

**Treatment of Immunologic Recurrent Miscarriage with Chinese Herbal Medicine: A
Literature Review Synthesis**

By

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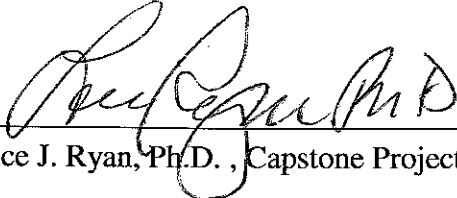
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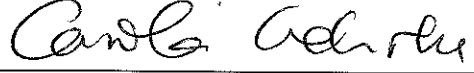
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Abstract

Over the years, many studies have been done to assess the effectiveness of various therapeutic modalities for the treatment of recurrent miscarriage (RM) due to immunological causes. No consensus has been reached, however, regarding the best therapeutic modality, and many concerns arise over the negative side effects associated with the long-term use of western medications such as aspirin, prednisone, and heparin. The objective of this study was to clarify the current literature available concerning the use of Chinese herbal medicine alone or the integrated use of Chinese herbs and Western medicine to treat immunological RM. In this retrospective literature review synthesis, the researcher employed a qualitative, thematic style of analysis to assess 30 articles which were selected from a variety of online search engines such as PubMed, Google Scholar, and Wanfang Data. The following data were recorded for each study: number of subjects, age range of subjects, number of previous miscarriages, observed immunological markers, treatment interventions, and control group interventions. Live birth rates, the percentages of patients who experienced a decrease in antibody titers, changes in immunological activity and trophoblast cell activity, number of weeks of sustained pregnancy, and the quality of research methodology and design were assessed and compared. Results were discussed in terms of the theoretical and clinical applications of the study, as well as limitations and further recommendations for future research on this subject.

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Chapter 1: Introduction

At present, the Western medical world has not yet found a truly safe and effective means of improving pregnancy outcomes in women with a history of recurrent miscarriage caused by immunological factors. Furthermore, there exists a considerable amount of uncertainty regarding the exact causes and mechanisms of this disease. Immunologic recurrent miscarriage encompasses a wide range of both autoimmune and alloimmune factors. Whereas autoimmune recurrent miscarriage involves an immune response against the self, alloimmune recurrent miscarriage is caused by an immunologic rejection and abnormal maternal immune response to paternally derived antigens located on the developing fetus. Whatever the exact cause may be, one of the complications associated with this immunological disorder includes an increased risk of recurrent early or late pregnancy loss, which can be quite a traumatic and debilitating experience for a woman wishing to conceive. Traditional Chinese medicine (TCM) is a system of medicine which has been used for thousands of years in China and has become an integral component of medicine in the Eastern world, and more recently, in the Western world as well. The use of Chinese herbal medicine, either alone or in combination with conventional Western medicine treatment modalities, to treat immunological causes of recurrent miscarriage has been a subject of research in China and Japan for the last ten to fifteen years, though it has been used for thousands of years to treat this disorder. Perhaps by combining the best of both Eastern and Western medicine traditions, we may be able to more effectively address this complicated disorder and improve pregnancy outcomes in women with recurrent pregnancy loss.

Immunologic Recurrent Miscarriage: A Western Approach

Autoimmune disorders associated with recurrent pregnancy loss include systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS). Both of these disorders are characterized by abnormally high levels of certain antibodies within the body, and as a result,

there is an increased risk of placental thrombosis, thromboembolic events, poor uteroplacental circulation, thrombocytopenia, and early or late pregnancy loss (Meroni et al., 2004). The presence of these antibodies may also inhibit trophoblast cell proliferation and thus result in impaired implantation (Chamley, Duncalf, Mitchell, & Johnson, 1998). APS is diagnosed in approximately 15% of patients with recurrent pregnancy loss (Kutteh, 1996), and among these cases, subsequent fetal loss rates of 60%-90% have been noted when the disease is left untreated (Lynch et al., 1994; Rai, Clifford, Cohen, & Regan, 1995). Conventional methods of treatment for autoimmune recurrent miscarriage include the administration of low molecular weight heparin (LMWH), unfractionated heparin, low dose aspirin (LDA), and immunosuppressive therapies such as prednisone and intravenous immunoglobulins. A meta-analysis of 13 randomized or quasi-randomized, controlled trials (849 patients) of interventions in pregnant women with APS recurrent miscarriage by the Cochrane Collaboration (Empson, Lassere, Craig, & Scott, 2005) concluded that the combined use of unfractionated heparin and aspirin may reduce pregnancy loss by 54%. A prospective, single-center trial of 50 pregnant women with a history of at least three consecutive miscarriages and who tested positive for antiphospholipid antibodies on two occasions found that the use of LMWH plus LDA resulted in an 80% live birth rate versus 44% in the group treated with aspirin only (Kutteh, 1996). The convenient once daily dosing of LMWH and the perception that it may have less impact on bone mineral density has made it the more favorable drug of choice compared to unfractionated heparin (Shefras & Farquharson, 1996). However, consensus on the efficacy of these two drugs varies widely, and more large-scale, randomized controlled trials are needed in order to fully explore the efficacy of these drugs as well as the difference between unfractionated heparin versus LMWH.

As mentioned above, alloimmune recurrent miscarriage involves an immunologic rejection of the developing fetus. Suggested mechanisms include maternal production of

antipaternal lymphocytotoxic antibodies, failure to produce maternal blocking antibodies to prevent a maternal cell-mediated immune attack on the developing embryo, increased natural killer cell activity, decreased suppressor T cell activity, and cytokine dysregulation involving an excessive T-helper lymphocyte-1 (also known as Th1 lymphocyte) inflammatory response that may be harmful to an implanting embryo (Speroff & Fritz, 2005). Immunostimulatory and immunosuppressive therapies such as paternal leukocyte immunization and administration of intravenous immunoglobulins, respectively, are currently used to treat alloimmune recurrent miscarriage, although there is no clear evidence that either of these therapies work. A more recent meta-analysis of treatment trials has found that paternal leukocyte immunization is not effective in the treatment of unexplained recurrent miscarriage (Porter, La Coursiere, & Scott, 2006).

The negative side effects of western drugs used to treat immunologic recurrent miscarriage may potentially outweigh the benefits. Prednisone, for instance, has been known to put pregnant women at an increased risk for premature delivery, pre-eclampsia (pregnancy-induced hypertension), gestational diabetes, and decreased bone density (Empson et al., 2005). Heparin also carries a low but potential risk of hemorrhage, thrombocytopenia, and when used long-term, fractures due to heparin-induced osteoporosis (Barbour et al., 1994; Lefkou, Khamashta, Hampson, & Hunt, 2010; Rai, Cohen, Dave, & Regan, 1997; Triolo et al., 2003). Patients with stomach sensitivities or allergies to aspirin cannot reap the anticoagulation benefits of aspirin therapy and have often been omitted from studies which investigate the use of aspirin for APS recurrent (Kutteh, 1996). From a clinical perspective, therefore, it is possible that using Chinese herbs in conjunction with western medicine can not only make the treatment more effective, but also decrease the dosage requirements and side effects associated with western medication.

Immunologic Recurrent Miscarriage: An Eastern Approach

Explanation of the underlying mechanisms and methods of treatment of immunologic recurrent miscarriage from a traditional Chinese Medicine (TCM) perspective varies greatly with that of Western medicine. One may think of Eastern and Western medicine as two different, but equally valid, ways of looking at the same thing. For example, if you look at satellite images of the Earth, you will realize that they vary greatly in scope and magnitude. Although the types of images created by different types of satellites look completely different from each other, they are in fact varying representations and aspects of the same reality. The same goes for TCM and Western medicine – they are simply two different systems used to understand and deal with the human body and its functions.

The essence of TCM lies in the belief that each individual is unique, and therefore the treatment method applied to each individual may vary depending on his or her current symptoms. This is contrary to Western medicine, in which the diagnosis is the same for all individuals regardless of their unique symptoms. Whereas TCM tends to look at the larger picture and tries to understand the overall pattern of symptoms within an individual, Western medicine tends to pinpoint and treat the specific disease, not taking into account that the disease may manifest in different ways in different people. According to Randine Lewis (2004), patients experiencing immunologic recurrent pregnancy loss tend to have symptoms associated primarily with Spleen Qi deficiency, Kidney Yin deficiency, Phlegm obstruction, Heat or Damp Heat, and/or Blood stasis. When Spleen Qi deficiency is present, the mother cannot “hold” the fetus; she may also exhibit other Qi deficiency symptoms such as loose stools, fatigue, over-worrying, and low appetite. The Kidneys are responsible for a women’s reproductive health and aging process. When Kidney Yin is deficient, short menstrual cycles, dry mouth, sore throat, constipation, dry eyes, tinnitus, irritability, a red, dry tongue, and a thin, rapid pulse may result. Phlegm

obstruction is characterized by symptoms such as fatigue, a feeling of heaviness through the limbs, and profuse vaginal discharge. Patients with Damp Heat suffer from yellowish discharge often accompanied by a foul odor, menstrual blood flow with slimy clots, vaginal or rectal itching, a reddish tongue with a thick yellow coat, and a thin, slippery, rapid pulse. Blood stasis is characterized by painful, often stabbing, cramps and large clots during one's period, a purplish tongue or one that has dark purplish discoloration or dots on the edges of the tongue, and a tight, wiry, or choppy pulse. Patients are prescribed Chinese herbs based on their TCM diagnosis .

The research available on this subject has focused mainly on Kidney and Spleen Qi tonifying herbs, and to a lesser extent, Blood moving and Heat clearing herbs before and often during pregnancy (Cheng & Ma, 2010; Cui and Hu, 2009; Zhan et al., 2009). From a Western medical perspective, Chinese herbs may exhibit an inhibitory effect on antibody titers. In a study comparing the integrated use of Chinese herbs plus Western medicine to treat antiphospholipid syndrome (APS), for instance, 86.7% (26/30) of patients in the treatment group experienced a significant decrease in antiphospholipid antibody titers compared to 66.7% (20/30) of patients in the Western medication only control group (Zhang, 2007). Other studies have shown that Chinese herbs have specific immune-modulating effects in patients with a history of immunologic recurrent miscarriage. Takakuwa et al. (1997) found that Chinese herbs cause “dynamic changes in peripheral blood lymphocyte subsets that [have been] examined in patients with recurrent abortion and positive for [antiphospholipid antibodies].” Furthermore, research on the use of a Chinese herbal formula composed of Xiao Chai Hu Tang and Wu Ling San have found that the herbs Chai Hu and Ren Shen possess anti-allergic effects and can be used to minimize the dose of corticosteroid medication necessary in patients with nephrotic syndrome (Takakuwa et al., 1997). Whereas western medications such as aspirin and heparin are designed merely as symptomatic treatments for the blood clotting that often occurs in patients

with autoimmune recurrent miscarriage, Chinese medicine, on the other hand, can effectively deal with the root cause of the disease by decreasing the levels of antibodies that are responsible for direct tissue damage, and without the side effects of immunosuppressive medications such as prednisone. In my clinical experience, patients are much less likely to experience negative side effects when taking Chinese herbs, as the herbal formulas themselves are usually comprised of anywhere from 10 to 20 herbs which, when taken together, help to balance out the different effects of the herbs.

Research Goals

Having encountered patients in my clinical practice with immunological disorders who have not responded favorably to conventional Western medicine but who have benefited greatly from the combined use of Chinese herbs in combination with Western medicine, it is the goal of this literature review synthesis to gain a better understanding of how Eastern and Western medicine are integrated in the clinical setting and to discover, in the end, what types of combined therapeutic modalities are the most effective in addressing this disorder.

A review and synthesis of the available literature regarding the treatment of immunologic recurrent miscarriage using Chinese herbal medicine aims to answer the following questions: What types of immunological effects does Chinese herbal medicine alone, or a combination of Chinese herbs and Western medicine modalities produce in the treatment of women with a history of immunologic recurrent miscarriage who seek successful pregnancy outcomes? How effective are these various treatment modalities in returning abnormally high antibody levels or T-helper lymphocyte subsets back to normal, and ultimately, how effective are they in achieving live birth in women with a history of recurrent miscarriage due to immunological factors? What types of Chinese herbs and/or herbal formulas, as well as basic TCM treatment principles, are used in the treatment of this disorder?

This study will begin to clarify on the current literature available concerning the use of Chinese herbal medicine alone or the integrated use of Chinese herbs and Western medicine to treat immunologic recurrent miscarriage. It will serve to uncover the strengths, weaknesses, and limitations as well as similarities and differences among the available research, and provide the research community with a basic foundation from which to construct future areas of research on this topic. It will seek to reveal the impact which Chinese herbs and Western medicine have on various aspects of pregnancy success, such as live birth rate, antibody titers, and lymphocyte subset levels. As there are few papers which have been published in the English language regarding this topic, it will be useful for traditional Chinese medicine practitioners trained in the West to understand and get a glimpse of the research which has been carried out in China so that they may use the knowledge gained from this research to more effectively treat their own patients. This study will be especially valuable and beneficial for women with a history of autoimmune or alloimmune recurrent miscarriage who do not react well to or have not had success with conventional Western medicine treatment modalities.

Definition of Terms

- **Antibody.** A protein substance produced by the body in response to a stimulating substance (antigen) (Marrs, Block, and Silverman, 1997).
- **Antigen.** Any foreign substance that causes the body's immune system to produce antibodies against it (Marrs et al., 1997).
- **Antiphospholipid syndrome.** Antiphospholipid syndrome (APS) refers to the presence of antiphospholipid antibodies, also known as anticardiolipin antibodies, which are a heterogenous group of acquired autoantibodies that are directed against negatively charged phospholipids, in the body. Phospholipids are normal components of all cell membranes, which help cells stick to each other. In simple

terms, they help the fetus “stick” to the uterus. Antiphospholipid antibodies interfere with this process, thus preventing the fetus from implanting and attaching to the uterus, and also causing problems with uterine and placental blood flow. APS causes constriction of blood vessels, decreased blood flow throughout the circulatory system, and damage to the blood vessel walls causing blood cells to stick to the site of injury, resulting in blood clots. Antiphospholipid antibodies can be detected by different assays such as the lupus anticoagulant, anticardiolipin antibody, and anti-cardiolipin- β 2 glycoprotein assays. (Empson et al., 2005; Kutteh, 1996; Marrs et al., 1997).

- **Blocking antibodies.** Protective antibodies that are formed by the mother’s immune system in response to her embryo during implantation. In a normal, healthy pregnancy, the mother initially sends out a rejection signal to the newly forming embryo, whose genetic material and tissue consists of both maternal and paternal elements. This initial rejection causes the embryo to send out a signal to the mother’s immune system, “telling” it to not reject the embryo even though its genetic makeup is different from the mother’s. The mother’s immune system then begins to produce a protective coat of blocking antibodies around the embryo, preventing it from being attacked by the maternal immune system (Marrs et al., 1997).
- **Cytokine.** Small cell-signaling protein molecules that are secreted by cells of the immune and nervous systems. They are used in intercellular communication and are sometimes used to refer to immune modulating agents such as interleukins and interferons (“Wikipedia,” 2011).

- **Intravenous immunoglobulin therapy (IVIG).** Intravenous administration of high doses of IgG (immunoglobulin G) pooled from the plasma of healthy individuals. This therapy has been shown to benefit patients with certain autoimmune disorders (Triolo et al., 2004).
- **Miscarriage.** The loss of a pregnancy before 20 weeks of gestation, or before the fetus weighs one pound (Speroff and Fritz, 2005).
- **Natural killer cells.** Large lymphocytes (white blood cells) that attach to cells and dissolve them by releasing cytotoxins. Excessive natural killer cells in the blood are correlated with pregnancy loss (“INCIID,” 2004).
- **Paternal leukocyte immunization.** The process of injecting a woman with her male partner’s white blood cells in order to increase her maternal blocking antibodies and lower her natural killer cells (“INCIID,” 2004).
- **Placental thrombosis.** Intravascular coagulation that occurs in the placenta and veins of the uterus (“The Free Dictionary,” 2011).
- **Recurrent miscarriage.** Usually defined as three or more pregnancy losses, which may or may not be consecutive. However, according to Speroff and Fritz (2005), “there is no specific number of miscarriages or firmly established criterion that justifies evaluation for recurrent pregnancy loss or defines the scope of investigation” (p. 1070).
- **Systemic lupus erythematosus.** Systemic lupus erythematosus (SLE) is an autoimmune disorder found mostly in females of reproductive age and is associated with recurrent pregnancy loss. It is a multi-system disorder with variable clinical manifestations ranging from mild rashes and musculoskeletal symptoms to involvement of major organs, including the kidneys, lungs, heart,

gastrointestinal, hematopoietic, and central nervous systems. It is characterized by the presence of autoantibodies known as antinuclear antibodies, antiphospholipid (also known as anticardiolipid) antibodies, lupus anticoagulant, and elevated serum concentrations of specific immune complexes (Speroff & Fritz, 2005).

