

Note: For a general infertility background study, read from page 1 through 10.

Review of Traditional Chinese Medicine Herbal Treatment for Antisperm Antibody Associated Female Infertility

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OCOM DAOM CAPSTONE PROJECT

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Abstract

Background Infertile subjects possessing Antisperm Antibody (AsAb) are classified as having immunologic infertility. The AsAb-associated with infertility induces agglutination and/or immobilization of sperm. AsAb may be exhibited in sexes with a worldwide occurrence.

Purpose This paper investigates AsAb-associated female infertility and its Traditional Chinese Medicine (TCM) herbal treatment. The primary objective is to evaluate the efficacy of TCM herbal treatment in comparison with biomedical treatment, so that future studies of this subject can be justified; other objectives are to provide information and discussion for composing formulas to further enhance treatment efficacy, and to formulate more standardized and stringent design criteria for future clinical trials.

Subjects TCM Classics, TCM and biomedical texts, clinical trials and studies are the primary subjects for investigation.

Methods Biomedical and TCM etiology and pathogenesis, and TCM treatments of various types of female infertility are addressed for background knowledge. Biomedical etiology, pathology, and treatment for AsAb-associated female infertility are briefly addressed. Detailed, systematic review of nine current, clinical trials and studies of AsAb-associated female infertility with TCM herbal treatment in China are given; to ensure the quality of the review, inclusion and exclusion criteria for selecting the clinical trials or studies have been identified during the screening process.

Discussion Strengths and weaknesses of reviewed current clinical trials and studies have been identified. Efficacy, herb frequency (appearing in formulas) list, and differentiated TCM patterns of reviewed clinical trials and studies have been derived and compiled to evaluate the TCM herbal treatment efficacy, and to facilitate future studies for better treatment formulas. A set of design criteria for future clinical trials of AsAb-associated female infertility is proposed.

Conclusion According to the average cure rate (fertility rate) of the compiled efficacy statistics, it is concluded that, at the current stage, TCM herbal treatment is significantly better than the biomedical treatment, and therefore, further research and study on TCM treatment for AsAb-associated female infertility will be valuable for managing this disorder.

Key Words

AsAb, Female Infertility, TCM, Chinese Herbs

Introduction

Infertility is generally defined as the inability of a couple to conceive within a certain period of time—usually one year in the USA, and two years in China¹. Infertility is not exactly a disease. The treatment goal is quite definite—a successful childbirth. Time, or age, is considered as a negative factor against the infertility, especially for females over thirty-five. Anxiety, emotional stress, feelings of inadequacy, anger, guilt, and frustration are often seen in couples with infertility.

Infertility affects about one of five couples in the USA; its increasing incidence partly reflects deferment of marriage and of birth of the first child. Etiologic factors are sperm disorders (35% of couples), ovulatory dysfunction (20%), tubal dysfunction (30%), abnormal cervical mucus (5%), and unidentified factors (10%)². Among the 10% couples with unidentified factors, a fair number of the couples are widely believed to be AsAb - related.

Diagnosis and treatment of infertility require thorough assessment of both partners of a couple. The organization of the infertility evaluation is based on a consideration of various individual factors required for successful fertilization.

This paper adopts biomedicine's categorization for infertility, and investigates AsAb - associated female infertility and its possible treatment. Biomedical and TCM etiology, pathogenesis and treatments of various types of female infertility are addressed for background knowledge. Detailed review of current clinical trials and studies of AsAb - associated female infertility with TCM treatment in China are given. This paper intends to summarize the efficacy, TCM pattern, and herb frequency (appearing in formulas) statistics of reviewed studies to facilitate future studies for better treatment methods. After strengths and weaknesses of current clinical trials and studies have been identified, a set of design criteria for future clinical trials will be proposed. This paper also intends to compare the efficacy of TCM treatment and biomedical treatment.

The Biomedicine Overview of the Female Infertility

In general, female infertility is divided into primary infertility and secondary infertility. Primary infertility applies to those who have never conceived, and secondary infertility applies to those who have conceived at some time in the past.

Other than male partner's healthy sperm, female's normal ovulation cycle and adequate fertilization environment are two key elements required for a female to conceive. The goals of the infertility evaluation are to determine the probable cause of infertility,

provide accurate information about prognosis, and derive options for treatment. To assist the diagnosis process, menstrual history (including BBT chart), physical examination, lab test, and laparoscopy are often used. Each of the key etiological factors causing female infertility is addressed below.

Ovulatory Factors An ovulatory dysfunction is responsible for approximately 20 -25%³ of infertility cases. The problem should be investigated first by review of historical factors, such as the onset of menses, present cycle length, and presence or absence of premenstrual symptoms.

Age is a definite factor for declined ovulation. The function of a woman's ovaries starts to decline after about 40 years of age. This decline results in the production of lesser quality eggs. Fertilization of these eggs is more difficult, and usually they do not develop as well after fertilization. When the ovary function declines, follicle stimulating hormone (FSH) levels increase in order to stimulate ovulation, but the high FSH also makes pregnancy more difficult to achieve. Even when pregnancy does occur, it is usually more difficult for the woman to carry the embryo to term, and miscarriage often results. In addition, estrogen and progesterone levels decrease, causing a thinning of the endometrium. All these factors produce implantation difficulty for the embryo.

Other anovulatory factors include polycystic ovarian syndrome (PCOS), endometriosis, and hormonal changes such as high prolactin (PRL), and ovarian cyst. These factors may cause irregular menstruation, amenorrhoea, or heavy uterine bleeding, which will result in infertility.

Fallopian Tube Factors The fallopian tube blockage is a common cause for infertility. The blockage may prevent the sperm from fertilizing the egg, usually due to adhesions caused by infection, endometriosis, or cyst.

Uterine Factors Uterine fibroid may deform the uterine cavity, or block the interstitial parts of the tubes; as a result, the fertilized egg may not be able to move freely into the uterus. Small uteruses are also a cause for infertility, as they do not allow normal embryo growth.

Cervical Factors Myoma, polyps, and infections at the cervical area can narrow the entrance to prevent sperm from entering the uterus. Abnormal cervical mucus can also limit the mobility of sperm and cause infertility.

Other Minor Factors Abnormal constitution from trauma, infection, or congenital factors can definitely cause infertility. Depression and stress are more significant factors in modern society. Life style factors such as tobacco use and the consumption of alcohol, and environmental factors such as radiation or high temperature are also becoming influential to fertility.

Unexplained Infertility After completion of the basic evaluation, a probable cause of infertility should be apparent. However, as mentioned earlier, there are about 10% of

married couples in the USA have unidentified infertility causes. Among the 10% couples with unidentified causes, a fair number of the couples are widely believed, by many researchers, to be AsAb-related.

The TCM Overview of the Female Infertility

Finding TCM categories for female infertility is no different than finding TCM categories for other disorders, as they are categorized into patterns. Although the above biomedical factors do not usually translate directly into specific TCM categories of infertility, the symptoms they manifest are easily analyzed and categorized to fit a TCM diagnostic pattern. In the following section's discussion, we will find that the etiology and pathology of female infertility have been discussed exhaustively in TCM Classics, in terms of regulating menstruation, while contemporary studies emphasize more on pattern differentiation, and integrative medicine.

