluate any history of pelvic inflammatory disease, sexually transmitted infections, and treatment of abnormal pap smears, as well as uncover any history of procedures or medications, which could be related to infertility. In addition, a review of systems should be conducted in order to evaluate whether a patient has symptoms of dyspareunia, hypo-/hyperthyroidism, pelvic or abdominal pain, galactorrhea, or hirsutism [34].

A family history of infertile couples should record in detail whether any family members have birth defects, mental retardation, genetic mutations, or fertility issues. The most common inherited cause of infertility is fragile X syndrome, which presents as premature ovarian failure (POF) in women, and which can lead to developmental delay or learning problems in men [35].

3.2. Physical examination

The physical examination can uncover signs indicative of latent causes of infertility. The patient's body mass index (BMI) and fat distribution should be measured and calculated, as an abnormally low BMI is related to infertility, whereas abdominal obesity is associated with insulin resistance [34].

In women, the presence of vaginal and cervical discharge or anatomic abnormalities may indicate an underlying infection or Müllerian anomaly, respectively. If the uterus is enlarged, irregular, or lacks mobility, this may suggest the presence of a uterine abnormality such as endometriosis, leiomyoma, or pelvic adhesions. Chronic pelvic inflammatory disease or endometriosis presents with tenderness, or with masses in the adnexa or posterior cul-de-sac (pouch of Douglas), while endometriosis also has palpable tender nodules at the rectovaginal septum or uterosacral ligaments [35].

Patients with Turner syndrome have absent periods, and distinctive morphological features including a squarely shaped chest, and a stocky, short body habitus. Those with hypogonadotropic hypogonadism have primary amenorrhea and unremarkable secondary sexual characteristics. The presence of galactorrhea, thyroid gland anomalies, or signs of androgen excess such as acne, hirsutism, virilization, and male pattern baldness indicate an endocrinopathy (e.g., polycystic ovarian syndrome, adrenal disorders, hyper- or hypothyroidism, hyperprolactinemia) [33, 35].

In men, anatomic abnormalities or discharge from the penis, scrotum, and urethral meatus may indicate the presence of an inguinal/femoral/scrotal hernia, cryptorchidism, or infection. Varicoceles, usually noted on the left side, are associated with infertility, whereas small, hard testes (<2 cm long) are suggestive of Klinefelter's syndrome [36].

3.3. Other diagnostic methods

Additional essential infertility evaluations include semen analyses, assessment of ovulatory function by laboratory tests, and a hysterosalpingogram to uncover underlying uterine abnormalities and evaluate tubal patency.

Diagnostic laparoscopy is recommended for women with suspected pelvic adhesions or endometriosis, during which chromotubation can assess tubal patency and hysteroscopy can assess the uterine cavity [29, 30].

Women older than 35 years and those younger but with risk factors for POF should measure estradiol and follicle-stimulating hormone (FSH) levels on day 3 in order to evaluate the ovarian reserve. Other tests such as antral follicle count, level of anti-Müllerian hormone (AMH), and the clomiphene citrate challenge test (CCCT) should be performed if necessary [35].

4. Conventional treatments and limitations

Assisted reproductive technology (ART), such as artificial insemination (AI), *in vitro* fertilization and embryo transfer (IVF-ET), and intracytoplasmic sperm injection (ICSI), is responsible for up to 4% of infants born in developing countries.

ART has several iatrogenic complications including the risk of multiples, low luteal phase insufficiency, disabled embryo implantation, ovarian hyperstimulation syndrome (OHSS), and other perinatal and long-term health conditions [37]. Furthermore, fertility treatments, especially IVF-ET and ICSI, are costly and risky [38].

Intra-uterine insemination (IUI), one form of AI, is a commonly used fertility treatment for couples with cervical factor infertility, unexplained subfertility, and subfertility in women with endometriosis after surgical resection [39]. IUI is more useful in some types of severe sexual dysfunction such as severe ejaculatory dysfunction or vaginismus; in cases of cervical factor or mild male factor infertility; and to prevent the transmission of sexually transmitted diseases such as hepatitis B/C virus (HBV/HCV) and human immunodeficiency virus (HIV) [40].