- **Thrombocytopenia.** A disorder characterized by an abnormally low number of platelets in the blood, which can cause abnormal bleeding (“PubMed Health,” 2010).
- **Trophoblast.** Cells which make up the outer layer of the blastocyst and eventually develop into the placenta. Trophoblast cells play an important role in embryo implantation (“Wikipedia”).

Chapter 2: Method

Introduction

The Method section will provide information pertaining to the research design, selection of data sources, sampling procedures and rationale, data collection instruments, data analysis, and study limitations of this literature review synthesis. This study will clarify the current literature available concerning the use of Chinese herbal medicine alone or the integrated use of Chinese herbs and Western medicine to treat women who suffer from recurrent miscarriage due to immunological causes. It will serve to uncover the strengths, weaknesses, and limitations as well as similarities and differences among the available research, and provide the research community with a basic foundation from which to construct future areas of research on this topic.

Research Design

This retrospective study used a qualitative research method to review, analyze, and generate appropriate and emerging themes and ideas relating to the available literature. A thematic style of analysis was appropriate for this literature review synthesis, for it allowed me to identify themes and patterns within the surplus of data available from all 30 studies. Through the process of identifying patterns, I was able to extract interrelated themes and sub-themes which helped bring meaning to data that would otherwise have been meaningless when viewed alone (Aronson, 1994). A thematic analysis of the data is an effective method of organizing, interpreting, and making sense out of already-existing data, and it is often appropriate as a groundbreaking preliminary study that will identify factors and variables that will be explained in subsequent systematic and controlled studies. Also, given the current limitations in time and availability of resources for this project, a qualitative literature review synthesis was therefore

the most appropriate method of investigating immunologic recurrent miscarriage for this capstone project.

Sample and Sampling Procedures

The source of data for this study includes research articles that have been extracted from a number of traditional Chinese medicine and Western medicine journals. The online research databases PubMed, Wanfang Data, CQVIP, World Cat, Google Scholar, EBSCOhost, and the UCLA online journal database were used to search for research articles and collect data pertaining to my capstone topic. The search was done in the principal investigator's house, at the UCLA Biomed library, or at the Yosan University library. A combination of the following key words or phrases were used in the search: immunologic miscarriage, chinese herbs, herbal medicine, herbal therapy, herb*, antiphospholipid antibody, anticardiolipin antibody, integrative medicine, recurrent miscarriage, recurrent spontaneous abortion, recurrent pregnancy loss, immunologic infertility, alloimmune miscarriage, autoimmune miscarriage, natural killer cell, blocking antibody, antisperm antibody. Case studies as well as larger sample studies were included in the search. Studies using different formulations of Chinese herbal medicine, such as patent pills, raw herbs, and intravenous injections were also included.

A search on PubMed generated a total of 28 citations; 19 abstracts were selected for review, and 13 articles were selected for possible inclusion in this literature review synthesis. Wanfang Data website generated a total of 184 articles; a total of 51 abstracts were reviewed, out of which 26 articles were selected for analysis. CQVIP yielded 215 citations; 42 abstracts were reviewed, and 15 articles were selected. World Cat search engine brought up 76 citations; 4 abstracts were reviewed; 1 was selected for review. Google Scholar brought up a total of 900 citations; 10 abstracts were reviewed, and 4 were selected for possible inclusion in this study. A search on EBSCO Host generated 4 citations, all of which were reviewed and included in this

literature review synthesis. Of the reviewed articles, 30 were selected for inclusion in the literature review synthesis based on the following criteria: Patients in these studies were 1) females who 2) were trying to get pregnant or who already were pregnant, 3) had a history of at least 2 or more miscarriages, 4) tested positive for autoimmune or alloimmune causes of miscarriage, 5) had no other genetic, anatomic, endocrine, male factor, or infectious complications related to infertility, and 6) the treatment intervention consisted of the administration of Chinese herbal medicine with or without Western medicine. Currently, recurrent pregnancy loss is usually defined as 3 or more pregnancy losses. However, most doctors will also treat women with a history of 2 consecutive miscarriages, and “there is no specific number of miscarriages or firmly established criterion that justifies evaluation for recurrent pregnancy loss or defines the scope of investigation” (Speroff & Fritz, 2005). I did not eliminate articles for review based on the quality of their research methodology. This was due to the presence of a minimum required number of articles to be reviewed in this capstone dissertation – 30 articles, to be exact - and the purpose of this paper was to synthesize and provide the reader with an overall view of the current available literature, irrespective of the quality of the study’s research design.

Instrumentation and Data Collection Procedures

Summary tables and matrices were used in order to organize, extract, and summarize information pertaining to each article. The information obtained from these tables was used to form the foundation by which major themes and conclusions would be drawn in the Results and Discussion sections of the paper. The 30 articles selected for analysis were scanned for major emerging themes and categories of data. A research question or major theme pertaining to each group of information was formed and translated into various tables that would allow the principal investigator to analyze and count the results of the data. The results or response categories

within each table were then counted by frequency in order to discover possible emerging themes within the data that would guide the researcher in formulating answers to the research questions pertinent to this literature review synthesis. Throughout the process, tables were modified or condensed together with other tables in order to form more coherent categories of information. A final review of the research articles, data analysis tables, and results of findings was conducted in order to ascertain that the information given in the text, the tables, and the results section of this paper were consistent with one another.

In order to address the issue of validity and trustworthiness of my data analysis technique, I cross-checked three studies together with my research supervisor in order to assess and confirm the consistency and reliability of the coding system used in my data analysis tables.

Data Analysis

This section will explain the process by which data were extracted and analyzed for the purposes of this study, as well as the types of data that were collected. Appendix A provides a list of the 30 research articles used in this literature synthesis, in order of study number. The use of tables to conduct my analysis and review of the literature was the most appropriate method of analysis, for it allowed me to conveniently organize, assess, add up, and total the results pertaining to each category of information. This study made use of a univariate analysis of the data. Counts, frequency counts, percentages, mean values, and range of values were calculated when applicable.

Overview of articles. The first part of the data analysis process included the task of summarizing the various treatment modalities used for both the treatment and control groups in the studies in order to get a general idea of the types of research available regarding this subject. The 30 studies were divided into five basic categories based on the types of treatments administered in the studies (see Appendix B): 1) Chinese herbs only, 2) Chinese herbs plus

Western medicine (no control group), 3) Chinese herbs only versus Western medicine only, 4) Western medicine only versus Chinese herbs plus Western medicine, and 5) Chinese herbs only versus Chinese herbs plus Western medicine versus Western medicine only (3 treatment groups). “Chinese herbs” refers to the use of Chinese herbs in pill form, decoction form, or by injection into the body. “Western medicine” refers to the use of any other non-herbal treatment modality such as aspirin, prednisone, vitamin supplements, heparin, or immune therapies such as the administration of intravenous immunoglobulin. A separate summary table for each of the five treatment categories was subsequently created, with a summary for each of the studies which fell under that category (see Appendices C through G). The following data were recorded for each study: number of subjects, age range of subjects, number of previous miscarriages, observed immunological markers (antiphospholipid antibodies, natural killer cells, antinuclear antibodies, lupus anticoagulant, etc), treatment intervention (herbs/medication, dosage, duration, method of administration), and control/placebo group treatment intervention.

Outcome measures and results. Next, the types of outcome measures related to treatment were analyzed and grouped into five different outcome categories: 1) Outcome 1– live birth rate, 2) Outcome 2– percentage of patients who experienced a decrease in antibody titers after treatment, 3) Outcome 3 – changes in immunomodulatory activity (e.g., lymphocyte subsets, cytokine levels), 4) Outcome 4 – number of weeks of sustained pregnancy, and 5) Outcome 5 – change in trophoblast cell activity. A table was created which listed and totaled the number of studies which measured each outcome (see Appendix H).

Afterwards, the results and researcher-derived conclusions for each study were recorded on a separate table, beginning with study number 1 and finishing with study number 30 (see Appendix I). Each study could have included multiple outcome measures, results, and conclusions. The data for outcome categories 1, 2, 3, and 4 (see above) were grouped into their

own sub-tables and further summarized; mean and range of values were calculated via univariate analysis of the data (see Appendices J through L).

Conclusion categories. The researcher-derived conclusions were based on the results of the studies. I reviewed the studies from a conservative perspective and only indicated that the effect of a study appeared to have a significant effect if statistical data indicated as such, or if the data appeared to show strong improvement. Each conclusion statement was then categorized into one of ten possible conclusion categories (See Table 4).

Herbs used. An Excel spreadsheet was used to chart the herbs which were used in each of the 30 studies and the frequency of their usage (see Appendix O). The frequency and percentage of use of each of the herbs was then calculated and summarized in Table 2.

Quality assessment of research methodology. Various factors relating to research methodology of the included studies were examined, and a researcher-derived assessment of the methodology and design of each study was conducted (see Appendix M). The validity and reliability of each study was based on the following criteria: 1) whether the research design was clearly stated, 2) whether the selection of subjects was randomized, 3) whether the description of randomization method was given, 4) whether the variables were clearly stated or not, 5) whether a control group was present, 6) whether inclusion and exclusion criteria were clearly stated, and 7) whether the description of treatment intervention was sufficient enough in detail that it could be repeated by others. The research design was clear if the study could be categorized into its appropriate research design category - experimental or non-experimental - and if it could be deciphered whether it was pre-experimental in nature, whether it contained a control group, whether it contained a quasi-experimental design, or what type of non-experimental research design it was. When deciding whether the description of the treatment was sufficient enough in detail so as to be replicable, the following criteria were examined: 1) Were the Chinese

medicine herbs used for the study described in sufficient enough detail so that others wanting to replicate the study would know which exact herbs to use? 2) Were the dosage, duration, time period, frequency, and method of administration of Chinese medicine or Western medicine usage clearly described? 3) Did the researcher clarify when and how often lab tests were administered? Articles were considered highly relevant if all seven criteria contained “yes” answers. Articles were considered “relevant” if the study fulfilled four to six criteria. Articles which met only two to three of the criteria were judged “somewhat relevant.” And articles which fulfilled only one or zero criteria were considered “not relevant.”

Summary of study designs. The purpose of the last data collection table was to summarize the research designs of the articles selected for the literature review synthesis. The table was divided into “experimental” and “non-experimental” sections. The “experimental” section was further subdivided into “pre-experimental,” “experimental,” and “quasi-experimental” sections. The “non-experimental” studies were limited to case studies or case series. See Appendix N for details.

Limitations

The limitations encountered in conducting this literature review synthesis include the fact that my literature review synthesis was conducted on only 30 studies, that most of the studies selected for analysis were small-scale studies or case studies, and that there was significant variability amongst the studies in regards to the combination of medicines used in the experimental and control groups, which resulted in more scattered, less coherent categories of treatment interventions and outcome results reported in this study. An obvious limitation of doing a retrospective literature review synthesis was the lack of control of the researcher over the variables of interest in the studies. For example, there was a lack of articles which compared Chinese medicine with aspirin and low molecular weight heparin as the control group. Therefore,

the research questions asked in this study could only be answered to the extent that there was sufficient literature available that could form the basis of the researcher's answers. Being that I was the only coder for this literature review synthesis, it was possible that the reliability of the data was compromised due to single rater limitations. Despite these issues, however, there still exists much information from these studies that can provide insights into the effectiveness and use of Chinese medicine to treat immunologic recurrent miscarriage.

Chapter 3: Literature Review

Introduction and Overview

This chapter will provide a summary and review of the literature which was used for this literature review synthesis. A description of the research designs, treatment strategies, and herbs or Western medication used throughout the studies will be provided. Results and findings of the studies will be briefly reviewed.

A total of 30 articles examining the use of Chinese herbs with or without Western medicine for various types of immunologic recurrent miscarriage satisfied the criteria for inclusion in this literature review synthesis. Of these articles, twelve examined the exclusive use of Chinese herbal decoctions or patent herbal formulas to treat immunologic recurrent miscarriage; seven articles compared Western treatment alone versus Chinese herbs plus Western medicine; six compared the effectiveness of Chinese herbs alone versus Western medicine treatment modalities; three studies assessed the effectiveness of the combined use of Chinese herbs and Western medicine; and two articles each consisted of three treatment groups comparing the use of Chinese medicine alone, Chinese herbs plus Western medicine, and Western medicine alone. A total of five articles were either case studies or case series. Below is a summary of these articles.

Studies Focusing on the Use of Chinese Herbs Alone

Sairei-to (Chai Ling Tang). There was a total of 12 research articles evaluating the effectiveness of different Chinese herbs or patent herbal formulas when used used alone. Three of these articles were based on research done in Japan on an herbal formula known in Japanese as “Sairei-to,” known in Mandarin as “Chai Ling Tang,” which is composed of two basic Chinese medicine formulas, Xiao Chai Hu Tang and a modification of the traditional Wu Ling San (Takakuwa et al., 1996; Takakuwa et al., 1997; Kano, Shimizu, & Kanda, 2010). Xiao Chai

Hu Tang is composed of the herbs Chai Hu, Ban Xia, Huang Qin, Da Zao, Ren Shen, Gan Cao, and Sheng Jiang. The modified Wu Ling San contains the herbs Zhu Ling, Fu Ling, Ze Xie, Bai Zhu, Cang Zhu, and Gui Zhi. In the study by Takakuwa et al. (1996), 12 patients with a history of two or more spontaneous abortions during the first trimester who were positive for one or more antiphospholipid antibodies (APA), also known as anticardiolipin antibodies (ACA) were treated with nine grams per day of Sairei-to in granule form starting from when they were not pregnant. After APA values returned to normal, patients were allowed to become pregnant. The formula was continued throughout pregnancy and discontinued after delivery. The main outcome measure was the APA titer values before, one month after, two months after, and three months after administration of the herbal formula, as well as at the first trimester of pregnancy. APA titers returned to normal in 75% (9/12) of the patients, and 83% (10/12) of these patients continued to have uneventful pregnancies and achieved live births. The author concluded that Sairei-to was an effective therapy for patients with APA positive recurrent miscarriage and that “there were no remarkable adverse effects accompanied by Sairei-To therapy.”

In another case series research paper by the same author (Takakuwa et al., 1997), an identical protocol was implemented on 11 patients who were positive for antiphospholipid antibodies (APA) and who had experienced two or more consecutive spontaneous abortions. In addition to measurements of APA levels, the presence of lymphocyte subsets (CD3, CD8, CD19, CD57, etc.) was also measured before and one and two months after administration of Sairei-to, and at the first trimester of the pregnancy. 82% (9/11) of the patients treated with Sairei-to delivered healthy offspring, and the remaining two patients experienced repeated abortions. APA levels during the first trimester went back to normal levels in all patients except for one. The percentage of CD19-positive cells (Cluster of Differentiation markers are specific cell surface protein markers located on lymphocytes) significantly decreased at two months after the

start of treatment and also at the first trimester of pregnancy. CD4-positive lymphocytes significantly increased at the two month mark, and the CD4/CD8 ratio also increased significantly. The author concluded that the successful continuation of pregnancies in a majority of the patients was due to Sairei-to's ability to suppress the expression of CD19-positive cells (and therefore excessive antibody production) and increase the CD4/CD8 ratio.