Review of the Etiology and Pathogenesis from Major TCM Classics of Gynecology

Female infertility is first mentioned in the chapter of Gu Kong Lun from the Suwen section of the earliest classics of Chinese medicine, the Yellow Emperor's *Neijing*. The main cause for female infertility cited was Du channel disorder. The chapter of Shang Gu Tian Zhen Lun from the Suwen, states: "Female at seven years of age, her Kidney Qi is abundant, and her teeth change and hair grows; at fourteen years of age, her Tianguai (dew of heaven) arrives, Ren channel is smooth, Chong channel is abundant, and menses flows monthly, so she can reproduce." This excerpt indicates that the Kidney Qi is the basis for Tianguai, and on this basis along with smooth passage of Ren channel and abundant nourishment of Chong channel, a female can achieve regular menses and reproduce.

The above discussion in *Neijing* provided important theoretical background about menses and reproduction for major practitioners later in history. Based on this background principle, major writers of gynecology later in history wrote and provided ample information about Qiusi (requesting descendent), Zhongzi (planting son), Tiaojing (regulating menses), and etc.

After *Neijing*, there are four famous books in gynecology generally considered as Four Classics in TCM Gynecology. These four Classics are *Fu Ren Da Quan Liang Fang* (Great Treatise of Beneficial Formula for Women, from Ziming Chen 1237), *Jing Yue Quan Shu* (The Complete Work of Jing Yue, from Jingyue Zhang 1624), *Fu Qing Zhu Ny Ke* (Qingzhu Fu's Gynecology, from Qingzhu Fu 1607-1684), and *Yi Zhong Jin Jian* (Golden Mirror of Medicine, from Qian Wu 1742). The following discusses these four Classics' viewpoints about infertility:

The chapter Qiu Si Men of the *Fu Ren Da Quan Liang Fang* states: "For females with disease and being infertile, it is all derived from exertions or damages/injuries generated Qi and Blood disorders, possibly manifested as amenorrhoea, uterine bleeding, or

leucorrhoea, which generate the imbalance of Yin and Yang, and the irregularity of menses blood, and in turn cause infertility... Other factors, such as inadequate life style, irregular meals, or wind cold attacking and obstructing the uterus, can also cause infertility.” It pointed out that infertility may be a secondary disorder from menses related diseases caused by exertions or damages/injuries generated Qi and Blood disharmony, or other factors.

The chapter Fu Ren Gui of the *Jing Yue Quan Shu* stated three key principles: First, “female’s constitution is Yin in nature, and is primarily based on blood; blood can produce essence, and with blood and essence then pregnancy is possible.” Second, “for female disorders, we should consider the menses blood as the highest priority.” And third, “when menses have been regulated, descent will be produced.” These three principles illustrate the important relationship between regular menses and pregnancy.

Fu Qing Zhu Nu Ke listed and extensively discussed ten causes of the female infertility; it also explained the false manifestations. These ten causes are:

- Thin and weak body: This indicates blood deficiency, or Kidney essence and Liver blood deficiency with empty fire flaring.
- Obesity: This indicates Spleen and stomach Qi deficiency with excessive dampness and phlegm causing internal obstruction.
- Insufficient Qi (low energy and spirit) and low strength with no appetite: This indicates Kidney Qi deficiency as the primary cause and Spleen, and Stomach deficiency as secondary.
- Deficient cold with poor digestion, chest distention and fullness, and vomiting and diarrhea: It indicates Kidney Yang (Ming Men Fire) and Heart Yang deficiency causing Spleen and Stomach deficient cold.
- Lower back soreness and abdominal distention with inability to sit and stand long: It indicates Ren and Du channels deficiency causing Dai channel prolapsed.
- Non-smooth urination and abdominal distention with feet edema: Kidney and urinary bladder Qi transformation function disorder is the cause for this syndrome.
- Steaming bone and night fever: It indicates Kidney Yin deficiency with empty fire flaring.
- Tightness in lower abdomen and sides: This indicates Dai channel tightness, and Spleen Qi deficiency can cause it.
- Lower body cold (cold uterus): Kidney and Heart Yang deficiency are the cause.
- Jealousy: This is caused by Liver Qi stagnation

The chapter Fu Ke Xin Fa Yao Jue (section Tiao Jing Men) of the *Yi Zong Jin Jian* states “Female infertility is caused by injured Chong and Ren channels, which can manifest irregular menses, leucorrhoea, and uterine bleedings; it can also be caused by blood stasis/cold/heat in the uterus, or phlegm/fat/nodules in the uterus.” This excerpt indicates that the primary cause for infertility is injured Chong and Ren channels.

Descriptions of infertility from other gynecological Classics have also been investigated. *Bei Ji Qian Jin Yao Fang* stated “For those who have no son, it is caused by the five over

exertions, seven damages/injuries, or hundred deficient diseases from the couple.” It pointed out that infertility may be caused by either the female or the male, or both. *Sheng Ji Zong Lu* stated “Female infertility is caused by Chong and Ren channels deficiency and Kidney Qi deficient cold.” *Nu Ke Yao Zhi* stated “Female infertility is all caused by irregular menses... The method of insemination is in regulating the menses.”

To summarize the Classics view of female infertility, there are many factors for normal fertility such as abundant nourishment in Chong and Ren channels, sufficient Tiangui, Kidney essence and Liver blood, and post heaven nourishment from Spleen and Stomach. Causes for infertility include the deficiency of factors for normal fertility, as well as excess, pathogenic factors, such as blood stasis, Qi/dampness/phlegm/cold/heat stagnation, etc. When it comes to treating the infertility, there is only one common goal, and that is to regulate the menses. Only after the regular and healthy menses is established is pregnancy possible; that is why all major gynecological practitioners in history have agreed that the method of conception is to regulate the menses.

Contemporary Studies of Etiology and Pathogenesis of Female Infertility

TCM texts usually describe six main etiological factors⁴ of female infertility. They are constitutional weakness, overwork, excessive physical work, excessive sexual activity at an early age, invasion of cold, and dietary factors.

Constitutional weakness of the Kidney Essence may be due to a woman’s mother having been too old when conceiving her, or the parents’ suboptimal health or constitution at the time of conception. Since Kidney Essence is the basis for Tiangui, the woman cannot conceive. Overwork for long hours without adequate rest and regular diet for years is a major cause of Kidney Yin deficiency. Kidney Yin is the basis for menstrual Blood and the Uterus and when it is deficient there may be infertility. Excessive physical work or strenuous exercise and sports weaken the Spleen and Kidney Yang. Excessive sexual activity at an early age seriously weakens the Kidneys and damages the Chong and Ren channels and may therefore cause infertility later in life. Invasion of Cold is a common cause for infertility among young girls. Cold in the Uterus obstructs the Uterus and Chong and Ren channels, preventing fertilization. Dietary factors include excessive consumption of cold, iced foods and drinks which leads to Cold in the Uterus. Excessive consumption of greasy foods and dairy products leads to the formation of dampness in the lower Jiao which also prevents fertilization.