It is a relatively simple surgical procedure whereby semen that has been washed in the laboratory is inserted into the uterine cavity by using a small catheter at the time of ovulation. IUI allows sperm to bypass the potentially hostile cervix, and thus increases the number of sperm that reach the uterine cavity and oocyte [40]. The technique can be performed either with or without added medications to encourage ovarian hyperstimulation (OH). In the latter method, follicular growth is monitored either via regular ultrasound monitoring to visualize the follicles or by measuring the preovulatory luteinizing hormone level rise in the serum or urine. In the former, ovulation is induced by an injection of human chorionic gonadotropin (hCG). Timed intercourse (TI), a less invasive method than IUI, involves giving couples information about cycle monitoring so that they can time intercourse appropriately.

Nevertheless, a systematic review revealed that there is no difference in live birth or multiple pregnancy rates in most couples with unexplained subfertility treated with either IUI or TI, both with and without OH [39].

5. Traditional Chinese medicine

Traditional Chinese medicine (TCM) formulas have been used to treat female and male infertility for hundreds of years. Classically, the TCM formulas are combined with several single herbs to treat a specific disease. Some of the single herbs that have been used in women include Semen Cuscutae, Semen Lantaginis, Herba Leonuri Japonici, and Fructus Ligustri Lucidi, and were first recorded in the Chinese classic Shi Jing (the Book of Songs) over 2000 years ago.

5.1. Female infertility

The results of one systematic review revealed that treatment with Chinese herbal medicine can increase pregnancy rates 2-fold in a 4-month period compared to western fertility drugs

or IVF [41]. This report also stated that evaluating the quality of the menstrual cycle is essential in order to effectively treat female infertility by TCM. However, in a recent well-controlled clinical trial, there was no significant difference in fertility outcomes after laparoscopy between women with minimal/mild endometriosis treated with oral contraceptives (OC), or OC and Dan&e mixture (composed of six herbs) [42]. A study from the National Health Insurance Research Database (NHIRD) in Taiwan has revealed the most commonly used TCM formulas for the management of female infertility [43]. At the top of the list are Dang-Gui-Sha-Yao-San and Wen-Jing-Tang; the former is used for abdominal pain during pregnancy, while the latter is used for dysmenorrhea and infertility, and acts by promoting blood circulation to prevent blood stasis, by warming the meridians to dissipate cold, and by tonifying qi to nourish the blood. The herbal formulas and single herbs commonly used for the treatment of female infertility are described below. The effects of these herbs on the endocrine regulation effects of the menstrual cycle and the ovulation rate will also be explored. Other commonly prescribed formulas that are used to relieve infertility-related symptoms and diseases such as premenstrual syndrome (Jia-Wei-Xiao-Yao-San), irregular menstrual cycles (Zou-Gui-Wan, You-Gui-Wan), uterine fibroids (Gui-Zhi-Fu-Ling-Wan), diarrhea during menstruation (Shen-Ling-Bai-Zhu-San), dysmenorrhea (Shao-Fu-Zhu-Yu-Tang), abnormal uterine bleeding (Gui-Pi-Tang), amenorrhea, or oligomenorrhea (Si-Wu-Tang), do not fall within the scope of this review.

5.2. Male infertility

A recent study revealed that changes in the metabolic pathways, which regulate aromatic amino acids, tricarboxylic acid cycle, and sphingolipid metabolism may play an important role in the origin of Kidney-Yang deficiency syndrome (KYDS)-associated male infertility [44]. This research offered a new way for metabolomics analysis of seminal plasma to differentiate TCM syndromes of infertile males. The Chinese medicine Huzhangdanshenyin is used for male immune-factor infertility and has been shown to be more effective than prednisone [45]. The medicine works by improving the antisperm-antibody-reversing ratio; and ameliorating sperm indexes such as sperm motility, viability, and density, without severe adverse effects. Another Chinese medicine, Bushen Shengjing Decoction (BSSJD), has the effect of decreasing semen levels of reactive oxygen species (ROS), improving the quality of sperm, and increasing the natural fecundity of patients with severe oligospermia and azoospermia (SOA), thus raising the viability of their sperm in order to increase the ovarian fertilization rate and clinical pregnancy rate in ICSI cycles [46].