The study by Kano et al. (2010) compared two variations of the Sairei-to formula on 52 patients who tested positive for antinuclear antibodies (ANA) or antiphospholipid antibodies (APA). Nine grams per day of Sairei-to granules were administered 30 minutes before a meal (the duration of treatment was not stated). 63% (17/27) of patients who were ANA positive experienced a decrease in antibody titers after treatment, but the article did not mention whether the results were significant or not. 100% (7/7) of patients who tested positive for a specific type of APA, known as anticardiolipin antibody immunoglobulin G (ACA IgG), experienced a decrease in antibody titers after treatment ($p < 0.04$). Another 59.3% (16/27) of patients who tested positive for a different type of APA known as anticardiolipin antibody immunoglobulin M (ACA IgM) showed reductions in antibody levels, although the results were not statistically significant ($p < 0.206$). After taking the second variation of the Sairei-to formula (which leaves out the herb Cang Zhu and uses Bai Zhu and larger doses of Zhu Ling, Fu Ling, and Gui Zhi instead), however, 93% (26/27) of patients experienced reduced antibody titers. Kano and researchers also recorded the pregnancy and live birth rates of patients in their study. 59.3% (16/27), 14.3% (1/7), and 48.1% (13/27) of patients in the ANA positive, ACA IgG positive, and ACA IgM positive groups, respectively, became pregnant. Out of those who became pregnant during the study, 62.5% (10/16), 100% (1/1), and 76.9% (10/13) of the ANA, ACA IgG, and ACA IgM positive patients, respectively, achieved live births. It is debatable, however, whether the herbal formulas were effective in improving overall live birth rates, however, because taken

as a whole, only 37% (10/27), 14.3% (1/7), and 37% (10/27) of the *total* subjects in the ANA, ACA IgG, and ACA IgM groups, respectively, had live births by the end of the study. As researcher, I came to the conclusion that the Chinese herbs did not appear to be effective in achieving live birth in a majority of patients even though a significant percentage of patients experienced decreases in antibody titers.

Antiphospholipid syndrome and other immunological factors. Studies 17 (Meng, 2006), 18 (Wang, 2004), 22 (Yuan & He, 2004), and 23 (Yuan, 2005) also focused on the treatment of patients who were positive for antiphospholipid antibodies (APA) with the use of only Chinese herbs. Study 17 (Meng, 2006) was a case study in which a 28 year old patient who had previously experienced three miscarriages was administered herbs for three months. Although it is not clear whether she was required to continue taking the herbs until she became pregnant the next year, it is assumed that she did. It was also inferred that she took herbs during her pregnancy, but it is not clear whether the same herbal formula was used. It appears that the Chinese herbs taken before and during pregnancy were effective in preventing miscarriage and achieving live birth in this one patient. Study 18 (Wang, 2004) examined the live birth rate and percentage of patients who experienced a decrease in APA titers in a group of 43 patients between the ages of 26 to 42 years old who had previously experienced three or more miscarriages and who were pregnant at the start of the study. The live birth rate was 86% (37/43), and the percentage of patients who experienced a decrease in APA titers was 55.8% (24/43). It appeared, then, that the Chinese herbal formula taken during pregnancy in particular helped improve the live birth rate, although the duration of treatment was not specifically stated.

Study 22 (Yuan & He, 2004) looked at 36 patients whose pregnancies had just been confirmed via ultrasound. The Chinese herbal tea Tai Er An Fang, which is composed of the herbs Dan Shen, Dang Gui, Chi Shao, San Qi, Tu Si Zi, and Huang Qi, was taken daily until

antiphospholipid antibody (APA) levels returned to normal, an ultrasound revealed a viable fetus, and patients who had previously been experiencing bleeding or spotting during pregnancy stopped bleeding. The study measured the percentage of patients who experienced a decrease in antibody titers after treatment. The authors stated that 86.1% (31/36) of patients either experienced a decrease in APA levels, stopped bleeding or spotting, or succeeded in having viable pregnancies or pregnancies which resulted in live births after treatment. It did not differentiate between these patients, and therefore it is impossible to know specifically how effective the herbs were for each of these measures of pregnancy success. The reliability and validity of the research design and methodology of this study were questionable.

Study 23 (Yuan, 2005) was also conducted by the same author in the following year. Bu Shen Yi Kang Tang, which consisted of the herbs Tu Si Zi, Shu Di Huang, Chuan Xu Duan, Gou Qi Zi, Lu Jiao Pian, Dang Gui, Bai Shao, Dan Shen, Fu Ling, and Zhi Gan Cao, plus the addition of other herbs which were based on the patients' individual diagnoses were administered during the non-pregnant state until APA levels normalized. APA levels returned to normal in 97.2% (35/36) of patients after two to three 10-day treatment cycles.

Study 5 (Si, 2007) examined the live birth rate of 191 patients who suffered from ABO incompatibility (an immune reaction that occurs when the blood type of the mother and fetus are incompatible), Rhesus (RH) incompatibility (a disease in which an Rh negative mother may produce RH antibodies against the fetus if the fetus' father is Rh positive), or the presence of antiphospholipid antibodies (APA) after being treated with Bao Chan Shen Xiao Fang herbal decoction and/or pills during pregnancy. 86.2% (25/29) of the patients had successful pregnancy outcomes.

Study 20 (Gui, Xu, Yu, & Li, 1997) focused on the use of Kidney and Qi tonifying, heat clearing, and fetus calming herbs to treat 68 patients who were less than three months pregnant

with a history of three or more miscarriages. Changes in immunomodulatory activity, hormone levels, and live birth rate were recorded. 88.2% (60/68) of patients showed signs of a viable pregnancy via ultrasound or had already experienced a live birth by the time the study was published. The researchers found a significant increase in blocking effect after treatment in the patients who originally had blocking antibody deficiency ($p < 0.05 \sim p < 0.01$).

Study 21 (Li et al., 2000) examined the effect of Yang Xue An Tai granules on suppressor T cell (also known as T lymphocyte) activity after three months of treatment in 56 patients who had a history of four or more miscarriages and had just recently confirmed that they were pregnant. A complete list of herbs in Yang Xue An Tai granules was not provided, unfortunately. 87.5% (49/56) of pregnancies resulted in live births, and suppressor T cell activity increased significantly in the second ($p < 0.01$) and third ($p < 0.001$) trimesters of pregnancy. Study 26 (Liu, Li, Yang, Wang, and Du, 2006) also looked at changes in T lymphocyte activity after administration of the herbal formula Yi Qi Gu Shen Tang, which contains the herbs Bai Zhu, Chai Hu, Gou Qi Zi, Huang Qi, Huang Qin, Shan Yao, Shan Zhu Yu, Shu Di Huang, Tu Si Zi, and Xu Duan. The herbal formula was prescribed for one to three months before pregnancy. CD4 (cluster of differentiation) and CD8 T lymphocyte levels were measured before and after treatment. After pregnancy was achieved, the herbs were continued intermittently until after the third month of pregnancy had been reached. 70% (21/30) of the patients achieved live birth (the pregnancy rate was not available), CD8 levels increased significantly ($p < 0.05$), and the CD4 /CD8 ratio significantly decreased after treatment ($p < 0.05$).

Study 29 (Cui and Hu, 2009) recorded changes in specific cytokines produced by TH1 (T helper 1) and TH2 (T helper 2) cells. An herbal formula known as Sang Qi Tang plus additional herbs based on the patients' individual diagnoses were administered. Duration of treatment and

directions on how to decoct the herbs were not explained. A significant decrease in the cytokines produced by TH1 cells – i.e., Interleukin-2 (IL-2) and tumor necrosis factor α (TNF α) - as well as in CD4 (cluster of differentiation 4) levels and the CD4/CD8 ratio occurred after treatment ($p < 0.05$), and a significant increase in IL-10 and CD8 levels was found ($p < 0.05$). Furthermore, the treatment group's cytokine levels by the end of treatment were the same as the comparison “normal” group's levels.

Western Medicine Treatment Alone Versus Chinese Herbs Plus Western Medicine

Seven articles compared the effectiveness of using Western medicine alone (Western Only) versus a combination of Chinese herbs and Western Medicine (CH/Western) in treating immunologic recurrent miscarriage. Study number 6, 8, 11, 13, and 14 focused on the treatment of antiphospholipid syndrome (APS), and study number 9 and 12 focused on other types of antibodies such as antisperm antibodies, anti-ovarian antibodies, and endometrial antibodies. The participants in these studies had a history of at least two or more miscarriages.

Antiphospholipid syndrome. Study 6 (Liu, Liu, Wu, Chen, and Liu, 2003) compared the effectiveness of using a combination of 100 mg/day of vitamin E and 10 mg, three times per day of folic acid in the Western Only control group, versus the same Western supplements combined with once daily intravenous injections of 250 ml of 5% glucose and 30 ml Dan Shen (*Salvia Miltiorrhiza*) solution. If the patient was already pregnant, treatment was continued for three to six months. 92.8% (26/28) of patients in the CH/Western medicine treatment group experienced a drop in anticardiolipin antibody levels, versus 14.3% (2/14) in the Western Only comparison group ($p < 0.01$).

Study 8 (Li, 2003) compared the use of Western medicine only with another group administered both Western medicine and An Tai Jiao Nang pills. After confirming a positive pregnancy blood test, 2000 Units of human chorionic gonadotropin (HCG) were intramuscularly

injected every other day, and Vitamin E supplements were also administered (the dosage and frequency of use were not reported). If the patient was experiencing bleeding or spotting, 20 mg of progesterone was also administered every other day via intramuscular injection, alternating with HCG. The western medicine treatment was the same for both groups. In the CH/Western group, An Tai Jiao Nang pills, which consist of the herbs Bai Shao, Bai Zhu, Chen Pi, Dang Shen, He Shou Wu, Nu Zhen Zi, Sang Ji Sheng, Tu Si Zi, Xu Duan, and Zhu Ma Gen, were administered three times per day, four pills each time. The treatment was continued for another two months if a fetal heartbeat was detected on ultrasound 50 days since the last menstrual period. The data for this article was inconsistent, but it can be inferred that the percentage of patients in the CH/Western treatment group who experienced a decrease in anticardiolipin antibody (ACA) titers was 83.3% (25/30), and in the Western Only control group, 60.0% (18/30), with a significant difference between the two groups ($p < 0.01$). The study also compared the number of patients in both groups whose pregnancies made it to ≥ 28 weeks. 93.3% (28/30) versus 73.3% (22/30) of patients in the treatment and control group, respectively, made it through 28 or more weeks of pregnancy ($p < 0.05$).

Study 11 (Shu, Miao, and Wang, 2002) examined and compared the live birth rates and percentages of patients who experienced a decrease in anticardiolipin (ACA) titers after treatment in a CH/Western group and Western Only group. In the CH/Western group, folic acid, Vitamin C, multi-vitamins, and Chinese herbs were administered for two to three months before attempting pregnancy and until ACA titers became negative. The herbs consisted of Bai Zhu, Dan Shen, Dang Shen, Dang Gui, Fu Ling, Huang Bai, Huang Qi, Huang Qin, and Yin Chen Hao. After pregnancy was confirmed, the same Chinese herbal formula was taken for five to ten days, and intramuscular injections of progesterone and human chorionic gonadotropin (HCG) were given. The Western medicine control group was only prescribed folic acid, vitamin C, and

multi-vitamins throughout the treatment program. The pregnancy rate was not reported, but the percentage of live births in the CH/Western treatment group was significantly greater than the control group – 82.6% (19/23) compared to 16.7% (3/18), ($p < 0.01$). A conclusion regarding the percentage of patients who experienced a decrease in ACA titers could not be drawn because the result for the control group was missing or unavailable.

Study 13 (Ye, 2008) compared the effectiveness of low dose aspirin (LDA) alone versus LDA plus Chinese herbs in the treatment of threatened miscarriage in patients who had tested positive for the presence of anticardiolipin antibodies (ACA) and who were in their first trimester of pregnancy and experiencing symptoms of threatened miscarriage at the start of treatment. The treatment was continued until ACA levels tested negative two consecutive times one month apart. Patients in the Western medicine only control group were given 50-80 mg of aspirin, once per day. Although none of the patients in the study achieved full-term pregnancies, but 92.3% (42/45) of the patients in the CH/Western treatment group achieved premature deliveries resulting in live births, compared to 75.6% (34/35) in the Western medicine only group. The difference between the two groups was significant ($p < 0.05$).

Study 14 (Zhang, 2007) compared the use of low dose aspirin (LDA) and Chinese herbs to a Western medicine only control group (Western Only) administered LDA and oral prednisone in the treatment of antiphospholipid syndrome. The CH/Western group was given 25 mg of LDA, twice per day, combined with a Chinese herbal formula made primarily of Kidney tonifying and Blood moving herbs – Chuan Xiong, Dan Shen, Sheng Gan Cao, Huang Qi, Nu Zhen Zi, Shan Zhu Yu, Shu Di Huang, Tu Si Zi, Yi Mu Cao, and Ze Lan. The Western medicine only group was administered 25 mg LDA and 5 mg oral prednisone, once per day. Patients were instructed to use condoms to prevent pregnancy while the treatment was continued for one to three months until anticardiolipin antibody (ACA) levels returned to normal. After treatment,

ACA levels changed from positive to negative in 92.3% (42/45) of patients in the CH/Western treatment group, compared to 66.7% (20/30) in the control group, with the differences between the groups being significant ($p < 0.05$).

Other immunological factors. Studies 9 (Chai and Zhao, 2002) and 12 (Zhang, 2002) looked at the use of Chinese herbs and/or Western medicine to treat immunologic recurrent miscarriage due to the presence of other antibodies such as antisperm antibodies, antiovarian antibodies, endometrial antibodies, and anti-HCG antibodies. The study by Zhang (2002) also included patients who tested positive for antiphospholipid antibodies. In Study 9, patients were instructed to use condoms to prevent pregnancy during the three to six months of treatment. Both the CH/Western treatment group as well as the Western Only group were required to take 5 mg of prednisone, three times per day for seven days starting from cycle day 3 of each month. Once the patient became pregnant, 20-40 mg of progesterone was administered once a day, along with an intramuscular injection of 2000 IU of HCG once every other day. After three months of pregnancy, the patient was gradually tapered off of the medication. In addition to the Western medication, the CH/Western patients also took a variety of Chinese herbs. Kidney deficiency patients were given a modified version of a traditional herbal formula known as Yu Ling Zhu, and patients diagnosed with Liver Qi stagnation were given a modified Jia Wei Xiao Yao San formula. During pregnancy, a different set of herbal formulas was administered for three to five months of the pregnancy. Kidney deficient patients were prescribed a modified Bu Shen Gu Tai Yin, while Qi and Blood deficient patients were prescribed a modified Yang Xue An Tai Tang formula. The percentage of patients in the CH/Western group who experienced a decrease in antibody titers was significantly greater than the Western Only control group ($p < 0.01$) - 77.8% (28/36) compared to 25% (5/20). The percentage of patients in the treatment group who made it

through more than 15 weeks of pregnancy was 52.8% (19/36), compared to 10% (2/20) in the control group ($p < 0.01$).

In study 12 (Zhang, 2002), prednisone and a vitamin E supplement were the only Western medications administered in both the CH/Western treatment group and Western Only control group. After 28 days of treatment, blood and vaginal mucous samples were taken, and antisperm antibody, endometrial antibody, and anticardiolipin antibody levels were measured. A total of three 28-day cycles of treatment was carried out. In the CH/Western combination treatment group, Liu Wei Di Huang Wan pills were taken, 10 grams three times per day. Once the patient became pregnant, the Chinese herbal formula Shou Tai Wan was administered in addition to 100 mg vitamin E, until the end of the first trimester. Although the overall live birth rate for both groups was not impressive, the CH/Western group had a significantly higher percentage of live births than the control group – 38.3% (18/47) compared to 28.6% (12/42). The CH/Western group also had a significantly higher percentage of patients who experienced a decrease in antibody titers – 74.5% (35/46) – compared to the Western Only group, in which 52.4% (12/42) of patients experienced a decrease ($p < 0.05$).

Chinese Herbal Medicine versus Western Medicine

A total of six studies compared the use of Chinese herbs alone versus Western medicine alone to treat immunologic recurrent miscarriage. The patients in all six of these studies had a history of two or more miscarriages and tested positive for anticardiolipin antibodies, endometrial antibodies, natural killer cells, or antisperm antibodies, and one study focused on the presence of maternal blocking antibodies.