TCM texts usually describe four main pattern categories⁵ of female infertility with subcategories. These four main categories are Kidney deficiency, Heart and Liver Qi stagnation, Blood stagnation and Phlegm-Damp accumulation.

The most common cause of functional infertility is Kidney deficiency. This condition often underlies or coexists with other causes given the Kidney stores essence and governs reproduction. The Heart is a very important organ when it comes to ovulating regularly and on time. TCM describes the importance of communication between the Heart and Uterus via the Bao vessel; a Heart disorder may be caused by emotional factors which

have precipitated the amenorrhea. The Liver is even more influenced by the emotions than the Heart, since it governs Qi movement. Blood stagnation often develops as the long-term consequence of other disorders (e.g. Cold, Damp-Heat or Kidney deficiency) and is a complex syndrome in any discipline; the menstrual cycle will be adversely affected by Blood stagnation. Like Blood stagnation, Phlegm-Damp accumulation also produces obstruction, such as in a case of polycystic ovarian syndrome. The subcategories of the four main categories are listed below:

Kidney deficiency:

- Kidney Jing deficiency
- Kidney Yin deficiency
- Kidney Yang deficiency
- Kidney Yin and Yang deficiency

Heart and Liver Qi stagnation:

- Heart Qi stagnation
- Liver Qi stagnation

Blood stagnation

Phlegm-Damp accumulation

Contemporary TCM Treatment Methods and Prospective for Female Infertility

According to the author's survey of clinical research in China, contemporary TCM treatment methods for infertility can be generally found in the following eight categories: pattern differentiation with different formulas, one basic formula with modification according to symptoms, a single empirical formula for all patterns, an artificially assisted menstrual period with herbal formulas, integrative TCM and biomedicine treatment, external treatment, acupuncture, and consultation method. These treatment methods are briefly discussed below:

Pattern differentiation with different formulas is the most traditional approach for most disorders, hence it is used with infertility; often times there will be modifications for each pattern according to symptoms. One basic formula with modification according to symptoms simplifies the previous method and uses one basic formula for infertility. A single formula for all patterns is the simplest form of formula treatment without any modification. The artificial period method basically adopts three formulas to enhance the female cycle: one formula to nourish the Kidney, Liver and Yin Blood after the menstrual flow for about 5 days (the follicle phase), one to tonify the Kidney and Qi and to invigorate the Blood and warm and unblock the channels before ovulation for about 4 days (the ovulation phase), one to warm and tonify the Kidney and Spleen for luteal phase, and finally during the menstrual flow to regulate and nourish the Blood for smooth flow. Integrative TCM and biomedicine treatment generally uses TCM formula in conjunction with hormone and vitamin treatment. External treatment includes TCM formula fluid retention in the colon or a wash in the vaginal and cervical areas, hot

patches, etc. Acupuncture treatment is usually for tube obstruction or ovulation disorders. Consultation is basically a stress management and educational program. These above methods are often used in a combination with one another.

Some examples of these contemporary methods are summarized here below:

Xia⁶ from Jiangsu Province TCM Hospital adopted the following principles loosely and treated infertility successfully for ovulatory disorders, luteal phase disorders, tubal obstruction and AsAb-associated disorders: Tonify Kidney and nourish blood, regulate Liver and tonify Spleen, and clear heat and remove stagnation.

Cai⁷ emphasized that Blood and Kidney Essence are two key factors for women's menstruation, and that the treatment method for female fertility is in the process of regulating the menstruation. She summarized four methods for regulating menstruation: treating from Kidney, Liver and Spleen, Dampness and Phlegm, and Blood stagnation. She also conducted scientific experiments objectively with six herbal formulas using animal experiments and biostatistics to prove the above theory.

Sha⁸ treated 78 cases of tubal inflammation-caused infertility with acupuncture in conjunction with moxa at the lower abdomen; the main points used were Du3, Du3, St36, Sp6, UB23, St29, K12, and Zigong (Ex). One treatment period is once a day for ten days, and there were 48 patients with successful pregnancy in two years.

Wu⁹ treated 25 infertility cases with the artificial period method. She used 6 bags over 6 days of Zhu Yun #1 (Heshouwu, shudi, danggui, shanyao, tusizi, xianmao, yinyanghuo, chaihu, xiangfu, nuzhenzi, roucongrong, dangshen) for follicle phase starting at the fifth day of a period, 4 bags over 4 days of Zhu Yun #2 (Shudi, danggui, gouqizi, hehsouwu, danshen, zelan, chongweizi, zhike, xiangfu) for ovulation phase, and 10 bags over 10 days of Zhu Yun #3 (Shudi, xuduan, danggui, dangshen, guiban, tusizi, roucongrong, bajitian, lujiaojiao, shanyao, chaihu, xiangfu) for luteal phase; after eighteen months, there were 22 pregnancies.

Liu¹⁰ in 2002, reviewed publications within the previous fifteen years related to AsAb infertility; Liu reviewed 40 journal articles, and discussed AsAb infertility associated etiology, pathogenesis, pattern differentiation and treatment methods. Liu concluded that Chinese herbs showing promising treatment results for AsAb infertility, however, there were weaknesses with the studies. For example, the diagnosis, treatment and clinical efficacy were not standardized, the designs were not stringent enough, and the curing mechanism was not totally understood. This is an important review for our subject, since it summarized trials and studies primarily prior to 1999.

Tang¹¹ investigated the TCM etiology, pathogenesis and treatment of the Yin deficiency type of immunological infertility, and stated that Kidney and Liver have a relationship with reproduction and immunology. Kidney deficiency is the root of immunological infertility, and Liver excess is the manifestation. Due to the fact that TCM considers Kidney and Liver having the same source, Tang would treat the Kidney and Liver at the

same time by sedating the Liver fire, and nourishing the Kidney Yin. Tang stated that, after systematically treating 150 AsAb-related infertile female patients, the results indicated that by nourishing the Kidney Yin and sedating the Liver Fire, this treatment could not only decrease the AsAb, but also regulate the immune function and reduce the autoimmune antibody.

Biomedical Pathology and Treatment of As Ab Associated Female Infertility

Female reproductive failure may be a consequence of immunological factors, during the fertilization process or pregnancy. These factors include, but are not limited to, AsAb, anti-endometrial antibodies (EMAb), anti-ovary antibodies (AOVAb) and anti-hCG antibodies (AhCGAb). Studies showed that infertility related to immunological factors has both autoimmune factor and secondary immune factor¹². The prime importance among these factors is the AsAb, and the secondary is EMA b; they are discussed below.