5.3. Chinese herbal formulas for infertility

5.3.1. *Dang-Gui-Sha-Yao-San*

Dang-Gui-Sha-Yao-San consists of *Angelicae sinensis Radix*, *Paeoniae Radix*, *Poriz*, *Atractylodis ovatae Rhizoma*, *Alismatis Rhizoma*, and *Ligustici Rhizoma*. According to the principles of TCM, Dang-Gui-Shao-Yao-San has the effect of nourishing liver blood, invigorating the spleen, and eliminating wetness. A previous study which used a Grading of Recommendations Assessment, Development and Evaluation method (GRADE) to evaluate

the quality of evidence for Dang-Gui-Sha-Yao-San concluded that this formula was likely to be beneficial and safe for the treatment of primary dysmenorrhea [47]. Another clinical study showed that it may be useful for resolving the symptoms of mild or moderate hypochromic anemia secondary to uterine myoma-induced menorrhagia [48].

5.3.2. *Wen-Jing-Tang*

Wen-Jing-Tang consists of Cinnamomi Ramulus, Evodiae Fructus, Ligustici Rhizoma, Angelicae sinensis Radix, Paeoniae Radix, Zingiberis Rhizoma Recens, Moutan Radicis Cortex, Ophiopogonis Tuber, Pinelliae Tuber, Ginseng Radix, Glycyrrhizae Radix, and Asini Corii Gelatinum. According to the principles of TCM, Wen-Jing-Tang has the effect of promoting blood circulation to dispel blood stasis, of dispelling cold by warming the meridians, of benefiting qi, and of nourishing the blood. Wen-Jing-Tang has been shown to effectively regulate endocrine conditions such as plasma LH and estradiol levels in PCOS patients with ovulatory dysfunction without taking eight-principle pattern identification into consideration. The study concluded that Wen-Jing-Tang can be used to treat PCOS in women with various constitutions (as determined by the matching theory of eight-principle pattern identification) in clinical management [49]. Another report showed that combined therapy with Wen-Jing-Tang and clomiphene induced ovulation without OHSS in infertile patients who did not respond to clomiphene citrate alone [50].

5.3.3. *Jia-Wei-Xiao-Yao-San*

Jia-Wei-Xiao-Yao-San consists of Moutan Radicis Cortex, Radix Paeoniae Rubra, Bupleuri Radix, Angelicae Sinensis Radix, Atractylodis Ovatae Rhizoma, Poria, Glycyrrhizae Radix, Zingiberis Rhizoma Recens, and Menthae Herba. According to the principles of TCM, Jia-Wei-Xiao-Yao-San disperses stagnated liver qi, suppresses heat, and nourishes the blood. According to the NHIRD in Taiwan, Jia-Wei-Xiao-Yao-San-based Chinese herbal medicine combinations were most frequently used for PMS and primary dysmenorrhea [51]. However, the exact mechanism whereby Jia-Wei-Xiao-Yao-San improves fertility is unclear. In one study, Jia-Wei-Xiao-Yao-San had no effect on serum levels of E2 and FSH, but did improve climacteric symptoms, especially in patients with hormone replacement therapy resistance who strongly complained of psychological symptoms [52]. These findings imply that Jia-Wei-Xiao-Yao-San may affect fertility via as-yet undiscovered mechanisms.

5.3.4. *You-Gui-Wan*

You-Gui-Wan consists of Rhizoma Rehmanniae Praeparata, Rhizoma Dioscoreae, Fructus Lycii, Fructus Corni, Eucommia ulmoides Oliv, Semen Cuscutae, Colla Cornus Cervi, Angelicae sinensis Radix, Radix Aconiti Praeparata, and Cinnamomum cassia Blume. According to the principles of TCM, You-Gui-Wan acts by gently reinforcing the Kidney-Yang, supplementing body essence, and replenishing blood. Previous research has shown that You-Gui-Wan medicated serum can significantly increase the percentage of mature oocytes, and modulate mRNA expression of a number of signaling molecules including protein kinase A (PKA), cAMP-response element binding protein (CREB), mitogen-activated protein kinases (MAPK), protein kinase C (PKC), protein kinase G (PKG), maturation promoting factor (MPF), as well