Aspirin versus Chinese herbal medicine as therapy for antiphospholipid syndrome.

Studies 2 (Cong, 2007) and 7 (Zhan et al., 2009) compared the effectiveness of 50 mg of low dose aspirin (LDA) per day versus Chinese herbs for the treatment of recurrent miscarriage

caused by antiphospholipid syndrome. In the study by Cong (2007), an herbal formula called Xiao Kang Tang, which is composed of Bai Shao, Bai Ji Tian, Dang Shen, Gou Qi Zi, Nu Zhen Zi, Sang Ji Sheng, Shan Yao, Sheng Di Huang, Tu Si Zi, Xian Mao, Xu Duan, and Yin Yang Huo, was administered for a total of six months in the Chinese herbs only group (CH Only), during which participants were required to wear condoms to prevent pregnancy. The Western medicine only group (Western Only) took the 50 mg of LDA for a period of six months as well. 63% (29/46) of patients in the CH Only group experienced a decrease in antibody titers, compared to 31.58% (6/19) in the Western Only group ($p < 0.05$). In the study by Zhan et al. (2009), the CH Only group was administered Xiao Kang Di Huang Tang formula, which is composed of Da Zao, Dang Shen, Fu Ling, Huang Qi, Ji Xue Teng, Mu Dan Pi, Shan Yao, Shan Zhu Yu, Shu Di Huang, Tao Ren, Tu Si Zi, and Ze Xie, plus other herbs based on the patients' individual diagnoses. Treatment in both the CH Only group and Western Only group continued for 45 days; if antibody titers were still positive after the first 45 days of treatment, treatment was continued for another 45 days. The percentage of patients who experienced a decrease in anticardiolipin antibody (ACA) titers in the CH Only treatment group was 91.6% (44/48), compared to 63.1% (24/38) for the Western Only group ($p < 0.01$).

Other immunological issues. Study 3 (Cheng and Ma, 2010) compared the effects of a Chinese herbal formula versus prednisone on patients who tested positive for endometrial antibodies or anticardiolipin antibodies. In the group of patients who were positive for endometrial antibodies, 90.2% (37/41) of the patients who took only Chinese herbs (CH Only) experienced a decrease in endometrial antibody titers, compared to 72.5% (29/40) in the Western medicine only group (Western Only) who was administered 10 mg of prednisone, once per day for three months. The difference between the two groups, however, was not significant ($p > 0.05$). There was also a greater percentage of patients who experienced a decrease in antibody

titers in the group of patients who tested positive for anticardiolipin antibodies and took only the Chinese herbs – 93.18% (41/44) compared to 80.95% (34/42) for the Western Only group - but the results were insignificant as well ($p > 0.05$).

Study 4 (Zhang, Li, and Tu, 2006) compared the use of a 100 mg, once-a-day dosage of a vitamin E supplement with the administration of 8 grams Yang Xue An Tai Ke Li pills, two to three times per day. After three months of treatment, changes in natural kill (NK) cell activity and trophoblast stem cell activity were recorded. The Chinese only group's NK cell activity decreased significantly from 17.52 ± 5.71 to 13.28 ± 5.09 after three months ($p < 0.001$), whereas the Western Only group's levels decreased insignificantly from 18.04 ± 5.34 to 16.99 ± 5.73 ($p > 0.05$). Furthermore, there was no significant difference in NK cell activity between the CH Only group post-treatment and a “normal” untreated comparison group ($p > 0.05$). The trophoblast stem cell activity increased significantly in the CH Only group ($p < 0.001$), from 53.39 ± 9.67 to 61.85 ± 11.73 post-treatment, but not in the vitamin E control group ($p > 0.05$).

Study 28 (Shen, 2009) compared the effect of Zhi Bai Di Huang Wan herbal pills versus prednisone in the treatment of recurrent miscarriage in patients with antisperm antibodies. 6 grams of the herbal pills were administered twice a day for the CH Only group, and 5 mg of prednisone three times a day for the Western medicine group. After two to three months of treatment, the percentage of patients in the CH Only group whose antisperm antibody levels returned to normal levels was 85.7% (30/35) compared to 58.8% (20/34) in the treatment group ($p < 0.05$).

The last study in this group (Liu, Xu, and Zhang, 2007), study 30, measured maternal blocking antibody levels after three months of treatment in a group treated with Bu Zhong Yi Qi Tang herbal decoction and another group undergoing paternal lymphocyte immunotherapy. The study found a significant improvement in the blocking effect of the maternal blocking antibodies

after treatment in both the Chinese medicine and immunotherapy participants. No significant difference was found between the two groups.

Chinese Herbs plus Western Medicine

Three studies explored the integrated use of Chinese herbal medicine and Western medication to treat patients with a history of at least two or more miscarriage who tested positive for the presence of anticardiolipin antibodies (Hou, 2004; Takakuwa et al., 2003; Wang, Wei, and Liu, 2006). In the case series study by Takakuwa et al. (2003), which included four patients, 9 grams of the herbal granule formula Sairei-to (known as Chai Ling Tang in Mandarin) was administered before pregnancy and during the prenatal course. 81 mg per day of low dose aspirin (LDA) was given during the prenatal course, and 30-40 mg per day of the corticosteroid prednisolone was given during the first trimester and then reduced to 5-10 mg per day during the rest of the pregnancy period. All four patients became pregnant and achieved live births.

The study by Hou (2004) was a single case study in which the patient was experiencing light spotting 49 days since her last period. She was given intramuscular injections of 1000 Units of human chorionic gonadotropin (HCG) once a day, and the shots were tapered off so that by three weeks, the shots were discontinued. An herbal formula focused on tonifying the Kidney and Spleen Qi and calming the fetus was also administered everyday during the first four months of pregnancy. The treatment resulted in a live birth.

The study by Wang, Wei, and Liu (2006) compared two different Chinese herb plus Western medicine (CH/Western) treatment groups. While the Western medicine therapy for both groups was the same – 1000 Units HCG and 20 mg progesterone injections once a day if the patients' HCG and/or progesterone levels were low – the first group was administered an intravenous injection made up of 20 ml Dan Shen (*Salvia Miltiorrhiza*) extract and 50 ml saline solution, and the second group was given the herbal decoction Shou Tai Wan (duration of

treatment not reported). The Dan Shen injections were administered for 10 days; another two rounds of 10-day treatment were given, with 10 days of rest between each round. The live birth rate was higher in the group of patients that took the Dan Shen injection compared to the group which took the Shou Tai Wan herbal formula – 70% (21/30) compared to 40% (6/15). The statistical significance of the results was not reported.

Three Treatment Groups: Chinese Herbs Only, Chinese Herbs Plus Western Medicine, and Western Medicine Only

Two studies (Wang et al., 2004; Wei and Li, 2004) each compared three different treatment groups – one group administered only Chinese herbs (CH Only), another group given a combination of Chinese herbs plus Western medicine (CH/Western), and a third group given only Western medicine (Western Only) – for the treatment of antiphospholipid syndrome and recurrent miscarriage.

In the study by Wei and Li (2004), a total of ninety non-pregnant subjects were split into three groups. The CH Only group was given one of two variations of Xiao Kang Tang herbal formula depending on whether they were Kidney Yin or Kidney Yang deficiency. The CH/Western group was prescribed the same Chinese herbal formula plus the addition of 25-50 mg of aspirin, once a day and 5 mg prednisone, three times per day. The Western Only group took only aspirin and prednisone. The live birth rate for the CH/Western group was the highest – 33.3% (10/30) – followed by 13.3% (4/30) for the CH Only group and 10% (3/30) for the Western Only group. There was no significant difference between the CH Only group and Western Only group in terms of live birth rate ($p > 0.05$). The researchers also calculated the percentage of patients whose pregnancies were still viable at more than 28 weeks of pregnancy and 20 weeks of pregnancy, as well as those whose pregnancies lasted less than 18 weeks and resulted in miscarriage. The results indicated that the CH/Western treatment group had a

significantly higher percentage of patients whose pregnancies were still viable at more than 28 weeks into the pregnancy – 40% (12/30) ($p < 0.05$). There was no significant difference in the number of weeks of sustained pregnancy between the CH Only group and Western Only treatment group ($p > 0.05$). The CH/Western group also experienced the greatest percentage of patients whose anticardiolipin antibody or lupus anticoagulant levels dropped – 73.3% (22/30) compared to 30% (9/30) for both the Western Only and CH Only groups.

In the study by Wang et al. (2004), the CH Only and CH/Western treatment groups were prescribed Tai Min Ling concentrated herbal granules 30 days into the pregnancy and taken until a half month before the expected due date. During the same time period, the Western Only treatment group was prescribed 5 mg prednisone once a day, 50 mg aspirin once a day, an intramuscular injection of 6125 Units of heparin every other day, and 2.5 grams of intravenous gammaglobulin every 21 days. The CH/Western group was prescribed Tai Min Ling herbal granules and the Western Only treatment minus the heparin shots. Tai Min Ling contains the following herbs: Bai Shao, Dan Shen, Di Gu Pi, Du Zhong, Sheng Gan Cao, Sang Ji Sheng, Sheng Di Huang, Tu Si Zi, Xu Duan, and Yu Jin. The study measured the live birth rate and changes in anticardiolipin antibody (ACA) titers after treatment. According to the researchers, 100% of the patients in all three treatment groups became pregnant. The CH/Western treatment group had a 94.3% (33/35) live birth rate, followed by 75% (21/28) in the Western Only treatment group and 41.7% (10/24) for the CH Only group. The difference between the CH/Western group and the other two groups was significant ($p < 0.05$ for the Western Only group and $p < 0.01$ for the CH Only group). The CH/Western combination treatment group also experienced the greatest drop in ACA levels post-treatment compared to both Western Only group ($p < 0.01$) and the CH Only group ($p < 0.05$), thus indicating that the participants in the CH/Western had overall better pregnancy outcomes.

Summary

A total of 30 articles examining the use of Chinese herbs with or without Western medicine for various types of immunologic recurrent miscarriage were reviewed for this literature review synthesis. A majority of articles were pre-experimental studies with no control group in which the effectiveness of Chinese herbal medicine in improving various measures of pregnancy success was assessed. Almost equal attention was given to research comparing the effectiveness of Western medicine treatment alone versus a combination of Chinese herbal medicine and Western medicine, and Chinese herbs alone versus Western medicine alone. In most of the studies using Western medicine, prednisone and aspirin were the treatment of choice, followed by human chorionic gonadotropin injections, vitamin E, and progesterone supplementation. Many of the herbs which were used throughout the studies overlapped, and Kidney and Qi tonifying, as well as Blood moving herbs were frequently used. Three studies were non-controlled studies assessing the effectiveness of the combined use of Chinese herbs and Western medicine. Lastly, two studies each consisted of three treatment groups comparing the use of Chinese medicine alone, Chinese herbs plus Western medicine, and Western medicine alone. Both of these studies appeared to indicate that the combined use of Chinese herbs and Western medicine was the most effective treatment modality in improving live birth rate and decreasing anticardiolipin antibody levels.

Chapter 4: Results

Data Overview

This study involved the synthesis of data from 30 published studies that pertained to the use of Chinese herbal medicine with or without Western medicine to treat recurrent miscarriage due to immunological factors. This chapter presents the data that emerged from the synthesis process. The first section provides a summary regarding number of subjects and their age demographic across the 30 studies reviewed. Following is an analysis of the specific immunological factors that constituted the focus of the 30 articles. The next data reporting section constitutes a critical factor in this study and reports the pregnancy and live birth rates observed in the studies reviewed. A further section examines the percentage of decrease in antibody titers across groups receiving different treatment modalities, followed by a section that reports changes in immunological activity as a result of treatment. Additional pivotal factors are reported in sections that provide data regarding the number of weeks of sustained pregnancy and changes in trophoblast cell activity among different treatment groups, as well as the herbs used in the studies. A further section of the chapter provides a summary of the conclusion categories drawn from the results of the 30 reviewed studies. In the final section of this chapter, the author presents assessment data regarding the research methods utilized in the studies.

Summary of Participants

The average number of participants in each of the 30 studies was 63.2, with a range of 11 to 191 subjects per study. Average age of participants was 32.5 years old, with a range of 21 to 44 years.

Observed Immunological Markers

The articles chosen for this literature review synthesis focused primarily on ten immunological factors relating to recurrent immunologic miscarriage. The majority of articles –

22 in total- were those relating to antiphospholipid (also known as anticardiolipin) antibodies. Three articles each concerned endometrial antibodies and anti-sperm antibodies; two articles on maternal blocking antibodies/anti-idiotypic antibodies and suppressor T-cell activity were analyzed. Lastly, one article each was found for immunologic recurrent miscarriage due to ABO and RH incompatibility, antinuclear antibodies, natural killer cells, anti-ovarian antibodies, and anti-HCG antibodies. Table 1 summarizes the types of observed immunological factors included in the studies, as well as the number of studies which observed each factor.

Table 1

Observed Immunological Markers

Type of Immunological Marker	Number of Studies
Antiphospholipid Antibody	22
Endometrial Antibody	3
Anti-Sperm Antibody	3
Maternal Blocking Antibody, Anti-Idiotypic antibody	2
Supressor T-Cell Activity	2
ABO and RH Incompatibility	1
Antinuclear Antibody	1
Natural Killer Cell	1
Anti-Ovarian Antibody	1
Anti-HCG Antibody	1

Pregnancy and Live Birth Rate

Seventeen articles examined the pregnancy and/or live birth rates of participants in the studies. Pregnancy rates were unavailable in thirteen of these studies. Of these thirteen studies, three were case series or single case studies and therefore had pregnancy and live birth rates of 100%; in one article, patients were already pregnant at the beginning of the research investigation. Among the four articles (study number 1, 15, 16, and 19) whose pregnancy rates

and live birth rates were both available, the mean pregnancy rate for patients in the Chinese Herbs Only (CH Only) group was 55.3%; the range was 0% to 100%. In study number 15 (Wang et al., 2004), which included a Chinese herbs plus Western medicine (CH/Western) group and a Western medicine only (Western Only) group, the pregnancy rate for both of these groups was 100%.

Among the 14 studies which recorded the live birth rate among study participants (see Appendix K), the CH Only group had the overall highest live birth rate values: a mean of 69.9% and percentages ranging from 0% to 100%. The mean live birth rate of the CH/Western groups in these studies was 66%, and the percentages ranged from 33.3% to 94.3%. The Western Only groups contained the lowest live birth rate values – a mean of 41.2% and a range of 10% to 75.6%. It should be noted that the live birth rate in Study 20 (Gui et al., 1997) included both live births and viable pregnancies, as there was no differentiation made between these two groups.

Percentage of Patients Experiencing Decrease in Antibody Titers

Eighteen studies observed the percentage of patients who experienced a decrease in antibody titers after treatment. Among these studies, there was one case series study and another article in which the control group's percentage of decrease was not reported. These two articles were, therefore, not included in the analysis. Among the remaining 16 studies, the group with the overall highest average percentage of patients who experienced a decrease in antibody levels post-treatment was the Chinese herbs plus Western medicine (CH/Western) group, which had a mean of 82.2% and a range of 73% to 93%. In the Chinese medicine only (CH Only) group, the mean percentage was 79.7%, and percentages ranged from 30% to 100%. In the Western medicine only (Western Only) group, which contained the lowest average percentage of patients

with decreased antibody levels after treatment, the average percentage of patients experiencing a decrease in antibody titers was 50.5%, with percentages ranging from 14.3% to 81%.

Change in Immunological Activity

A total of eight studies observed changes in immunological activity after treatment with Chinese herbs and/or Western medicine.

Study 4 (Zhang et al., 1006) compared changes in natural killer (NK) cell activity between the treatment group, which used the herbal patent pill Yang Xue An Tai Ke Li, and the control group, in which participants took 100 mg vitamin E supplement for 3 months. NK cell activity significantly decreased in the CH Only group from 17.52 ± 5.71 to 13.28 ± 5.09 after three months of treatment ($p < 0.001$). The control group's NK cell activity decreased from 18.05 ± 5.34 pre-treatment to 17.99 ± 5.73 post-treatment. However, this change was not significant ($p > 0.05$). When comparing the treatment group's NK cell activity post-treatment to a "normal" comparison group's NK cell activity which was 12.74 ± 4.91 , there was no significant difference between the two group's values ($p > 0.05$).