AsAb The AsAb associated with infertility induces agglutination and/or immobilization of sperm. Infertile subjects possessing AsAb are classified as having immunologic infertility. Although the AsAB can agglutinate and/or immobilize human sperm, a cause-effect relationship to infertility has not been established¹³. The major obstacle is the complexity of the AsAb. It is composed of numerous antibodies interacting with multiple sperm components, so that no single predominant target antigen has been identified¹⁴. AsAb can be produced by both sexes. Males can produce autoantibodies against their own spermatozoa and females can produce antibodies against a male's spermatozoa. In males, AsAb production arises from either systemic or local immune responses, and AsAb are found in semen, seminal plasma, and sera or are bound to the outer sperm plasma membrane. In females, AsAb are found in blood, ovarian follicular fluid, and vaginal or cervical secretions. In males, AsAb may be produced before fertilization if the blood-testis barrier is breached and sperm antigens prompt an inflammation of mechanical obstruction of the genital tract.

EMAb Normal fall-off of the endometrium during menses will not trigger off antibody production, but in endometriosis or uterine myoma disorder, the inflammation will trigger the production of the antibodies. EMAb may also affect reproductive outcomes and can be detected; however, there are opposing views on the relationship between endometriosis and infertility.

Since the primary cause for females to generate AsAb is the absorption of sperm during intercourse, and each unprotected intercourse will increase the AsAb density furthermore, therefore, the most logical, biomedical treatment for AsAb associated female infertility is to use condoms during the treatment period or non-ovulation period. Another popular treatment is a daily dosage of about 10mg of cortisone. Vitamins and/or antibiotics are also used for treatment, as well as artificial insemination methods.

Current TCM Treatment Methods for AsAb Associated Female Infertility

As mentioned earlier, since the diagnosis, treatment and efficacy have not been standardized in China for AsAb-associated infertility, parameter normalization and/or adjustment for certain clinical data are necessary in order to have meaningful statistical results. Therefore, to review clinical trials or studies, a set of critique standards must be identified first.

Critique Standards Adopted for Review of Clinical Trials and Studies

The development of clinical trials in China is still maturing to this day. The major weakness of clinical trials in China can be attributed to the lack of stringent design and conduct as compared to trials done in the USA. In addition, there are not many trials to choose from so inclusion and exclusion criteria for selecting published trials or studies should be evaluated and identified during the screening process of the journal articles. The inclusion criteria are: the trial or study must be AsAb-related for female alone, or male and female patients; the trial or study must use herbal formulas as a TCM treatment method; the trial or study must have at least 20 patient cases; the trial must report a cure rate of at least 25%, and total effective rate 70%. The exclusion criteria are: the trial or study was published before 1999; the trial or study adopted commercial patent formulas; the trial or study did not include ingredients for proposed herbal formulas; the trial or study adopted acupuncture treatment; the trials or study included infertility factors in addition to immunological factors; the author's qualification (position in hospital or university) was not mentioned. The cure rate mentioned above is defined to represent pregnancy within two years of treatment, and the total effective rate is to represent patients who are AsAb-negative, including those pregnant within two years of treatment. The above inclusion and exclusion criteria are required to guarantee that a clinical trial or study is significant and they will contribute to an acceptable quality of review.

To critique the published clinical trials or studies, each of the following items is checked against the trial or study. These items are used to evaluate the quality of the clinical trial or study design as well as treatment results.

- Is the randomization mentioned?
- Are patients female, or both male and female?
- Are patients' age mentioned? Are they a good sample population?
- Are patient inclusion and exclusion criteria mentioned?
- Are formula, dosage, and treatment session duration mentioned? Reasonable?
- Is there a control group?
- Is there any other treatment (such as using condom) working in conjunction with the TCM formula treatment?
- Is efficacy data mentioned? Meaningful? Effective?
- Is there a section for the author's discussion?
- Is there a follow-up exam to identify any lasting treatment effect (such as an AsAb test two years after the treatment)?

Review of Nine Qualified Clinical Trials or Studies Associated with As Ab Infertility

Liu¹⁵ conducted a basic, clinical study for 40 female patients (aged approximately 20 -40) that tested AsAb positive. There was no randomization. The author differentiated patterns into four types with their associated treatment formulas. First Kidney deficiency pattern uses Liu Zi Tang to modify, and the ingredients consist of tusizi 15g, fupenzi 12g, gouqizi 12g, nuzhenzi 15g, wuweizi 10g, jinyingzi 15g (if Yang deficiency is present, add xuduan 15g, bajitian 10g, roucongrong 12g, suoyang 10g, rougui 3g, fuzi 10g; if Yin deficient, add sangshen 15g, shudi 20g, huangjing 15g, shanzhuyu 10; if the palms are hot and the mouth is dry, add digupi 15g, xuanshen 15g, baishao 12g, xiaohuanchai 12g; if there is an obvious heat sign, add zhimu 12g, huangbai 10g, mudanpi 10g, pugongying 12g). Next, the Liver stagnation pattern uses Kai Yu Tang to modify, and the ingredients consist of foshou 10g, xiangfu 12g, yujin 15g, yanhusuo 15g, suxinhua 10g, zhike 12g, chaihu 10g, baishao 15g (if there is Liver fire, add jiaoshanzhizi 10g, shengdi 12; if there is breast tenderness, add lulutong 12g, gualou 10g, if there is leaking milk, add raw maiya 60-100g; if there is Liver Yin deficiency, add shashen 12g, maidong 12, gouqizi 15g). The third type, a Blood stagnation pattern uses Shi Xiao San and Si Ni San to modify, and the ingredients consist of yanhusuo 15g, wulingzhi 12g, chaihu 10g, baishao 15g, zhike 12g, gancao 6g, plus taoren 10g, honghua 6g, sanleng 10g, erzhu 10g, wangbuliuxing 15g, lulutong 20g, tianqi 6g. The final pattern, Damp heat uses Jie Du Huo Xue Tang to modify, and the ingredients consist of lianqiao 12g, gegen 15g, chaihu 12g, zhike 12g, danggui 10g, chishao 15g, shengdi 15g, honghua 6g, taoren 12g, gancao 6g, plus qiyeyizhihua 30g, maodon gqing 30g, wangbuliuxing 15g. No data related to the treatment session was provided. After one year of treatment, Liu obtained a cure rate of 37.5%, and a total effective rate of 87.5%. There was no control group. Use of condoms during the treatment time was not mentioned. Liu discussed that AsAb-associated infertility has root deficiency in the form of Kidney Yin and Kidney Yang, and manifestation excess in the form of heat burning away essence and blood, essence and blood accumulation, essence out of its normal path, and phlegm obstructed in the uterus. The minor strength of this case study is that it has clear pattern differentiation. The weakness of this design is that it did not clearly mention the age group, and it did not mention the treatment session duration and follow-up exams. This case study is a weak design in general, and it can only provide basic data for our statistical evaluation.