as concentrations of cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), and nitric oxide (NO) [53]. It has also been reported that patients treated with You-Gui-Wan had higher rates of successful IVF compared to those treated with FSH (with or without normal serum). In animal studies, You-Gui-Wan has been shown to increase sperm fertilizing ability by increasing sperm acrosin activity and promoting the acrosome reaction, which resulted in a higher percentage of zygotes in mice treated with You-Gui-Wan compared to control mice [54].

5.3.5. *Zou-Gui-Wan*

Zou-Gui-Wan consists of Colla Cornus Cervi, Colla Plastris Testudinis, Rhizoma Rehmanniae Praeparata, Rhizoma Dioscoreae, Fructus Lycii, Fructus Corni, Radix Cyathulae, and Semen Cuscutae. According to the principles of TCM, You-Gui-Wan gently reinforces the Kidney-Yang, supplements body essence, and replenishes the marrow. Zou-Gui-Wan has also been shown to affect gene expression within germ cells, whereas You-Gui-Wan has stronger effects on estradiol production during the differentiation of stem cells derived from human first trimester umbilical cords into oocyte-like cells *in vitro* [55]. Another report showed that Zou-Gui-Wan promptly and effectively restores ovarian function in patients with POF after failed treatment with clomiphene citrate for 8 months [56].

5.4. Single Chinese herbs for infertility

5.4.1. *Herba Cistanche*

Herba Cistanche, also called Rou Cong Rong in Chinese, originated from Cistanche deserticola Y.C. Ma. According to the principles of TCM, Herba Cistanche invigorates the kidney-yin, and replenishes the vital essence and the blood. It is used as a roborant in a formula for chronic renal disease, impotence, female infertility, morbid leucorrhea, profuse menorrhagia, and senile constipation [57]. It also controls the hypothalamic-pituitary-adrenal (HPA) and HPG axes, which may induce a balanced and smooth sexual energy effect [58]. Herba Cistanche also has aphrodisiac effects and can increase serum levels of progesterone and testosterone, improve sperm count and sperm motility, and decrease the number of abnormal sperm [59].

5.4.2. *Semen Cuscutae*

Semen Cuscutae, also called Tu Si Zi in Chinese, originated from Cuscuta chinensis Lam. According to the principles of TCM, Semen Cuscutae tonifies the kidney and is also believed to arrest spontaneous emission and prevent abortion. It has a multitude of other uses, including antiaging and anti-inflammatory, antiabortifacient, and aphrodisiac, among others [60]. One study has demonstrated that flavonoids obtained from semen cuscutae (FSCs) can be used in the treatment of ovarian endocrine dysfunction in psychologically stressed rats through increasing luteinizing hormone receptor (LHR) expression in the ovaries and estrogen receptor (ER) expression in the hippocampus, hypothalamus, and pituitaries, but without any effect on follicle-stimulating hormone receptor (FSHR) expression in the ovaries [61]. Another study demonstrated that total flavones from semen cuscutae (TFSC) treatment can improve Kidney-Yang deficiency symptoms by recovering the levels of testosterone and increasing androgen receptor (AR) mRNA and protein expression in the testicles and kidneys [62].

5.4.3. *Herba Leonuri Japonici*

Herba Leonuri Japonici, commonly called Chinese motherwort, originated from *Leonurus japonicus* Houtt (Labiatae). Related variants of this species include *Leonurus sibiricus* auct. pl., *Leonurus artemisia* (Lour.) S.Y. Hu., *Leonurus heterophyllus* sweet, and *Stachys artemisia* Lour [63]. According to the principles of TCM, *Herba Leonuri Japonici* promotes blood flow to regulate menstruation and induces diuresis to alleviate edema. It is also referred to as *Yi Mu Cao* in Chinese, which translates literally into “beneficial herb for mothers,” and is used to manage dysmenorrhea, amenorrhea, menoxenia, lochia, edema, and other gynecological problems but is contraindicated in pregnancy due to the possibility of stimulating the uterus [63]. The aqueous extract from the aerial part of *Leonurus artemisia* has the potential to treat dysmenorrhea by increasing the serum progesterone level, inhibiting inflammation, relaxing uterine spasms, and decreasing prostaglandin F2 α (PGF2 α) and prostaglandin E2 (PGE2) concentrations in uterine smooth muscle [64].