Study 16 (Takakuwa et al., 1997) looked at the changes in CD (cluster of differentiation) cells before and after treatment. After two months of treatment with the Chinese herbal formula Chai Ling Tang (known as Sairei-to), 54.5% (6/11) of subjects experienced a decrease in CD19-positive cells, and 63.6% (7/11) experienced a decrease during pregnancy in successful pregnancy cases only, but not in patients who continued to experience repeated abortion ($p < 0.05$). The CD4/CD8 ratio *increased* significantly in 90.9% (10/11) of patients after two months of treatment ($p < 0.05$), but not at the pregnant state (54.5%), in both successful pregnancy cases as well as patients who continued to experience repeated abortions. In contrast with the results of study 4, studies 26 (Liu & Li, 2006) and 29 (Cui & Hu, 2009) found significant *decreases* in CD4/CD8 ratios after treatment with Chinese herbal medicine ($p < 0.05$ in both studies).

In addition to calculating the ratio of CD4- and CD8-positive cells before and after treatment, study 29 also found a significant decrease in the pro-inflammatory cytokine Interleukin-2 (IL-2) levels from 15.60 ± 0.23 pre-treatment to 8.47 ± 1.23 post-treatment, and in tumor necrosis factor-alpha (TNF- α) levels from 10.98 ± 1.24 to 5.46 ± 1.15 . Levels of the anti-inflammatory cytokine Interleukin-10 (IL-10) were found to have increased from 5.67 ± 1.36 pre-treatment to 8.29 ± 1.23 post-treatment, and CD8 levels also increased significantly, from 6.42 ± 1.4 to 10.48 ± 1.9 ($p < 0.05$). By the end of this study, there was no significant difference between the treatment group's cytokine levels and a comparison "normal" group's cytokine levels ($p > 0.05$).

Study 20 (Gui et al., 1997) recorded changes in blocking effect (BE), anti-idiotypic antibody (AIA) levels, and anti-paternal cytotoxic antibody (CTA) levels in patients with blocking antibody deficiency (BAD). In BAD patients whose pregnancies were viable or who delivered live offspring, BE, AIA, and CTA significantly increased after treatment ($p < 0.05 \sim p < 0.01$) compared to before treatment. In BAD patients whose pregnancies resulted in miscarriage despite treatment, there was no significant difference in BE, AIA, and CTA levels before and after treatment ($p > 0.05$). In a comparison "normal" untreated group whose pregnancies were viable or who had live births, there was no significant difference in antibody levels pre- and post-treatment ($p > 0.05$). The study also examined patients with normal blocking antibody (BAN) levels and found that patients in this group whose pregnancies were viable or which resulted in live births did not exhibit a significant change in antibody levels pre- and post-treatment ($p > 0.05$). On the other hand, BAN patients whose pregnancies were not viable or which resulted in miscarriage after treatment experienced a significant decrease in BE, AIA, and CTA levels ($p < 0.01$). Study 30 (Liu et al., 2007) also recorded changes in BE in patients undergoing either paternal lymphocyte immunotherapy or treatment with Chinese herbs. A

significant increase in BE was found in both the Chinese herbs only (CH Only) group and the paternal lymphocyte immunotherapy group after treatment ($p < 0.05$). The results from both of these studies indicate that successful pregnancy outcomes may be associated with sufficient levels of blocking antibodies during pregnancy, and that Chinese herbs as well as paternal lymphocyte immunotherapy can both increase blocking antibody levels in pregnant women.

Study 21 (Li et al., 2000) observed changes in suppressor T-cell activity in patients taking Yang Xue An Tai Chinese herbal granules. Suppressor T-cell activity increased significantly from 38.05 ± 8.03 in the first trimester to 45.63 ± 15.89 in the second trimester and 54.24 ± 7.01 in the third trimester of pregnancy ($p < 0.001$). These results were accompanied by an 87.5% (49/56) live birth rate among participants in this study.

Study 15 (Wang et al., 2004) observed changes in antiphospholipid antibody (APA) titers before and after treatment. All three groups – a Chinese herb only (CH Only) group, a Chinese plus Western medicine (CH/Western) group, and a Western medicine only (Western only) group – experienced a drop in APA titers after treatment, but in varying degrees. The CH/Western group, in which a combination of Tai Min Ling herbal granules, prednisone, aspirin, heparin, and intravenous gammaglobulin were administered, experienced a significantly greater decrease in APA levels compared to both the CH Only and Western Only treatment groups ($p < 0.05$) – from 32.67 ± 9.30 pre-treatment to 20.02 ± 7.51 post-treatment. On the other hand, there was no significant difference in the drop in APA levels between the CH Only and Western Only groups post-treatment ($p > 0.05$). The CH/Western group also had the highest live birth/viable pregnancy rate compared to the other two groups – 94.3% compared to 41.7% for the CH Only group and 75% for the Western Only group.

Number of Weeks of Sustained Pregnancy

A total of five articles examined the number of weeks in which pregnancies were still viable post-treatment (See Appendix L). Studies 8, 10, and 27 looked at the effect of treatment on antiphospholipid antibody (APA) levels; study 9 involved patients who tested positive for antisperm antibodies, anti-ovarian antibodies, endometrial antibodies, and/or anti-human chorionic gonadotropin (anti-HCG) antibodies; study 21 observed changes in suppressor T-cell activity.

Study 9 (Chai & Zhao, 2002), which compared a group using both a Chinese herbal formula - either Yu Ling Zhu or Jia Wei Xiao Yao San - plus Western medicine (CH/Western) to a Western medicine only (Western Only) group using a combination of prednisone, progesterone, and HCG, found that a significantly greater percentage - 52.8% (19/36) - of pregnancies were still viable at > 15 weeks in the CH/Western group compared to only 10% (2/20) in the Western Only group ($p < 0.01$).

Study 10 (Wei & Li, 2004) looked at the percentage of patients whose pregnancies lasted <18 weeks and resulted in miscarriage, as well as the percentage of pregnancies that were still viable at >20 weeks and ≥ 28 weeks. The CH/Western group, in which patients were given a combination of Xiao Kang Tang #1 or #2, aspirin, and prednisone, had the overall greatest percentage of patients whose pregnancies made it past 28 weeks— 40% (12/30) compared to 20% (6/30) for the Western Only group and 16.7% (5/30) for the CH Only group. 53.3% (16/30) of patients in both the CH Only and Western Only groups made it past >20 weeks of pregnancy, compared to 20% (6/30) in the CH/Western group. The percentage of pregnancies which resulted in miscarriage or did not make it past 18 weeks was 6.6% (2/30), 13.3% (4/30), and 16.7% (5/30) for the CH/Western, CH Only, and Western Only groups, respectively. Study 8 (Li, 2003) also found a greater percentage of viable pregnancies at ≥ 28 weeks in the CH/Western group, in which patients were given a combination of An Tai Jiao Nang pills and treatment with

progesterone, human chorionic gonadotropin (HCG) injections, and vitamin E. The percentage of viable pregnancies in this study was 93.3% (28/30) and 73.3% (22/30) for the CH/Western and Western Only groups, respectively.

Study 27 (Wang et al., 2006) compared the number of weeks of sustained pregnancy between two groups using different combinations of eastern and western treatment modalities. 70% (21/30) of patients in X₁ group, in which a combination of Dan Shen Saline injection solution, progesterone, and HCG were administered, had full term live births compared to 40% (4/15) in the X₂ group, whose treatment consisted of Shou Tai Wan pills, progesterone, and HCG. The percentage of patients in the X₁ group who were 26-31 weeks pregnant at the time the article was published was 23.3% (7/30); in the X₂ group, 33.3% (5/15) were 20-26 weeks pregnant at the time of the article's publication. In the X₁ group, 6.6% (2/30) miscarried at <60 days into the pregnancy compared to 26.7% (4/15) in X₂ group.

Study 21 (Li et al., 2000), which was a pre-experimental study observing the effect of Yang Xue An Tai Chong Ji herbal granules on pregnancy outcomes, found that 98.2% of pregnancies lasted ≥ 28 weeks.

Change in Trophoblast Cell Activity

Study 4 (Zhang et al., 2006), which compared trophoblast cell activity in a treatment group administered Yang Xue An Tai Ke Li pills to a control group given Vitamin E supplements, found a significant increase in trophoblast cell activity in the treatment group, but not the control group. The treatment group's trophoblast cell activity increased from 53.39 ± 9.67 to 61.85 ± 11.73 after three months ($p < 0.001$) compared to the control group, whose trophoblast cell activity increased from 52.76 ± 10.13 to 54.27 ± 8.92 ($p > 0.05$). There does not appear to be a significant difference in the treatment group's post-treatment trophoblast cell activity with that of an untreated comparison "normal" group's values, which was 64.59 ± 11.00 .

Herbs Used

A total of 83 different herbs were used across the 30 studies to treat immunologic recurrent miscarriage. The herb which was used with the greatest frequency was Tu Si Zi (*Semen Cuscutae*), which accounted for 66.7% (20/30) of the articles reviewed in this literature synthesis. Following closely were the herbs Bai Zhu (*Rhizoma Atractylodis Macrocephalae*) and Xu Duan (*Radix Dipsaci*), which were used in 53.3% (16/30) and 50% (15/30) of the studies, respectively. Dan Shen (*Radix Salviae Miltiorrhizae*), Dang Gui (*Radix Angelica Sinensis*), and Bao Shao (*Radix Paeoniae Alba*) each appeared in 43.3% (13/30) of the articles. Huang Qin (*Radix Scutellariae*) and Sang Ji Sheng (*Herba Taxilli*) were each used 40% (12/30) of the time, followed by Dang Shen (*Radix Codonopsis*), Sheng Gan Cao (*Radix Glycyrrhizae*), Huang Qi (*Radix Astragali*), and Shan Yao (*Rhizoma Dioscoreae*), which were used in 36.7% (11/30) of the 30 articles. There were also many herbs which were used in only a few of the 30 articles selected for this literature review synthesis. For a complete list of the specific herbs used throughout the studies and the frequency of their usage, see Table 2.

Western Treatment Modalities Used

Among the 30 studies, prednisone and aspirin were the most frequently used, accounting for 26.7% (8/30) and 23.3% (7/30) of the observed articles, respectively (see Table 3). Human chorionic gonadotropin (HCG) injections were seen in 16.7% (5/30) of the studies, while vitamin E and progesterone supplementation were encountered in 13.3% (4/30) of the articles used for analysis. Intravenous gammaglobulin therapy, paternal lymphocyte immunotherapy, Vitamin C and multi-vitamins, and heparin were each used in only one of the 30 studies.

Conclusion Categories

In total, there were 66 various conclusion statements made based on the results of the studies.

Table 2

Frequency and Percentage of Herb Use

Herbs	Percentage and Frequency of Studies in which Herb was Used
Tu Si Zi (1)*	66.7% (20/30)
Bai Zhu (1)	53.3% (16/30)
Xu Duan (1)	50% (15/30)
Dan Shen, Dang Gui, Bai Shao (1)	43.3% (13/30)
Huang Qin (2), Sang Ji Sheng (1)	40% (12/30)
Dang Shen (2), Huang Qi, Sheng Gan Cao, Shan Yao (2)	36.7% (11/30)
Fu Ling	33.3% (10/30)
Shu Di Huang	26.7% (8/30)
Chai Hu, Du Zhong, Yi Mu Cao, Ze Xie	23.3% (7/30)
Ren Shen (1)	20% (6/30)
Chuan Xiong (1), Gou Qi Zi, Gui Zhi, Nu Zhen Zi, Sheng Jiang, Zhi Gan Cao (1)	16.7% (5/30)
Ban Xia, Cang Zhu, Chi Shao (1), Da Zao, E Jiao (1), Mu Dan Pi (1), Sheng Di Huang (1), Zhi Mu (1), Zhu Ling	13.3% (4/30)
Ba Ji Tian (2), Chen Pi (1), Huang Bai (1), Lian Zi Rou (1), Sha Ren, Zhu Ma Gen (1)	10% (3/30)
Bai Hua She She Cao (1), Lu Jiao Shuang (1), Tao Ren, Xiang Fu, Yin Chen Hao, Yin Yang Huo, Ze Lan, Zi Su Geng	6.7% (2/30)
Ai Ye, Bai Bian Dou (1), Bo He, Chuan Bei Mu, Chuan Jiao, Da Huang, Di Gu Pi, Di Yu Tan (1), E Zhu, Gou Ji, He Shou Wu, Hong Hua (1), Hou Po, Ji Xue Teng, Jing Jie, Lian Qiao, Lu Jiao Jiao, Lu Jiao Pian, Mai Dong, Mu Xiang, Pu Gong Ying (1), Qian Shi (1), Qiang Huo, Rou Cong Rong, Rou Gui (1), San Qi, Sha Shen, Sheng Ma, Xian Mao, Xian He Cao (1), Xiao Hui Xiang (1), Yu Jin, Zhi Ke, Zi He Che (1)	3.3% (1/30)

Note. Numbers in parentheses indicate the number of studies in which herb may or may not have been used, depending on diagnosis.

Table 3

Types of Western Treatment Modalities

Type of Western Treatment Modality	Number of Studies
Prednisone	8
Low Dose Aspirin	7
Human Chorionic Gonadotropin	5
Vitamin E	4
Progesterone	4
Intravenous Gammaglobulin	1
Paternal Lymphocyte Immunotherapy	1
Vitamin C and Multi-Vitamin	1
Heparin	1

These 66 statements were categorized into 10 possible types of conclusions based on the effectiveness of the Chinese herbal (CH) or Western medicine treatments (See notes at the bottom of Appendix I for a complete list of conclusion categories). I reviewed each article from a conservative perspective and only indicated that the effect of the study appeared to have a positive effect if statistical data indicated as such, or the data appeared to show a strong improvement. The greatest percentage of conclusions drawn came from Conclusion 1 (C1), which stated that Chinese herbs (CH) alone appeared to be effective. Conclusion 5 (C5), which stated that CH plus Western medicine (CH/Western) treatment appeared to be more effective than Western medicine alone, also made up a higher percentage of conclusions statements - 21.2%. Conclusion categories 4 (C4) and 7 (C7) were the least popular, garnering a total of 1.5% and 0%, respectively, of the total statements. Below (Table 4) is a summary of the types of conclusions categories and the percentage of conclusion statements which fell into each category:

Table 4

Conclusion Categories

C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Other
33.3%	6.1%	4.5%	1.5%	21.2%	7.6%	0%	12.1%	3.0%	9.1%	10.6%

Note. C1=Chinese herbs (CH) alone appears to be effective. C2=CH alone does not appear to be effective. C3=CH plus Western medicine appears to be effective. C4=Western medicine alone appears to be more effective than CH alone. C5= CH plus Western medicine appear to be more effective than Western medicine alone. C6=CH plus Western medicine appears to be more effective than CH alone. C7=Western medicine alone appears to be more effective than CH plus Western medicine. C8=CH alone appears to be more effective than Western medicine alone. C9=CH alone and Western medicine alone appear to be equally effective. C10=A Conclusion cannot be made. For “Other” category, refer to notes at the end of Appendix I for specific conclusions made.