Shan¹⁶ conducted a clinical randomized control trial for 20 female patients, aged 21 -40, married 2-10 years, who tested AsAb-positive. The treatment group was differentiated into three patterns with different formulas. First, the Yin deficiency with empty fire pattern adopted Zhi Bai Di Huang Tang to modify (zhimu, huangbai, shudi, shanyao, shanzhuyu, zexie, fuling, mudanpi). Second, the Kidney Yang deficiency pattern adopted Jin Kui Shen Qi Wan to modify (fuzi, guizhi, dihuang, shanzhuyu, shanyao, fuling, gouqizi, yinyanghuo, bajitian). Finally the Qi and Blood stagnation pattern adopted Xue Fu Zhu Yu Tang to modify (danggui, shengdi, taoren, honghua, zhike, chishao, chaihu, gancao, jiegeng, chuanxiong, niuxi, jixueteng, danshen, sanqi, paoshanjia). Each treatment session was 30 days with daily dosages. After 90 days of treatment, Shan obtained a cure rate of 30%, and a total effective rate of 85%. There was a control group of 15 female patients whose only treatment was using condoms during their non -

ovulation period. This group obtained a cure rate of 20%, and a total effective rate of 53% ($P < 0.01$). Only the control group used condoms during non-ovulation period as treatment. Shan discussed that according to western pharmacological research on Chinese herbs, yinyanghuo, fuzi and shanyao obviously lower the rising rate of the immunoglobulin in the serum, and blood invigorating herbs such as danggui and danshen can improve the circulation and repair the immunological disorders. Shan also summarized, through this trial, that pattern differentiation is important because each individual has a unique constitution. Another point is that during the treatment period, patients should pay special attention to avoid allergy-causing food. Treatment for immunological related infertility is longer than normal disorders, therefore patient needs to be advised to take herbs regularly without a break. The strength of this trial design is that, despite having only 20 cases, it mentioned the inclusion and exclusion criteria, and covered most aspects of a clinical trial with reasonable data. The weakness of this design is that it did not mention the follow-up exam, or a specific dosage for any formula in a given pattern.

Wei¹⁷ conducted a clinical study for 82 patients (22 males and 60 females; aged 25-32; infertility history 2-8 years) including 22 males with autoimmune AsAb, 41 female AsAb-subjects, 10 females with autoimmune EMAB, and 9 females with anti “B” blood type antibodies. The author used self-made, single formula Xiao Kang Tang without modification for treatment. The ingredients are: zhihuangqi 30g, chaobaizhu 20g, fangfeng 10g, shudi 20g, danggui 20g, huangqin 10g, tusizi 10g, xuchangqing 10g, danshen 30g, sanqi powder 4g (dissolve to drink), gancao 6g, dazao 10pcs. One bag of the formula was taken per day; the minimum treatment was 20 bags, and the maximum was 40. After 2 years of treatment, Wei obtained a cure rate of 90%, and a total effective rate of 95%. During the treatment period, condoms were used. There was no control group. Wei discussed that this disorder is a root deficiency and manifests as an excess pattern. The treatment principle is to tonify the upright Qi, invigorate the Blood, clear the heat and remove the toxicity. Wei combined modern, western pharmacological knowledge to create the formula by using huangqi, chaobaizhu, shudi, danggui and huangqi to boost the immunity; huangqin, xuchangqing and gancao to treat allergies; and danshen and sanqi to remove and dissolve the accumulated antigen antibody complement. The strength of this trial design is that it showed a single formula treating immunological infertility, and it clearly discussed the function of the formula. The weakness of this design is that it did not mention any randomization, or follow-up exams. This study made vague statements about treatment sessions and durations. This study showed excellent clinical results, however, due to its young age group, the efficacy statistics can only be used for basic statistical evaluation, and not be compared with other studies or trials with a even, wide age spread.

Li¹⁸ conducted a clinical randomized control trial for 56 female patients, aged 25-38, who were infertile for 1-8 years, and tested AsAb-positive. The author used a self-made formula, Xiao Kang Tang, for treatment. The ingredients are: shengdi 15g, baishao 15g, maidong 12g, huangjing 15g, hanliancao 12g, guiban 15g, shanzhuyu 12g, shanyao 15g, mudanpi 12g, danshen 18g, huangbai 12g, yiyiren 24g. The modification for damp-heat is to add yuxingcao 15g, zesie 15g; for heart and liver stagnation fire, add chaihu 6g,

zhizi 9g; for spleen and stomach deficiency, subtract shengdi and add baizhu 15g, biandou 24g. Each treatment session was 30 days with a daily dosage. After one year of treatment, Li obtained a cure rate of 48.2%, and a total effective rate of 82.1%. There was a control group of 56 patients, aged 25-37, who were infertile for 1-9 years, and tested AsAb-positive. This group was given cortisone (5mg, bid) as an equivalent treatment, and it obtained a cure rate of 25%, and a total effective rate of 60.7% ($P < 0.05$). Both groups used condoms during non-ovulation period as part of the treatment. Li discussed that AsAb-associated infertility is not yet totally understood, but most practitioners believe that females with vaginal infections, sexually transmitted diseases, or traumatic factors (such as pelvic inflammatory disease, vaginitis, cervicitis), suffer from a damaged enzyme system in the reproductive channel. As a result, the local immune dysfunction is generated, and AsAb appears in blood or cervix. Most AsAb patients were observed with lower back pain, abdominal pain, and/or leucorrhea disorders. The main patterns observed were Liver and Kidney Yin deficiency, damp-heat, and blood stagnation. Xiao Kang Tang was used whereby shengdi, baishao, maidong, huangjing, hanliancao, guiban nourished the Yin and cooled the blood; shanzhuyu tonified Liver and Kidney; shanyao tonified the Spleen and Kidney; danshen invigorated the Blood; mudanpi cooled the Blood; and huangbai and yiyiren drained the damp-heat. The strength of this trial design is that it precisely covered almost all aspects of a clinical trial with reasonable data; the article was presented in a good professional format, and all technical data were presented very professionally. The only weakness of this design is that it did not mention follow-up exams. With its reasonable clinical results, it is worthwhile to conduct further studies on Xiao Kang Tang to further enhance its efficacy.

Xu¹⁹ conducted a clinical randomized control trial for 128 patients (72 males aged 24-45, and 56 females aged 23-38; married 3-12 years) including patients that tested AsAb and/or EMAB-positives. The author used the self-made formula Yu Kang Tang for treatment. The ingredients are: wujiapi 15g, lingzhi 15g, yinyanghuo 15g, roucongong 12g, gouqize 12g, tusizi 15g, nuzhenzi 15g, huangqi 25g, huanggen 30g, lufengfang 20g, yimucuo 30g, danpi 10g, baihuasheshecao 30g, honghua 6g. The modification for Liver and Kidney deficiency is to add huangjing, wuweizi, shanzhuyu, sangshenzi, xuduan; for Spleen and Lung Qi deficiency to add shanyao, baizhu, baihe, dangshen, dongchongxiacao, gejie, taoren; for Qi and Blood deficiency to add heshouwu, jixueteng, shudi, danggui, renshen; for damp-heat to add yiyiren, tufuling, cheqianzi, jinyinhuo, pugongyin; for Qi and Blood stagnation to add chaihui, yanhusuo, danshen, xiangfu, niuxi. Each treatment session was 30 days with a daily dosage. After 180 days of treatment, Xu obtained a cure rate of 81.2%, and a total effective rate of 90.6%. There was a control group of 64 patients (male 26, female 28), using cortisone treatment. This group obtained a cure rate of 29.7%, and a total effective rate of 39.1% ($P < 0.01$). Both groups used condoms during the non-ovulation period as treatment. Xu discussed that AsAb-associated infertility is about 3% of the total infertility population. This disorder has a root deficiency as the immune system, manifests as excess damp-heat and Qi and Blood stagnation. Yu Kang Tang used yinyanghuo, roucongong, tusizi, gouqizi, nuzhenzi to tonify Kidney, Liver and Essence; huangqi, lingzhi, huanggen to tonify Qi and Blood; and wujiapi, baihuasheshecao, lufengfang to expel wind damp and clear heat and toxicity. Both males and females can use Yu Kang Tang without side effects, and the treatment