6. Acupuncture and moxibustion

As with TCM and single Chinese herbal therapy, acupuncture and moxibustion have also been used to treat female or male infertility for hundreds of years. Traditionally, acupuncture and moxibustion were performed by inserting needles or burning moxa sticks into specific points (acupoints) on the meridians. Acupuncture and moxibustion work by regulating energy flow, also called *Qi* in Chinese, over the meridians. Newer therapeutic methods include electro-acupuncture (EA), laser-acupuncture, burning moxa granules on the top of the needles, points pasting, and far-infrared moxibustion. Some meridians or acupoints have been indicated for the management of gynecological or obstetric problems, and these include Taichong (LR 3), Taixi (KI 3), Sanyinchiao (SP 6), and Gongsun (SP 4). These points were the earliest recorded in the Chinese classic *Huangdi Neijing* (the Classic of Inner Canon of Huangdi) around the time of the Han dynasty, and in the Chinese classic *Zhenjiu Jiayi Jing* (the A-B Classic of Acupuncture and Moxibustion) during the Jin dynasty.

6.1. Male infertility

Gonadotropin-releasing hormone (GnRH) is released by the hypothalamus and stimulates ovulation and sperm production in women and men, respectively. Thus, its deficiency contributes to both male and female infertility [65]. One study showed that repeated EA on the arcuate nucleus (Arc) can regulate the function of the HPG axis by suppressing Arc discharge, serum testosterone, sperm count, and GnRH mRNA expression [66]. Therefore, electrical stimulation may be an effective alternative to medications to regulate the HPG axis [67]. Another clinical trial in humans showed that 10-Hz EA stimulation of the abdominal acupuncture points ST-29 (guilai) increased testicular blood flow (TBF), but simple needle insertion and 2-Hz EA stimulation did not [68]. The combination of acupuncture and moxibustion treatment has also been shown to increase the percentage of normal-form sperm in infertile patients with oligoastenoteratozoospermia in a prospective, controlled, and blinded study, but the mechanisms remain unknown [69]. Another study revealed that acupuncture can improve

quick sperm motility, increase the normal sperm ratio, and improve fertilization rates and embryo quality in cases of idiopathic male infertility with failed ICSI [70]. According to the results of a systemic review from China regarding the treatment of male infertility, acupuncture appears to be as effective as TCM and more effective than western medicine alone, and its ability to improve sperm concentration and increase the level of grade a pulse b sperm is increased when applied together with either TCM or western medicine [71].

6.2. Female infertility

There is evidence to suggest that acupuncture stimulation of acupoints of the conception vessel, spleen, kidney, and bladder meridians improves clinical symptoms in patients with diminished ovarian reserve (DOR), and also lowers serum FSH, LH, and estradiol [E(2)] levels through regulation of the hypothalamic-pituitary-ovarian (HPO) axis [72]. A randomized, prospective, controlled clinical study revealed that acupuncture during the luteal phase of IVF/ICSI cycles increased clinical pregnancy and ongoing pregnancy rates [73]. Acupuncture improves IVF outcomes through four potential mechanisms: (1) by increasing blood flow to the uterus; (2) by regulating neuroendocrinological factors and the ovaries; (3) by modulating cytokine levels; and (4) by decreasing levels of anxiety, stress, and depression [74]. A successful pregnancy relies on the presence of adequate uterine blood flow and endometrial thickness, and these factors are especially important in pregnancies conceived through IVF and ET [67]. A study of infertile women with a high pulsatility index (PI) and downregulated with a GnRH analog to exclude any fluctuating endogenous hormone effects on the PI, revealed that EA reduced uterine artery blood flow impedance [75]. However, the literature on the efficacy of acupuncture treatment for endometriosis, immune and pelvic inflammatory disease-related infertility or subfertility is sparse. One study on women with steroid-induced polycystic ovaries demonstrated that EA modulates the neuroendocrinological state of the ovaries by inhibiting endothelin-1 and nerve growth factor (NGF), and NGF mRNA expression, most likely by modulating sympathetic activity in the ovaries [76]. Another similar study on estradiol valerate-induced polycystic ovaries demonstrated that EA treatments change the neuroendocrinological state in the ovaries by suppressing corticotropin-releasing factor, which may play an important role in reproductive failure [77]. Finally, the results of the Fertility Problem Inventory (FPI) and Beck Anxiety Inventory (BAI) questionnaires revealed that women suffer greater anxiety and sexual infertility stress than men [78]. High levels of stress affect female hormone levels and disrupt ovulation by affecting the HPO axis [67]. These studies all highlight a need for additional research into the potential benefits of acupuncture and moxibustion for the management of infertile patients.