Quality Assessment of Research Methodology

The quality assessment (QA) of the research methodology among the 30 articles used in this literature review synthesis consisted of six measures, each containing a “yes” or “no” response (see Appendix M). “Yes” responses received one point, whereas “No” responses received zero points. The first QA measure - which asked the question “Was the research design made clear?” – earned a total of 90% (27/30) positive “yes” responses and 10% (3/30) “no” responses. The second QA measure, which examined the percentage of studies which were randomized or not randomized, found that a little more than half - 53.3% (16/30) - of the studies were non-randomized (“no” response) versus 46.7% (14/30) which were randomized (“yes” response). The third measure, which examined whether variables within the studies were clearly described, resulted in a total of 86.7% (26/30) positive “yes” responses and 13.3% (4/30) “no” responses. The fourth measure was based on whether the study contained a control group or not. 53.3% (16/30) of the studies did, while 46.7% (14/30) did not. The fifth QA measure examined whether the inclusion and exclusion criteria were clearly stated. 80% (24/30) of the article clearly stated inclusion and exclusion criteria, while 20% (6/30) did not. In regards to the sixth QA measure, which assessed the replicability of the study and whether the description of the

treatment was sufficient enough in detail that it could be repeated by others, 60% (18/30) of studies had a “yes” response, while 40% (12/30) were not replicable. The “researcher derived quality measure” (RDQM) ranged from a score of 1, indicating that the study had ≤ 1 “yes” response and therefore had “no relevance”, to a score of 4, which indicated that the study had 6 “yes” responses and was therefore “highly relevant.” The percentage of studies which were not relevant and had a score of 1 was 3.3% (1/30); the percentage with a score of 2, contained two to three “yes” responses, and which were somewhat relevant was 33.3% (10/30); the percentage of studies deemed relevant, contained four to five “yes responses, and had a score of 3 was 30% (9/30); another 30% (9/30) of the articles were considered highly relevant and had a score of 4. The mean RDQM for all 30 articles was 2.83, indicating that on average, most studies fell slightly short of being relevant.

Chapter 5: Discussion

Summary of Findings

This study was a retrospective literature review synthesis which compared the use of Chinese herbs alone (CH Only), Chinese herbs plus Western medicine (CH/Western), or Western medicine alone (Western Only) in the treatment of recurrent miscarriage due to immunological factors. Through a qualitative research design which made use of a thematic approach to data analysis, the effects of CH, CH/Western treatment, and Western medicine treatment on pregnancy outcomes, immunological markers, and antibody titers were examined and analyzed. Furthermore, a summary of the types of herbs used and the frequency of their usage was also provided.

The highest overall live birth rate came from the CH Only group, which had a mean live birth rate of 69.9%, followed closely by the CH/Western group and lastly, the Western Only group. Overall results, however, appeared to indicate more favorable pregnancy outcomes in the CH/Western group based on the number of weeks of sustained pregnancy among the three treatment groups. The CH/Western group also had the highest average percentage of patients who experienced a decrease in antibody titers after treatment, followed closely by the CH Only and Western Only groups. A correlation between successful pregnancy outcomes and specific changes in immunological activity was also found. The next pivotal piece of information gained from the data analysis process was the pattern of herb usage among the 30 studies. From these studies, it was discovered that besides Kidney and Spleen Qi tonifying herbs and Blood nourishing herbs, herbs that move the Blood such as Dan Shen were used in many of the studies. The following data analysis section looked at the types of conclusions extracted from the studies and found that the greatest percentage of conclusions seemed to point favorably towards the combined use of Chinese herbs and Western medicine. Lastly, a quality assessment of the

research methodologies of the 30 studies revealed that on average, most studies fell slightly short of being relevant, thus indicating issues of validity and reliability within the studies themselves.

Implications for Theory

Chinese herbal medicine has long been used and widely accepted in China and, increasingly, in other countries as a way of enhancing fertility. In China, the integrated use of Chinese herbal medicine and Western medicine has been common protocol for doctors treating women with recurrent miscarriage due to immunological factors. The purpose of this literature review synthesis was to serve as an introduction to and provide an overview of studies aimed at evaluating the efficacy of Chinese herbs only (CH Only) or Chinese herbs plus Western medicine (CH/Western) treatment regimens in the treatment of immunologic recurrent miscarriage. The results of the studies appear to indicate that Chinese herbal medicine may in fact be of value as an adjunctive therapeutic modality in the treatment of immunologic recurrent miscarriage. The mechanisms, although unclear, may indeed lie in the herbs' ability to modulate the immunological activity of pregnant women, as evidenced by the decrease in various antibody titers throughout the studies and a change in levels of immune modulating cytokines. It is believed that successful pregnancies result from a balanced ratio in cytokine release between two different T-Helper (Th) cell lymphocyte systems- Th1 and Th2. According to Fujii et al. (2000), autoimmune disorders such as antiphospholipid syndrome (APS) are a result of an excessive shift to Th2 cytokines, such as Interleukin (IL) 10 and IL-4, whereas alloimmune causes of miscarriage, in which the developing fetus is being attacked by maternal killer cells, are a result of an excessive secretion of Th1 cytokines such as IL-2, IFN- γ (interferon gamma), and TNF- α (tumor necrosis factor alpha). In study 29 (Cui & Hu, 2009), the use of herbs which tonified the Kidneys and Qi were shown to have an inhibitory effect on IL-2 and TNF- α . According to Cui

and Hu, these two Th1 cytokines are known to increase natural killer cell activity and hence can harm the fetus if not balanced out by Th2 cytokines such as IL-4, IL-6, and IL-10.

In terms of the changes in CD4/CD8 (cluster of differentiation) ratios, the study by Takakuwa et al (1997) found an increase in the CD4/CD8 ratio, whereas studies 26 (Liu & Li, 2006) and 29 (Cui & Hu, 2009) found significant decreases in CD4/CD8 ratio. It is not entirely clear, then, what type of impact CD4/CD8 ratio may have on pregnancy success. Whereas Takakuwa et al. (1997) claimed that the increase in CD4/CD8 ratio might have improved the autoimmune state in patients with recurrent miscarriage who were positive for antiphospholipid antibodies, Liu & Li (2006) and Cui & Hu (2009) claimed that an increase in CD4/CD8 would cause an increase in natural killer cell activity and therefore increased risk of miscarriage, and a decrease in CD4/CD8 ratio could prevent maternal immunological rejection of the fetus.

An analysis of the herbs used among the 30 studies has supported the traditionally accepted theory that herbs, which from a Chinese medicine perspective help to tonify the Kidneys, strengthen the Spleen Qi, nourish the Blood, and calm the fetus, such as Dang Shen, Tu Si Zi, Bai Zhu, Dang Gui, Xu Duan, Sang Ji Sheng, Shan Yao, and Huang Qin, may help improve pregnancy outcomes in women with a history of recurrent miscarriages. Dang Shen, for instance, has immune regulating effects, whereas Huang Qin can inhibit allergic reactions in the body (Yan, 1991). In addition to Kidney and Spleen tonifying herbs, however, herbs which are known to move and invigorate the Blood, such as Dan Shen, Yi Mu Cao, Tao Ren, Hong Hua, and Chuan Xiong, were used throughout the first trimester or more of pregnancy in many of the reviewed articles. Currently, traditional Chinese medicine (TCM) doctoral programs specializing in Oriental reproductive medicine do not teach or promote the use of Blood moving herbs during pregnancy, for it is traditionally considered unsafe and harmful towards the fetus to use herbs which invigorate and move the Blood. An overview of the 30 articles, however,

appears to indicate that when combined with Western therapies such as aspirin or prednisone, mild Blood moving herbs may, in fact, help preserve pregnancy, particularly in women with antiphospholipid syndrome (APS) who have an increased risk of thromboembolic events during pregnancy. Research has shown that Blood moving herbs can dilate the blood vessels and inhibit platelet aggregation, thus normalizing sticky platelets and preventing the formation of thrombosis or blood coagulation (Liu et al., 2003; Yan, 1991). Dan Shen injections, in particular, exhibit immune modulating effects via the suppression of elevated T-helper/T-suppressor ratio and the decrease in IL-2 (Interleukin-2) in the body (Chen et al., 2001). Herbs such as Dan Shen, Yi Mu Cao, Dang Gui, Huang Qin, and Sheng Di Huang can prevent the formation of IgG (immunoglobulin G) antibodies involved in APS and also modulate T-cell function (Liu et al., 2003).

Traditionally, treatment for threatened miscarriage has been taught in a broader sense and with a focus on treating the patient according to Traditional Chinese Medicine (TCM) diagnosis principles based on the patient's pattern of symptoms. Students of TCM are taught to prescribe herbs based on whether the patient's symptoms manifest as Qi and Blood deficiency, Kidney and Spleen deficiency, or Blood heat, for instance. Very little is taught or mentioned about how and in what context immunological causes of recurrent miscarriage fall into these treatment schemes, and in particular, the usefulness of Blood moving herbs for certain populations of patients who exhibit symptoms of Blood stagnation during pregnancy. There needs to be more research done in this area of reproductive medicine, therefore, so that TCM practitioners can be taught safe and effective protocols in school curricula for the treatment of recurrent miscarriage due to immunologic causes.

The Western medical community is, for the most part, closed off to the idea of incorporating Chinese herbal medicine into their teaching curricula, and nowhere can one find in

Western medical textbooks any mention of Chinese herbs. There is obviously a disconnect between the Western medicine and the TCM approach to treating immunologic recurrent miscarriage, and as of now, there has been little or no integration of Chinese and Western medicine in the treatment of immunologic miscarriage within the school curriculum. The data extracted from this literature review synthesis nonetheless appear to support previous literature which states that Chinese herbs do exhibit positive immunological effects in pregnant women which may be preventive against miscarriage. The specific mechanisms by which herbs exert an effect on various immunological markers should be taught within the TCM reproductive medicine curriculum so that practitioners can better understand and relate to Western medical professionals when discussing immunologic factors relating to recurrent miscarriage in both the educational and clinical setting.

Implications for Practice

The evidence drawn from this literature review synthesis is encouraging, for the results of these studies appear to indicate that the combined use of Chinese and Western medicine may produce the overall best clinical outcomes for women with a history of immunologic recurrent miscarriage. Even in recent years, the efficacy of Western medicine modalities such as aspirin, prednisone, and heparin are still in question, and doctors who I have talked to or worked together with who specialize in infertility have often admitted that they themselves do not have a firm grasp on how to prevent miscarriage in women with certain autoimmune or alloimmune issues. Aspirin, prednisone, heparin, and/or progesterone are diligently administered according to textbook protocols, but to no avail. While there is certainly a percentage of patients who respond well to Western medical therapy alone, there are still many who continue to suffer from repeated miscarriages despite treatment. In addition, there are many possible adverse side effects associated with long-term use of heparin and prednisone, such as osteoporosis, gestational

diabetes, pre-term premature rupture of membranes, increased risk of bleeding, etc. (Empson et al., 2005; Lefkou et al., 2010; Silver et al., 1993). From a clinical perspective, therefore, the use of herbs can help to minimize the needed dose of western medication and the side effects associated with these medications. That said, the treatment groups in which only Chinese herbs were used also did not have as favorable an overall outcome as the combined CH/Western groups. In several of the more “relevant” studies, Chinese herbal medicine was given for several months in order to bring antibody titers down before the patient attempted pregnancy; often, administration of the herbs continued throughout the first trimester of or further into the pregnancy, usually in combination with Western medicines such as aspirin, prednisone, folic acid, and progesterone. It is not clear, though, whether a decrease in antibody levels is directly correlated with the success of the pregnancy and the chances of a woman achieving live birth. For example, in study 1 (Kano et al., 2010), 100% (7/7) of the patients in the anticardiolipin IgG positive group experienced a decrease in antibody titers after treatment. However, only one of these patients actually became pregnant by the end of the study. On the other hand, 55.8% (24/43) patient in the Chinese Medicine Only group in study 18 (Wang, 2005) experienced a decrease in anticardiolipin antibody titers after treatment, but 86% (37/43) of these patients had live births. These conflicting results do bring to bear the question of whether decreasing antibody titers through the use of herbs or western medicine can directly predict pregnancy outcomes.

An analysis of the herbs used throughout the 30 studies appears to indicate that the use of herbs which support the Kidneys and Spleen, tonify Qi and Blood, calm the fetus, and move the Blood can be used safely and in combination with Western therapeutic modalities to treat immunologic recurrent miscarriage. The most commonly used western medications were prednisone. It is very likely, then, that an integrated approach – one which combines the best of

both Eastern and Western medicine – may produce the most favorable pregnancy outcomes in women with a history of immunologic recurrent miscarriage. There are, however, several areas that require further research before herbs can be fully integrated into the clinical setting. For instance, there were many herbs which were used sporadically in only one or a few of the 30 studies, and therefore the clinical significance of their usage is in question. Furthermore, the method and timing of administration of the herbs varied from one study to another. Some studies administered the herbs several months before pregnancy was attempted, others only during the first trimester, and still others throughout the entire duration of the pregnancy up to half a month before expected delivery. Therefore, it was difficult to figure out the most effective or common method of administration of the herbs. Proper dosage, method of administration, and duration of administration of Chinese herbal medicine must be established first so that TCM practitioners can safely and effectively treat immunologic recurrent miscarriage, particularly in women with clotting issues who may concurrently be taking other blood-thinning medications such as heparin or aspirin during pregnancy.

Limitations of the Current Study

The first limitation of the current study lies in the nature of the study itself – that is, the fact that a literature review is a secondary analysis of studies which have previously been conducted by others. Because of this limitation, I was greatly limited in the choice of studies and variables engaged in this research synthesis. As a result, the data actually generated in this study were in some ways not fully in sync with the original research objective. For instance, instead of focusing on just one or two types of western medicine treatments and comparing them with Chinese herbal medicine, because of the diversity of variables engaged in the studies reviewed, I was forced to incorporate into the current study a wider array of western medicine treatment methods. Some studies looked at the use of folic acid and vitamin supplements, while others

looked at prednisone and aspirin. This factor may have been one of the reasons why the range of values for the results of the studies was quite variable at times. The wide range or inaccuracy of result values could also have been due to a heterogeneous group of subjects in the studies and a wide variety of symptoms or diagnoses at the start of the study. While all of the studies had to do with immunological causes of recurrent miscarriage, some patients were already pregnant at the start of the study, while others were not yet pregnant; some studies looked at patients who had antiphospholipid syndrome, while others looked at other types of immunological issues such as endometrial antibodies, antisperm antibodies, and natural killer cells. Thus, I felt that the results of my data analysis may have been skewed by the fact that there was an unequal amount of attention and emphasis given to articles relating to APS recurrent miscarriage, and not enough weight given to articles relating to anti-sperm antibodies, anti-endometrial antibodies, blocking antibody deficiency, or miscarriages due to excessive natural killer cell activity. There was also a lack of articles available for analysis regarding my subject matter that also happened to match my inclusion criteria requiring that the participants of the studies include women with a history of at least two or more miscarriages. Overall, my small sample size and the heterogeneity of treatment plans and participant demographics were undoubtedly limiting factors in this study. Nevertheless, given that different immunologic types of recurrent miscarriage are caused by similar immunological imbalances and pathologies, I feel that the results of the study are still relevant and can provide insight into integrative treatment options for immunologic recurrent miscarriage.

The sheer lack of articles for each different type of western medicine treatment made it difficult to assess the effectiveness of specific western treatment modalities. For instance, only prednisone and aspirin were used in a more significant number of articles, whereas there were only a few articles containing other western treatment modalities. In particular, heparin is a

western medication which is commonly used to prevent miscarriage when there is a chance that the mother may have clotting issues during pregnancy, but it was only seen in one article out of all 30 articles. Outcomes for the Western medicine treatments might have been better if the patients had been on heparin therapy, especially since 73% of the articles had to do with antiphospholipid syndrome. So although the articles indicate that Chinese medicine can be an effective treatment modality, no conclusion can be made as to whether Western medicine, particularly heparin therapy, is more or less effective than Chinese medicine alone.

While every effort was made to be as objective as possible in assessing the quality and relevance of the research methodology and design of the articles selected for this study, the possibility of my own researcher bias was present when deciphering whether the variables and inclusion/exclusion criteria of the studies were clearly described or whether the description of the treatments were sufficient enough in detail so as to be replicable. Because the data analysis was done by a single rater, there was an increased possibility of inaccurate recording and misinterpretation of data. It should also be noted that even though a majority of the conclusion statements extracted from the studies maintained that Chinese herbs used alone appear to be effective, this observation is due to the fact that 40% (12/30) of the studied were pre-experimental, non-controlled studies focusing on the use of Chinese medicine only. It cannot be concluded, therefore, that Chinese medicine alone is the most effective treatment modality for immunologic recurrent miscarriage. Rather, the results only indicate that a majority of the studies found for my literature review synthesis were pre-experimental studies focusing only on the use of Chinese herbs, and that a majority of the results of these studies indicated that the herbs were effective.