period is relatively short with good efficacy. The strength of this trial design is that it covered most aspects of a clinical trial with reasonable data. The weakness of this design is that it did not mention follow-up exams. With its excellent clinical results, it is certainly worthwhile to conduct further studies of Yu Kang Tang to confirm and further enhance the results.

Wang²⁰ conducted a basic, clinical study for 42 female patients, married 1 -4 years, aged 22-31 who tested AsAb-positive. There was no randomization. The author used the self-made, single formula Yi Kang Tang for treatment. The ingredients are: shengdi 10g, danggui 10g, shanzhuyu 10g, baishao 10g, huangjing 10g, huangqi 15g, taizishen 15g, danpi 15g, danshen 15g, xuchangqing 20, jixueteng 20g, gancao 6g; the modification was according to patient's pattern, but no information on modification was given. Each treatment session was 40 days with a daily dosage. The treatment duration was not specified, but Wang claimed to have obtained a cure rate of 76.3%, and a total effective rate of 95.3%. There was no control group. Condoms were used during treatment period. Wang discussed that AsAb-associated infertility has primarily Kidney and Liver Yin deficiency. The treatment principle would be to tonify Kidney Yin, disperse Liver and cool blood, expel wind and toxicity. Yi Kang Tang used shengdi, baishao, shanzhuyu, huangjing, huangqi, and taizishen to tonify Kidney and Liver Yin; danpi, danshen to invigorate blood; and gancao to simulate the hormone function. This case study has clearly stated patient inclusion and exclusion criteria, but otherwise it is a weak study. The weakness of this design is that it did not mention the treatment session duration, herbal modification according to patterns, or follow-up exams. This case study is a weak design in general, and can only provide basic data for our statistical evaluation. This study showed excellent clinical results; however, due to its young age group, the efficacy statistics can only be used for basic statistical evaluation, and not to be compared with other studies or trials with a even, wide age spread.

Ma²¹ conducted a clinical randomized control trial for 47 female infertile patients who tested AsAb-positive. There was a control group with similar patients. The age, infertile duration and history were processed according to biostatistics for an even distribution for both groups, but no data was mentioned. The author used the self-made, single formula Ren Dong Teng Tang for treatment without modification; the ingredients are: rendongteng 45g, huangqi 24g, gancao 9g, yinyanghuo 15g. Each treatment session was 20 days (after menstrual flow is clear) with a daily dosage. After three sessions of treatment, Ma obtained a cure rate of 55.3%, and a total effective rate of 72.3%. There was a control group of 47 patients, of similar age, duration of infertility, and case history, that used Prednisone (10mg, qid) and Vitamin E (0.1, qid) as equivalent treatment. This group obtained a cure rate of 29.8%, and a total effective rate of 85.1%. Both groups used condoms during the non-ovulation period as treatment. Ma discussed that AsAb-associated infertility has a root deficiency and manifestation as excess. The treatment principle is to clear the heat and toxicity, and tonify the Qi and invigorate the blood. Ren Dong Teng Tang has rendongteng as the chief herb to clear the heat without hurting the Yin; huangqi to tonify the upright Qi and assist rendongteng to clear the heat as a deputy; raw gancao to clear the heat and remove toxicity as a deputy as well; yinyanghuo to tonify Liver and Kidney, and to assist the function of blood invigoration as the assistant,

and gancao also serves to harmonize all herbs as the *envo y*. Modern pharmacological research discovered that both *rendongteng* and *gancao* can increase the function of Interferon (IFN) which can regulate the immunological function. *Huangqi* is known as an immunity booster, and *yinyanghuo* regulates the endocrine system, and serves as a blood thinner. The strength of this trial design is that it precisely covered most aspects of a clinical trial with reasonable data, it used a single formula without modification with good results, the article was presented in a good professional format, and all technical data were presented very precisely and professionally. The weakness of this design is that it did not provide duration of infertility data for patients. The other minor weakness of this design is that it did not mention follow-up exams. Even though the control group had a higher total effective rate, the treatment group had significantly higher cure rate ($P < 0.05$). Therefore it is worthwhile to conduct future studies about *Ren Dong Teng Tang* to further enhance the efficacy.

Wu²² conducted a basic, clinical study for 85 female infertile patients that tested AsAb - positive, aged 23-38, without tube or ovarian disorders. There was no randomization. The author used the self-made, single formula *Yi Kang Tang* for treatment without modification. The ingredients are: *danshen*, *chishao*, *danggui*, *taoren*, *huangqi*, *houqizi*, *tusizi*, *lujiaoshuan*, *yizhiren*, *xiangfu*. No dosage data was given. Each treatment session was 30 days with a daily dosage. After three sessions of treatment, Wang obtained a cure rate of 24.7%, and a total effective rate of 86.3%. There was no control group. The use of condoms during treatment time was not mentioned. Wang discussed that AsAb - associated infertility has Blood stagnation and Kidney deficiency as the primary pathogenesis, and the main treatment principle is to invigorate the blood and tonify the Kidney Yang. This is a very basic case study report without randomization, however, it did mention inclusion and exclusion criteria. The result was below average. The weakness of this design is that it did not mention the ingredient dosage for *Yi Kang Tang*, did not mention if condoms were used during the treatment period, and it did not mention any follow-up exams; the discussion was insignificant. This case study is a fairly weak design in general, and can only provide basic data for our statistical evaluation.

Tian²³ conducted a clinical study for 30 patients (11 males and 19 females; aged 23 -42; infertile for at least 2 years). Infertility due to female ovarian factors, cervical factors, uterus factors and tubal factors, and male genitals deformity, reproductive cell disorder, endocrine disorder, varicose vein on funiculus spermaticus and ductus deferens obstruction were excluded. The author used a self-made formula *Hua Shi Xiao Kang Ti Tang* for treatment. The ingredients are: *bexie* 12g, *chishao* 15g, *danpi* 12g, *hongteng* 30g, *tufuling* 15g, *cheqianzi* 10g, *rendongteng* 15g, *shenggancao* 4.5g, *yiiren* 30g, *jinyinhua* 12g, *lianqiao* 9g. The modification for increasing leucorrhea is to add *chungenpi* 15g, *baijinhua* 15g, *chuanhopo* 9g, for Qi deficiency to add *huangqi* 15g, *dangshen* 15g, *shanyao* 15g, for loose stool to add *chaobiandou* 15g, *lianzirou* 12g, for excessive menstrual flow to add *xianhecao* 30g, *ganngiengen* 15g, for Kidney Yin deficiency to subtract *bixie*, *fuling*, *cheqianzi*, and add *buiban* 9g, *shengdihuang* 15g, and for lower back soreness to add *sanjisheng* 15g, *gouji* 12g. Each treatment session was 30 days with a daily dosage. After 180 days of treatment, Tian obtained a cure rate of 30%, and a total effective rate of 83.3%. During the treatment period, condoms were used.