7. Conclusions

Infertility results in a country with a low birth rate and an aging population, and thus there is vested interest in treating this problem by using both complementary and alternative therapies, in addition to conventional western medicine. There is increasing scientific evidence to support a role for TCM in the management of male and female infertility, but further studies are needed to elucidate the efficacy of this alternative therapy.

Abbreviations

AI	artificial insemination
AMH	anti-Müllerian hormone
AR	androgen receptor
ART	assisted reproductive technology
BAI	Beck Anxiety Inventory
BMI	body mass index
BSSJD	Bushen Shengjing Decoction
cAMP	concentrations of cyclic adenosine monophosphate
CCCT	the clomiphene citrate challenge test
cGMP	cyclic guanosine monophosphate
CREB	cAMP-response element binding protein
DOR	diminished ovarian reserve
E2	estradiol
EA	electro-acupuncture
ER	estrogen receptor
FPI	Fertility Problem Inventory
FSCs	flavonoids from Semen cuscuteae
FSH	follicle-stimulating hormone
FSHR	follicle-stimulating hormone receptor
GnRH	gonadotropin-releasing hormone
GnRHa	gonadotrophin-releasing hormone analogue
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBV/HCV	hepatitis B/C virus
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HPG	hypothalamic-pituitary-gonad
ICSI	intracytoplasmic sperm injection
IUI	intra-uterine insemination
IVF-ET	<i>in vitro</i> fertilization and embryo transfer
KYDS	Kidney-Yang deficiency syndrome
LH	luteinizing hormone
LHR	luteinizing hormone receptor
MAPK	mitogen-activated protein kinases
MPF	maturation-promoting factor

mRNA	messenger ribonucleic acid
NGF	nerve growth factor
NHIRD	National Health Insurance Research Database
NO	nitric oxide
OCs	oral contraceptives
OH	ovarian hyperstimulation
OHSS	ovarian hyperstimulation syndrome
Pap	Papanicolaou
PCOS	polycystic ovary syndrome
PGE2	prostaglandin E2
PGF2 α	prostaglandin F2 α
PHA	hypothalamic-pituitary-adrenal
PKA	protein kinase A
PKC	protein kinase C
PKG	protein kinase G
PMS	premenstrual syndrome
POF	premature ovarian failure
ROS	reactive oxygen species
SOA	oligospermatism and azoospermia
TBF	testicular blood flow
TCM	traditional Chinese medicine
TFSC	total flavones from Semen cuscutae
TI	timed intercourse
WHO	World Health Organization

Author details

Yen-Nung Liao¹, Wen-Long Hu^{1, 2, 3} and Yu-Chiang Hung^{1, 4*}

*Address all correspondence to: hungyuchiang@gmail.com

1 Department of Chinese Medicine, Kaohsiung Chang Gung Memorial Hospital and School of Traditional Chinese Medicine, Chang Gung University College of Medicine, Kaohsiung, Taiwan

2 Kaohsiung Medical University College of Medicine, Kaohsiung, Taiwan

3 Fooyin University College of Nursing, Kaohsiung, Taiwan

4 School of Chinese Medicine for Post Baccalaureate, I-Shou University, Kaohsiung, Taiwan

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