Issues of internal validity such as small sample size were present in some of the studies. While the research design and description of variables were clearly stated in a majority of the

articles, a little more than half of the 30 studies were not randomized and did not contain control groups. The issue of selection bias was therefore present. Due to the nature of studies focusing on the use of Chinese herbs for fertility, the participants and researchers were not blinded to the treatment they were receiving, and therefore, the potential for author/experimenter and participant bias were both present. Source bias was also a possible limitation of this study, for it possible that many of the articles were published in journals which only publish articles in favor of the use of Chinese herbal medicine. Other possible confounding factors such as improved diet, placebo effect, or the concurrent usage of other unstated treatment modalities such as acupuncture or massage, might have also been present. Furthermore, treatment with Chinese herbs in many of the studies did not include only one single formula which was used on all the patients in a particular study. Two different formulas were often used, based on the patients' individual diagnoses. Study 9 (Chai & Zhao, 2002) included four different formulas used throughout the study. Five of the articles did not even state all the herbs which were used for that particular study. In addition, it was impossible to track the dosages of the herbs, as they varied between studies or sometimes were not mentioned at all. So while the one-size-does-not-fit-all approach to Chinese herbal medicine treatment in these studies may have given the studies good external validity, since they resembled more-or-less how Chinese medicine is practiced in the clinical setting, the internal validity of the studies often appeared to be lacking, and details of dosage and usage of herbs were sometimes missing.

In several studies, the data provided by the researchers appeared to be incomplete or in error. There was either a mistake in the reporting of results, or some other undisclosed factor was present. For example, study 8 (Li, 2003) reported that 25 out of 30 patients in both the treatment and control groups experienced a decrease in antibody levels, which would be

calculated as 83.3%. However, the study reported the percentages as being 80.33% for the treatment group and 60% for the Western medicine only control group.

One last aspect worth mentioning is that the studies did not discuss complications that could have arisen from treatment. While in western medicine research, it has been discovered that certain western therapies such as heparin or prednisone come with possible health risks to the mother and fetus during pregnancy such as osteopenia and nephrotic syndrome, the articles in my literature review synthesis did not specifically mention whether there were specific complications associated with herb usage. It is possible that there are overall less negative side effects associated with herb use, but there have not been specific studies available to validate or negate this statement.

Recommendations for Future Research

If future prospective, large-scale, randomized, controlled trials regarding this topic can be carried out, perhaps the Western medical community will be more accepting of the integrative use of Chinese herbal medicine to treat recurrent miscarriage due to immunological causes. More rigorous, transparent methodology and a more focused approach that examines just one or two main variables are necessary to be able to better understand whether a specific treatment protocol is effective or not. Quantitative statistical analysis of the results of these types of studies is also recommended for future research in order to determine the statistical validity of study results. Studies focusing on pregnancy and live birth rates in women undergoing integrative treatment are recommended, since live birth rate is the ultimate predictor of pregnancy success and the effectiveness of the treatment. Different types of immunological causes of recurrent miscarriage should be studied separately in order to discover whether Chinese herbal medicine varies in effectiveness from one type of immunological miscarriage to another. Studies comparing the use of Chinese herbal medicine and heparin therapy are also recommended, as there are not enough

present studies comparing the effect of these two treatment methods when used alone or in combination with each other.

Conclusion

The purpose of this retrospective literature review synthesis was to serve as a groundbreaking study aimed at bringing clarification to the current literature available concerning the use of Chinese herbal medicine alone or the integrated use of Chinese herbs and Western medicine to treat immunologic recurrent miscarriage. The results, similarities, differences, and limitations among the available research were analyzed and discussed, and recommendations for future research were given. Theoretical and clinical applications of my findings were also mentioned. The evidence seems to strongly suggest that Chinese herbal medicine may be of value as an adjunctive therapeutic modality in the treatment of immunologic recurrent miscarriage. An analysis of the herbs used among the 30 studies has supported the traditionally accepted theory that herbs, which from a Chinese medicine perspective help to tonify the Kidneys, strengthen the Spleen Qi, nourish the Blood, and calm the fetus may help improve pregnancy outcomes in women with a history of recurrent miscarriages due to their immunomodulating effects. In addition, however, herbs which are known to move and invigorate the Blood may also be useful for preventing recurrent miscarriage, particularly in women suffering from antiphospholipid syndrome. Proper dosage, method of administration, and duration of administration of Chinese herbal medicine must be established first so that TCM practitioners can safely and effectively treat immunologic recurrent miscarriage, particularly when used together with western medical therapies. Lastly, due to issues of internal validity of these studies, it is recommended that more long-term, prospective, randomized, and controlled research studies with rigorous methodology be carried out in the future if Chinese herbal medicine is to be accepted by the public and those in the western medical field.

References

- American Psychological Association. (2010). *Publication Manual of the American Psychological Association* (6th ed.). Washington, D.C.: American Psychological Association.
- Angeli, E., Wagner, J., Lawrick, E., Moore, K., Anderson, M., Soderlund, L., . . . Keck, R. (2011). Reference list: Author/authors. In *Purdue Online Writing Lab*. Retrieved from <http://owl.english.purdue.edu/owl/resource/560/06/>
- Aronson, J. (1994). A pragmatic view of thematic analysis. *The Qualitative Report*, 2(1).
- Barbour, L.A., Kick, S.D., Steiner, J.F., LoVerde, M.E., Heddleston, L.N., Lear, J.L., & Barón, A.E. (1994). A prospective study of heparin-induced osteoporosis in pregnancy using bone densitometry. *Am J Obstet Gynecol*, 170(3), 862-869.
- Branch, D.W., Peaceman, A.M., Druzin, M., Silver, R.K., El-Sayed, Y., Silver, R.M., . . . Harger, J. (2000). A multicentre, placebo-controlled pilot study of intravenous immune globulin treatment of antiphospholipid syndrome during pregnancy. The pregnancy loss study group. *Am J Obstet Gynecol*, 182(1), 122-127.
- Chai, L.H. & Zhao, W. (2002). Zhong xi yi jie he zhi liao mian yi xing fan fu xing zao qi liu chan 56 lie fen xi [East West integrative medicine to treat 56 cases of immunologic early recurrent miscarriage]. *Chinese Archives of Traditional Chinese Medicine*, 20(4), 538-539.
- Chamley, L., Duncalf, A., Mitchell, M., & Johnson, P. (1998). Action of anticardiolipin and antibodies to beta2-glycoprotein-1 on trophoblast proliferation as a mechanism for fetal death. *Lancet*, 352, 1037-1038.
- Chen, G., Liu, R.X., Zhang, W.G., Wang, B., Fu, J., Feng, Y.G., & Zhang, X.B. (2001). Effect of *Salvia Miltiorrhiza bunge* injection on anticardiolipin antibody production induced by beta2 glycoprotein I. *Acta Pharmacol Sin*, 22(12), 1125-1129.

- Cheng, J.L. & Ma, S. H. (2010). Bu shen jian pi huo xue jie du fa dui mian yi xing xi guan xing liu chan kang ti de gan yu [The impact of kidney and spleen tonifying, blood moving, and toxin removing methods on antibodies in the treatment of immunological recurrent miscarriage]. *Hebei Medical Journal*, 32(13), 1720-1721.
- Cong, Y. (2007). Xiao kang tang zhi liao mian yi xing fan fu zi ran liu chan kang xin lin zhi kang ti yang xing 46 lie [The treatment of 46 cases of antiphospholipid antibody positive recurrent miscarriage with Xiao Kang Tang formula]. *Jilin Journal of Traditional Chinese Medicine*, 27(9), 19-20.
- Creswell, J. W. (2007). *Qualitative inquiry & research design: choosing among five approaches*. (2nd ed.). Thousand Oaks, CA: Sage Publications.
- Cui, Y. & Hu, L. S. (2009). Bu shen yi qi fa zhi liao tong zhong mian yi xing fu fa xing liu chan 30 lie lin chuang guan cha [Clinical observation of the use of kidney tonifying and qi strengthening methods to treat recurrent miscarriage of similar immunologic etiology]. *Practical Clinical Journal of Integrated Traditional Chinese and Western Medicine*, 9(6), 41-42.
- Elder, M., De Swiet, M., Robertson, A., Floyd, E., & Hawkins, D. (1988). Low-dose aspirin in pregnancy. *Lancet*, *i*, 410.
- Empson, M. B., Lassere, M., Craig, J. C., & Scott, J. R. (2005). Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant (Review). *Cochrane Database of Systematic Reviews*, (2). doi:10.1002/14651858.CD002859.pub2.
- Farquharson, R.G., Quenby, S., & Greaves, M. (2002). Antiphospholipid syndrome in pregnancy: A randomized , controlled trial of treatment. *Obstet Gynecol*, 100(3), 408-413.
- Fujii, T., Kanai, T., Kozuma, S., Hamai, Y., Hyodo, H., Yamashita, T., . . . Taketani, Y. (2000). Theoretical basis for herbal medicines, Tokishakuyaku-San and Sairei-To, in the treatment

- of autoimmunity-related recurrent abortion by correcting T helper-1/T helper-2 balance. *Am J Reprod Immunol*, 44, 342-346.
- Gui, S.Q., Xu, J., Yu, E.K., & Li, D. J. (1997). Zhong yao zhi liao zi ran liu chan dui feng bi kang ti, beta-hCG, yun tong, ci er chun de ying xiang [The use of Chinese herbs in the treatment of spontaneous miscarriage and its effects on blocking antibody, beta-hCG, progesterone, and estradiol levels]. *Chinese Journal of Integrative Medicine*, 17(11), 645-648.
- Hou, X. P. (2004). Zhong xi yi jie he zhi yu kang xin lin zhi kang ti yang xing zhi liu chan 2 lie [The integrative treatment of 2 cases of antiphospholipid antibody positive miscarriage]. *Jiangxi Journal of Traditional Chinese Medicine*, 35(12), 43.
- Kano, T., Shimizu, M., & Kanda, T. (2010). Differences in individual efficacy of two Sairei-to preparations (Sojyutu-Sairei-to and Byakujyutu-Sairei-to) on recurrent spontaneous abortions of autoimmune etiologies evaluated by antinuclear antibody and anticardiolipin antibody titers. *Am J Chin Med*, 38(01), 27-36. doi:10.1142/S0192415X10007658
- Kutteh, W. H. (1996). Antiphospholipid antibody-associated recurrent pregnancy loss: Treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. *Am J Obstet Gynecol*, 174(5), 1584-1589.
- Laskin, C.A., Spitzer, K.A., Clark, C.A., Crowther, M.R., Ginsberg, J.S., Hawker, G.A., . . . Gent, M. (2009). Low molecular weight heparin and aspirin for recurrent pregnancy loss: Results from the randomized, controlled HepASA Trial. *J Rheumatol*, 36(2), 279-287.
- Lefkou, E., Khamashta, M., Hampson, G., & Hunt, B. J. (2010). Review: Low-molecular-weight heparin-induced osteoporosis and osteoporotic fractures: a myth or an existing entity? *Lupus*, 19(1), 3-12. doi:10.1177/0961203309353171
- Lewis, R. (2004). *The infertility cure* (pp. 202-206). New York: Little, Brown and Company.

- Li, E.,T., Li, M.J., Gao, A.P., Sha, W.X., Jin, Y.H., Tu, X.M., . . . Zhou, O. L. (2000). Yang xue an tai chong ji fang zhi xi guan xing liu chan ji dui duan shou ming yi zhi xing T xi bao de ying xiang [The prevention of recurrent miscarriage with Yang Xue An Tai Chong Ji granules and their impact on short-lived T suppressor cell activity]. *Chinese Journal of Integrative Medicine*, 20(4), 248-250.
- Li, W. H. (2003). Zhong xi yi jie he zhi liao kang xin lin zhi kang ti suo zhi fan fu zi ran liu chan lin chuang guan cha [Clinical observations on the integrative treatment of antiphospholipid antibody positive recurrent miscarriage]. *Guangxi Journal of Traditional Chinese Medicine*, 26(3), 23-24.
- Liu, H.L., Li, Z.R., Yang, H.Y., Wang, Y.Z., & Du, W. H. (2006). Yi qi gu shen tang zhi liao bu ming yuan yin xi guan xing liu chan de liao xiao fen xi [Assessment of the effectiveness of herbal formula Yi Qi Gu Shen Tang to treat unexplained recurrent miscarriage]. *Journal of Reproductive Medicine*, 15(3), 172-174.
- Liu, R.X., Liu, Y.Q., Wu, X.L., Chen, G., & Liu, L. L. (2003). Effect of salvia miltiorrhiza bunge and its compound on the patients of anticardiolipin antibody-positive recurrent spontaneous abortion (AARSA). *Journal of Zhejiang College of Traditional Chinese Medicine*, 27(4), 38-39.
- Liu, Y.L., Xu, Z.L., & Zhang, L. (2007). Observation of Buzhong Yiqi decoction on adjustive immunity of recurrent spontaneous abortion patients of insufficient materno-fetal recognition. *Zhejiang Journal of Integrated Traditional Chinese and Western Medicine*, 17(10), 602-604.
- Lubbe, W., Butler, W., Palmer, S., & Liggins, G. (1983). Fetal survival after prednisone suppression of maternal lupus-anticoagulant. *Lancet*, *i*, 1361-1363.

Lynch, A., Marlar, R., Murphy, J., Davila, G., Santos, M., Rutledge, J., & Emlen, W. (1994).

Antiphospholipid antibodies in predicting adverse pregnancy outcome. A prospective study.

Ann Intern Med, 120(6), 470-5. Retrieved from

<http://www.ncbi.nlm.nih.gov/pubmed/8093135>

Mak, A., Cheung, M., Cheak, A., & Ho, R. (2010). Combination of heparin and aspirin is

superior to aspirin alone in enhancing live births in patients with recurrent pregnancy loss

and positive anti-phospholipid antibodies: A meta-analysis of randomized controlled trials

and meta-regression. *Rheumatology*, 49, 281-288. doi:10.1093/rheumatology/kep373

Marrs, R., Bloch, L. F., & Silverman, K. K. (1997). *Dr. Richard Marrs' fertility book: America's*

leading fertility expert tells you everything you need to know about getting pregnant. New

York, NY: Dell Publishing.

Mendeley Support Team. (2011). *Mendeley Desktop*. London (Version 1.1) [Software].

Available from <http://www.mendeley.com>

Meng, D.H. (2006). Bu shen huo xue fa zhi liao kang xin lin zhi kang ti yang xing zhi zao qi ren

shen liu chan [The use of kidney tonifying and blood moving treatment method to treat

antiphospholipid antibody positive early miscarriage]. *Shanxi Journal of Traditional*

Chinese Medicine, 22(2), 35.

Meroni, P.L., Simone, N.D., Testoni, C., D'Asta, M., Acaia, B., & Caruso, A. (2004).

Antiphospholipid antibodies as cause of pregnancy loss. *Lupus*, 13, 649-652.

doi:10.1191/09612033041u2001oa

Paternal leukocyte immunization. (2004). *The InterNational Council on Infertility Information*

Dissemination, Inc. Retrieved from <http://www.inciid.org/article.php?cat=glossary&id=70>

Paternal leukocyte immunization. (2004). *The InterNational Council on Infertility Information*

Dissemination, Inc. Retrieved from <http://www.inciid.org/article.php?cat=glossary&id=70>

Placental thrombosis. (n.d.). Retrieved from <http://medical-dictionary.thefreedictionary.com/placental+thrombosis>

Porter, T.F., La Coursiere, Y., & Scott, J. R. (2006). Immunotherapy for recurrent miscarriage. *Cochrane Database of Systematic Reviews*, (2), CD000112.
doi:10.1002/14651858.CD000112.pub2

Rai, R. S., Clifford, K., Cohen, H., & Regan, L. (1995). High prospective fetal loss rate in untreated pregnancies of women with recurrent miscarriage and antiphospholipid antibodies. *Hum Reprod*, 10(12), 3301-4.

Rai, R., Cohen, H., Dave, M., & Regan, L. (1997). Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ*, 314, 253-257.

Roberts, C. M. (2010). *The dissertation journey: A practical and comprehensive guide to planning, writing, and defending your dissertation*. (2nd ed.). Thousand Oaks, CA: Corwin.