There was no control group. Tian discussed the general pathology of AsAb infertility, and stated that the cause for male AsAb was an autoimmune disorder, which was due to damage to the blood testicle barrier. This disorder has many causes, but the main cause is damp-heat in the lower jiao. Hua Shi Xiao Kang Ti Tang used hongteng, bixie, yiyiren, cheqianzi, jiyinhua, lianqiao and tufuling to clear the heat, remove the toxicity, and remove the dampness. Chishao and danpi were used to invigorate the blood. Shengdahuang, as an important herb, was used to dissolve the AsAb, clear the heat and remove the toxicity. Gancao was also used to harmonize all herbs. Western pharmacological research has shown that yiyiren inhibited fluid immunity. The strength of this trial design is that it clearly discussed the inclusion and exclusion criteria, and western pathology of AsAb infertility for both men and women. The weakness of this design is that it did not mention the infertile duration of the patients, and the follow-up exams.

Discussion

To summarize the strengths and weaknesses of the above reviewed nine clinical trials and studies, the following four tables have been compiled.

Table 1 contains the key parameters for the reviews. Table 2 contains the average efficacy which consists of the average cure rate and the total effective rate for both the TCM treatment group and biomedical control group. For better accuracies, both rates have been calculated by using actual head counts (for total patients, pregnancies and AsAb negatives), rather than using each trial or study as a unit. Table 3 contains the herb (appearing in formulas) frequency list; this data is useful for the rationalization of formulas, matching differentiated patterns and serving as a guide for future formula composition. Table 4 summarizes the nine aforementioned trials and studies, including the strengths and weaknesses of each trial in terms of the criteria mentioned above.

The differentiated patterns were not compiled into a table, because they were not clearly defined, however, the primary patterns appeared are listed here for general reference purpose. They are listed as priority: Damp heat, blood stagnation, heat toxicity, Kidney and Liver Yin deficiency, Kidney Yang deficiency, Qi and blood stagnation, cold stagnation, Spleen Qi deficiency, Liver Qi stagnation and Qi and blood deficiency.

Table 1: Key Parameter Table of the Nine Reviewed Trials and Studies

| | | | | | | | | | |
|---------|------------|-------------|------------|-----------|-----------|-------------|-----------|-----------|-------------|
| Primary | Liu | Shan | Wei | Li | Xu | Wang | Ma | Wu | Tian |
|---------|------------|-------------|------------|-----------|-----------|-------------|-----------|-----------|-------------|

| | | | | | | | | | |
|-------------------------|-------|-------|--------|-------|-------|-------|-------|-------|-------|
| Author | | | | | | | | | |
| Trial or Study | Study | Trial | Study | Trial | Trial | Study | Trial | Study | Study |
| Male & Female Patients | | | Yes | | Yes | | | | Yes |
| Treatment Duration | 12 mo | 3 mo | ~24 mo | 12 mo | 6 mo | >40d | 3 mo | 3 mo | 6 mo |
| SF w/o Mod | | | Yes | | | | Yes | Yes | |
| SF with Mod | | | | Yes | Yes | Yes | | | Yes |
| MF per Pattern | Yes | Yes | | | | | | | |
| TG # of Patients | 40 | 20 | 82 | 56 | 128 | 42 | 47 | 85 | 30 |
| TG Cure Rate | 37.5% | 30% | 90% | 48.2% | 81.2% | 76.3% | 55.3% | 24.7% | 30% |
| TG Total Effective Rate | 87.5% | 85% | 95% | 82.1% | 90.6% | 95.3% | 75.3% | 86.3% | 83.3% |
| TG Use Condom | | | Yes | Yes | Yes | Yes | Yes | | Yes |
| CG # of Patients | | 15 | | 56 | 64 | | 47 | | |
| CG Cure Rate | | 20% | | 25% | 29.7% | | 29.8% | | |
| CG Total Effective Rate | | 53% | | 60.7% | 39.1% | | 85.1% | | |
| CG Use Condom | | Yes | | Yes | Yes | | Yes | | |

Note: SF=Single Formula, MF=Multiple Formula, TG=Treatment Group, CG=Control Group

Table 2: Average Efficacy

| | | |
|---|-----|---|
| TCM Treatment Group: Average Cure Rate | 59% | Calculated with 9 groups by actual head counts |
|---|-----|---|

| | | |
|--|-------|---|
| TCM Treatment Group: Average Total Effective Rate | 87.7% | Calculated with 9 groups by actual head counts |
| Biomedical Control Group: Average Cure Rate | 27.5% | Calculated with 4 groups by actual head counts |
| Biomedical, Control Group: Average Total Effective Rate | 58.8% | Calculated with 4 groups by actual head counts |

Table 3: Herb Frequency (Appearing in Formulas) List

| | |
|-------------------|--|
| Appearing 6 Times | Gancao |
| Appearing 5 Times | Gouqizi, baishao, danggui, shengdihuang, mudanpi, huangqi |
| Appearing 4 Times | Zhike, chaihu, chishao, shanzhuyu |
| Appearing 3 Times | Tusizi, taoren, shanyao, yinyanghuo |
| Appearing 2 Times | Nuzhenzi, xiangfu, yanhusuo, honghua, huangbai, fuling, shudi, jixueteng, yiyiren, sanqi, xuchangqing, huangjing, rendongteng, lianqiao |
| Appearing 1 Times | Gegen, fupenzi, wuweizi, jingyingzi, foshou, yujin, suxinghua, wulingzhi, zexie, zhimu, fuzi, guizhi, bajitian, jiegeng, chuanxiong, niuxi, chuanshanjia, baizhu, huangqin, fangfeng, dazao, maidong, hanliancao, guiban, wujiapi, lingzhi, roucongrong, huanggen, lufengfang, yimucao, baihuasheshecao, hong hua, taizishen, lujiaoshuang, yizhiren, bixie, hongteng, tufuling, cheqianzi, shenggancao, jinyinhua |

Table 4: Weakness and Strength of the Nine Reviewed Trials and Studies

| | | | | | | | | | |
|----------------|------------|-------------|------------|-----------|-----------|-------------|-----------|-----------|-------------|
| Primary Author | Liu | Shan | Wei | Li | Xu | Wang | Ma | Wu | Tian |
| Trial or Study | Study | Trial | Study | Trial | Trial | Study | Trial | Study | Study |
| Randomization | | Yes | | Yes | Yes | | Yes | | |

| | | | | | | | | | |
|---------------------------|---------|---------|-------------|-----------|------------|---------------|------------------|------------------|-----------|
| Male & Female Patients | | | Yes | | Yes | | | | Yes |
| Patients Age | ~20-40 | 21-40 | 25-32 | 25-38 | 23-38 | 22-31 | Not noted | 23-38 | 23-42 |
| Inclusion/Exclusion (I&E) | Yes/No | Yes/Yes | Yes/No | Yes/No | Yes/Yes | Yes/Yes | Yes/Yes | Yes/Yes | Yes/Yes |
| Dose & TX Mentioned | -TX | - Dose | -TX | | | -Dose | | -Dose | |
| Treatment Duration (TD) | 12 mo | 3 mo | ~24 mo | 12 mo | 6 mo | >40d | 3 mo | 3 mo | 6 mo |
| SF w/o Mod | | | Yes | | | | Yes | Yes | |
| SF with Mod | | | | Yes | Yes | Yes | | | Yes |
| MF per Pattern | Yes | Yes | | | | | | | |
| TG # of Patients | 40 | 20 | 82 | 56 | 128 | 42 | 47 | 85 | 30 |
| TG Cure Rate | 37.5% | 30% | 90% | 48.2% | 81.2% | 76.3% | 55.3% | 24.7% | 30% |
| TG Total Effective Rate | 87.5% | 85% | 95% | 82.1% | 90.6% | 95.3% | 75.3% | 86.3% | 83.3% |
| TG Use Condom | | | Yes | Yes | Yes | Yes | Yes | | Yes |
| Control Group Provided | | Yes | | Yes | Yes | | Yes | | |
| CG # of Patients | | 15 | | 56 | 64 | | 47 | | |
| CG Cure Rate | | 20% | | 25% | 29.7% | | 29.8% | | |
| CG Total Effective Rate | | 53% | | 60.7% | 39.1% | | 85.1% | | |
| CG Use Condom | | Yes | | Yes | Yes | | Yes | | |
| Follow-up Exam | No | No | No | No | No | No | No | No | No |
| Design Strength | | I&E | SF | All Items | Most Items | I&E | SF, & Most Items | | I&E |
| Design Weakness | Age, TX | Dose, | Age, TX, TD | | | Age, TX, Dose | Age | Dose, Most Items | |
| Overall Evaluation | Weak | Fair | Weak | Very Good | Good | Very Weak | Good | Weak | Fair Weak |

Note: TX=Treatment Session Duration

As mentioned earlier, in 2002, Liu[10] reviewed 40 journal articles related to AsAb infertility, and concluded Chinese herbs showed promising treatment results for AsAb caused infertility. However there were weaknesses in the studies, such as that the diagnosis, treatment and clinical efficacy were not standardized, the designs were not stringent enough, and the curing mechanism was not totally understood. From our nine reviewed journal articles, we found that since 1999, while there have been some improvements (such as the diagnosis methods and standards, and patients inclusion and exclusion criteria), the designs were still generally not stringent enough, treatment and

clinical efficacy were not standardized, and the curing mechanism was not totally understood.

There were more specific weaknesses found in these nine studies. First of all, none of the studies discussed any follow-up exams, which can tell us if a treatment has lasting effect, and hence has more value. Also, the age spread showed uneven distribution among studies, which can dramatically affect the treatment results. In addition, the use of condom during treatment was not adopted by all studies; this is one aspect that should be standardized, since its biomedical mechanism is clear and efficient;

Throughout the above review process and studies, a more standard and stringent set of design criteria for clinical trials of AsAb-associated female infertility has been formulated and proposed for future clinical randomized control trials to follow. The criteria are listed below:

- Author's credentials must be presented, obviously for correct diagnosis and effective formula prescription, and hence a creditable trial.
- There must be at least 20 patients for treatment group or control group, in order to have meaningful statistics.
- Patient inclusion and exclusion criteria must be clearly mentioned; ovulatory and tubal factors must be excluded, as well as any known cause other than immunological factors.
- The blinding must be described, if any. The blinding does not seem to be a very important factor, since the placebo effect has never been proven to be an affecting factor in this kind of trial.
- The randomization must be mentioned, for even statistical distribution.
- If patients include both male and female, distribution must be clearly presented. It is valid to treat male as well, but it needs to be mentioned for clear differentiation.
- Patients' age must be stated; it is proposed to have an age spread from around 24 to 43, bell-curve distributed. Otherwise, comparing efficacy results will not be meaningful.
- Formula, dosage, and treatment session and duration must be mentioned; treatment duration is proposed to be 12 months. Without this information in a trial, comparing efficacy results will not be meaningful.
- Treatment must select one of the following: Single formula without modification, single formula with modification per pattern differentiation, and multiple formulas per pattern differentiation.
- For standardization, condoms must be used during treatment period.
- The cure rate must be defined as pregnancy, for apparent reason.
- The effective rate must be defined as patients tested AsAb-negative for at least 3 months; this means that there will be at least 3 chances for pregnancy.
- The treatment principle and formula composition must be discussed, for a quality presentation.
- The control group randomization, age, sex and case history must show insignificant difference from the treatment group through statistical calculation.
- The control group's treatment must be clearly stated to indicate it as a valid treatment.

- A follow up exam to identify any lasting treatment effect is proposed to be 6 months and 12 months after the 12-month treatment period.
- For integrative TCM and biomedical treatment clinical trials, cortisone is proposed to be the primary treatment, since that is the most commonly used biomedical treatment; condom should be used during the treatment period.

The most important item of these trials, studies, reviews and discussions is the treatment efficacy. According to the derived average cure rate shown in Table 2, the treatment group average cure rate was 59% with respect to the control group 27.5%, and the treatment group average total effective rate of 87.7% over the control group 58.8%. This showed the TCM herbal treatment as superior. With these statistics, we may confidently state that, even though the trial numbers are limited, the TCM treatment group has significantly higher cure rate and total effective rate. The cure rate is the deciding factor; no matter how high an effective rate we may obtain, without fertility, it does not serve the purpose.

Conclusion

In this paper, detailed, systematic review of nine current, clinical trials and studies of AsAb-associated female infertility with TCM herbal treatment in China are given. The strengths and weaknesses of these clinical trials and studies have also been identified. Efficacy, herb frequency (appearing in formulas) list, and differentiated TCM patterns of reviewed clinical trials and studies have been derived to evaluate the treatment efficacy, and to facilitate future studies for better treatment methods. A set of design criteria for future clinical trials of AsAb-associated female infertility is proposed.

According to the cure rate (fertility rate) of the compiled efficacy statistics, it is concluded that, at the current stage, TCM herbal treatment is significantly better than all types of biomedical treatment. During this review process, an informal review of clinical trials of integrative TCM and biomedicine treatment for AsAb-associated female infertility with comparable backgrounds was also conducted. It was found that its general efficacy was very similar to the TCM treatment alone. This finding implies that TCM treatment alone is sufficient for this disorder. Therefore, further research and study on TCM treatment for AsAb-associated female infertility will be valuable for managing this disorder.

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