Shefras, J., & Farquharson, R. (1996). Bone density studies in pregnant women receiving heparin. *Eur J Obstet Gynecol Reprod Biol*, 65, 171-174.

Shen, Y. C. (2009). Zhi ba di huang wan zhi liao fan fu liu chan hou kang jing zi kang ti yang xing de liao xiao guan cha [Clinical observation on the effectiveness of Zhi Bai Di Huang Wan formula to treat antisperm antibody positive recurrent miscarriage]. *China Modern Doctor*, 47(24), 215, 219.

Shu, J., Miao, P., & Wang, R. J. (2002). Clinical observation on effect of Chinese herbal medicine plus human chorionic gonadotropin and progesterone in treating anticardiolipin antibody-positive early recurrent spontaneous abortion. *Chinese Journal of Integrated Traditional and Western Medicine*, 22(6), 414-416.

- Si, X. R. (2007). Bao Chan Shen Xiao Fang zhi liao mian yi xing fan fu liu chan 28 lie [28 cases of recurrent miscarriage treated by Bao Chan Shen Xiao Fang herbal formula]. *China Practical Medicine*, 2(9), 76-78.
- Silver, R.K., MacGregor, S.N., Sholl, J.S., Hobart, J.M., Neerhof, M.G., & Ragin, A. (1993). Comparative trial of prednisone plus aspirin versus aspirin alone in the treatment of anticardiolipin antibody-positive obstetric patients. *Am J Obstet Gynecol*, 169, 1411-1417.
- Speroff, L., & Fritz, M. A. (2005). *Clinical gynecologic endocrinology and infertility* (7th ed.). Philadelphia, PA: Lippincott Williams & Wilkins.
- Takakuwa, K., Arakawa, M., Honda, K., Imai, T., Tamura, M., Yasuda, M., & Tanaka, K. (1997). Alterations of lymphocyte subsets in patients with recurrent fetal wastage positive for antiphospholipid antibodies treated with Chinese herbal medicine. *J Perinat Med*, 25, 385-387.
- Takakuwa, K., Ishii, K., Takaki, Y., Natsume, N., Adachi, H., Kurata, H., . . . Kenichi, T. (2003). Effect of Sairei-to combined with aspirin and prednisolone on four recurrent reproductive failure women who are positive for anti-phospholipid antibodies. *Am J Chin Med*, 31(4), 659-63. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/14587888>
- Takakuwa, K., Yasuda, M., Hataya, I., Sekizuka, N., Tamura, M., Arakawa, M., . . . Tanaka, K. (1996). Treatment for patients with recurrent abortion with positive antiphospholipid antibodies using a traditional Chinese herbal medicine. *J Perinat Med*, 24(5), 489-494. doi:10.1515/jpme.1996.24.5.489, //1996
- Triolo, G., Accardo-Palumbo, A., Ciccia, F., Cadelo, M., Castelli, A., Perino, A., & Licata, G. (2004). IVIG in APS pregnancy. *Lupus*, 13, 731-735. doi:10.1191/0961203304lu2011oa
- Triolo, G., Ferrante, A., Ciccia, F., Accardo-Palumbo, A., Perino, A., Castelli, A., . . . Licata, G. (2003). Randomized study of subcutaneous low molecular weight heparin plus aspirin

- versus intravenous immunoglobulin in the treatment of recurrent fetal loss associated with antiphospholipid antibodies. *Arthritis Rheum*, 48(3), 728-31. doi:10.1002/art.10957
- Trophoblast. (2011). *Wikipedia: The Free Encyclopedia*. Retrieved from <http://en.wikipedia.org/wiki/Trophoblast>
- Vaquero, E., Lazzarin, N., Valensise, H., Menghini, S., Di Pierro, G., Cesa, F., & Romanini, C. (2001). Pregnancy outcome in recurrent spontaneous abortion associated with antiphospholipid antibodies: A comparative study of intravenous immunoglobulin versus prednisone plus low-dose aspirin. *Am J Reprod Immunol*, 45(3), 174-179.
- Wang, B.J., Huo, S., Bai, B.M., Xiong, X.Y., Luo, S.P., Wang, Y.F., . . . Han, L. Y. (2004). Clinical studies of Taiminling combined with Western medicine in treating recurrent abortion induced by anti-phospholipid antibody. *Journal of Guangzhou University of Traditional Chinese Medicine*, 21(1), 21-23.
- Wang, L.N., Wei, A.W., & Liu, W.X. (2006). Fu fang dan shen zhu she ye zhi liao fan fu xing liu chan 30 lie [The treatment of 30 cases of recurrent miscarriage with Dan Shen compound injection]. *Journal of Sichuan of Traditional Chinese Medicine*, 24(5), 79-80.
- Wang, X. (2004). Zhong yao zhi liao kang xin lin zhi kang ti yang xing xi guan xing liu chan 43 lie fen xi [Analysis of 43 cases of antiphospholipid antibody positive recurrent miscarriage treated with Chinese medicine]. *Chinese Archives of Traditional Chinese Medicine*, 22(5), 945.
- Wang, Y. F., & Lu, Q. B. (2008). Bu shen huo xue fa zhi liao kang xin lin zhi kang ti yang xing mian yi xing liu chan de yan jiu jing zhan [Progress in research on the the use of kidney tonifying and blood moving method to treat antiphospholipid antibody positive immunological miscarriage]. *Gansu Journal of Traditional Chinese Medicine*, 21(1), 8-9.

- Wei, A.W. & Li, Y. (2004). Zhong xi yi jie he zhi liao kang xin lin zhi kang ti zhi fan fu xing liu chang 30 lie [Integrative treatment of 30 cases of antiphospholipid antibody positive recurrent miscarriage]. *Journal of Sichuan of Traditional Chinese Medicine*, 22(9), 57-58.
- Yan, Z. H. (Ed). (1991). *Chinese Herbal Pharmacology* (pp. 116-806). Beijing: People's Medical Publishing House.
- Ye, L. Q. (2008). Bu shen huo xue fa he a si pi lin zhi liao ACA yang xing fu fa xing liu chan 45 lie [The use of kidney tonifying and blood moving methods plus aspirin to treat 45 cases of ACA positive recurrent miscarriage]. *Jiangxi Journal of Traditional Chinese medicine*, 39(10), 63-64.
- Yuan, H. X. (2005). Bu shen yi kang tang zhi liao fan fu liu chan hou kang xin lin zhi kang ti yang xing 36 lie lin chuang yan jiu [Clinical observation of the treatment of recurrent miscarriage in 38 antiphospholipid antibody positive patients with Bu Shen Yi Kang Tang formula]. *Journal of Shaanxi College of Traditional Chinese Medicine*, 28(6), 28-29.
- Yuan, H.X. & He, J. (2004). Zhong yao tai er an fang zhi liao kang xin lin zhi kang ti yang xing zhi hua tai [The treatment of antiphospholipid antibody positive recurrent miscarriage with Tai Er An Fang herbal formula]. *Journal of Shaanxi College of Traditional Chinese Medicine*, 27(4), 39.
- Zhan, X.L., Ping, Z.W., Mao, L.Z., Luo, X.P., Chai, R.Y., & Lai, Y. X. (2009). Xiao kang di huang tang dui fan fu zi ran liu chan kang xin lin zhi kang ti de ying xiang [The impact of Xiao Kang Di Huang Tang on antiphospholipid antibodies in patients with recurrent miscarriage]. *Chinese Journal of Information on TCM*, 16, 40-41.
- Zhang, X. Z. (2002). Zhong xi yi jie he zhi liao mian yi xing fu fa xing liu chan 47 lie [Integrative East West medicine to treat 47 cases of immunologic recurrent miscarriage]. *Hunan Journal of Traditional Chinese Medicine*, 18(3), 55-56.

- Zhang, Y., Li, M.J., & Tu, X.M. (2006). Yang xue an tai ke li dui fan fu zi ran liu chan huan zhe fei yun qi NK ji Ts xi bao huo xing de ying xiang [The effect of Yang Xue An Tai pill on NK and Ts cell activity in non-pregnant patients with a history of recurrent spontaneous miscarriage]. *Chinese Journal of Birth Health and Heredity*, 14(6), 55, 66.
- Zhang, Z. X. (1007). Zhong xi yi jie he zhi liao kang xin lin zhi kang ti yang xing huan zhe 30 lie liao xiao guan cha [Observations on the use of a combination of Chinese and Western medicine to treat 30 patients who tested positive for antiphospholipid antibodies]. *Shandong Medical Journal*, 47(11), 42-43.
- Zhu, Q. F., & Lu, Q. B. (2007). Zhi liao kang xin lin zhi yang xing suo zhi mian yi xing liu chan de yan jiu jing zhan [Progress in research on treating antiphospholipid antibody positive immunological miscarriage]. *Gansu Journal of Traditional Chinese Medicine*, 20(5), 50-51.

Appendix A: Articles Used for Research Synthesis, Listed in Order of Study Number

Appendix A: Articles Used for Research Synthesis, Listed in Order of Study Number

1. Kano, T., Shimizu, M., & Kanda, T., (2010)
2. Cong, Y. (2007)
3. Cheng, J.L., & Ma, S.H. (2010)
4. Zhang, Y., Li, M.J., & Tu, X.M. (2006).
5. Si, X.R. (2007)
6. Liu, R.X., Liu, Y.Q., Wu, X.L., Chen, G., & Liu, L.L. (2003)
7. Zhan, X.L., Ping, Z.W., Mao, L.Z., Luo, X.P., Chai, R.Y., & Lai, Y.X. (2009)
8. Li, W.H. (2003)
9. Chai, L.H., & Zhao, W. (2002)
10. Wei, A.W., & Li, Y. (2004)
11. Shu, J., Miao, P., & Wang, R.J. (2002)
12. Zhang, X.Z. (2002)
13. Ye, L.Q. (2008)
14. Zhang, Z.X. (2007)
15. Wang, B.J., Huo, S., Bai, B.M., Xiong, X.Y., Luo, S.P., Wang, Y.F., . . . Han, L.Y. (2004)
16. Takakuwa, K., Arakawa, M., Honda, K., Imai, T., Tamura, M., Yasuda, M., & Tanaka, K. (1997)
17. Meng, D.H. (2006)
18. Wang, X. (2004)
19. Takakuwa, K., Yasuda, M., Hataya, I., Sekizuka, N., Tamura, M., Arakawa, M., . . . Tanaka, K. (1996)
20. Gui, S.Q., Xu, J., Yu, E.K., & Li, D.J. (1997)
21. Li, E.T., Li, M.J., Gao, A.P., Sha, W.X., Jin, Y.H., Tu, X.M., . . . Zhou, O.L. (2000)
22. Yuan, H.X., & He, J. (2004)
23. Yuan, H.X. (2005)
24. Takakuwa, K., Ishii, K., Takaki, Y., Natsume, N., Adachi, H., Kurata, H., . . . Tanaka, K. (2003)
25. Hou, X.P. (2004)
26. Liu, H.L., Li, Z.R., Yang, H.Y., Wang, Y.Z., & Du, W.H. (2006)
27. Wang, L.N., Wei, A.W., & Liu, W.X. (2006)
28. Shen, Y.C. (2009)
29. Cui, Y., & Hu, L.S. (2009)
30. Liu, Y.L., Xu, Z.L., & Zhang, L. (2007)

Appendix B: Overview of Articles

Appendix B: Overview of Articles

Type of Treatment(s) Administered	Studies Which Observed These Treatment Modalities (Listed by Study Number)	Total Number of Studies
CH* Only (no control group)	1, 5, 16, 17, 18, 19, 20, 21, 22, 23, 26, 29	12
Western versus CH/Western	6, 8, 9, 11, 12, 13, 14	7
CH versus Western	2, 3, 4, 7, 28, 30	7
CH/Western**(no control group)	24, 25, 27	3
CH versus CH/Western versus Western (3 treatment groups)	10, 15	2

* CH – Chinese Herbs

** “Western” refers to the use of Western medicine in the study.

Appendix C: Summary of Chinese Herbs Only Studies

Appendix C: Summary of Chinese Herbs Only Studies

Study#	# of Subjects	Age Range (years)	# of previous miscarriages ($\geq x$)	Observed Immunological Markers (APA/ACA, LA, NK cells, ANA, APTT, etc)*	Treatment Intervention(s) X ₁ , X ₂ , X ₃ ...	Control Group (non-Chinese medicine) Intervention X ₀
1	52	28-42	≥ 3	ANA (27), APA/ACA (34)	X ₁ – Herbal formula: Sojyutu Sairei-to, 9g/day, 30 minutes before meal. X ₂ – Herbal Formula: Byakujyutu Sairei-to, 8.1g/day, 30 minutes before meal. Duration of treatment not stated.	N/A
5	191	23-44	≥ 2	ABO Incompatibility – Anti-A antibody, Anti-B antibody Rh Incompatibility, - Anti-D antibody APA/ACA	T ₁ - Bao Chan Shen Xiao Fang herbal decoction, 1 bag of herbs cooked twice and divided into 2-3 servings per day, taken on an empty stomach. When the patient was pregnant again or preparing to become pregnant again and if a blood test showed that anti-A and/or anti-B antibodies were $\leq 1:64$, or anti-D antibodies were within normal range, or APA levels were within normal range, then herbal pills were used instead of the herbal decoction. Each pill was 9 grams and taken twice a day, one pill each time on an empty stomach with warm water. Whether the patient was pregnant or not pregnant at the time of the visit, if antibody levels were abnormally high, the herbal medicine was used until delivery.	N/A
16	11	N/A	≥ 2	APA/ACA	Herbal formula: Sairei-to (Chai Ling Tang)- 9 g/day starting during non-pregnant state. After APA values normalized, px allowed to try for pregnancy. Herbs were continued during pregnancy and discontinued after delivery.	N/A
17	1	28	3	APA/ACA	X ₁ - Administered herbal decoction once daily, for 3 months, and not taken when the patient had her period. It is not clear whether the herbs were continually administered until the patient became pregnant in February of 2004 (treatment was started on May 2, 2003). Herbal tx was continued during pregnancy, but it is not clear whether herbs used were the same as before.	N/A
18	43	26-42	≥ 3	APA/ACA	X ₁ - 1 bag of herbal formula was decocted and drunken 3 times per day, 100 ml each time. Patients were already pregnant. The duration of treatment was not specifically stated.	N/A
19	12	25-41	≥ 2	APA/ACA	X ₁ - 9 grams/day of Sairei-to (Chai Ling Tang) patent herbal powder was administered during nonpregnant state. After APA values normalized, patients allowed to attempt pregnancy. Herbal formula was continued throughout pregnancy and discontinued after the delivery.	N/A
20	68	24-42	≥ 3	Blocking antibody	X ₁ - Herbal decoction was made into concentrated granules to be dissolved in water. Patients were less than 3	N/A

					months pregnant. Each packet of granules contained 15 grams. 1 packet taken twice a day. One treatment cycle consisted of 1 month of treatment. Patients were treated until the end of the third month of pregnancy, or until they made it past the time at which they had experienced previous miscarriages.	
21	56	26-40	≥ 4	Suppressor T Cell	X ₁ - As soon as pregnancy was confirmed in the patient, Yang Xue An Tai Chong Ji herbal granules were administered three times a day, 8 grams each time. At 3 months, T suppressor cell activity was measured. If the TS cell activity values increased and the patient made it through the time of pregnancy in which she had her previous spontaneous miscarriages, then the herbal granules were discontinued. For some patients who did not have their TS cell activity measured during the second trimester, the herbs were taken for 7 months and then discontinued.	N/A
22	36 (plus one case study)	24-35	≥ 2	APA/ACA	X ₁ -Once patients were confirmed pregnant via ultrasound, herbal formula was prescribed: 1 bag of herbs cooked once per day and divided into two doses. Every 10 days, ACA titers and Ultrasound were taken. Herbs were taken until ACA titers became negative and ultrasound revealed a viable fetus and resorption of blood in patients who were previously experienced bleeding/spotting during pregnancy.	N/A
23	36 (plus one case study)	23-35	≥ 2	APA/ACA	X ₁ - Herbal formula Bu Shen Yi Kang Tang was administered, with other herbs added in depending on symptoms and diagnosis: one bag cooked once per day and divided into 2-3 doses daily. One treatment cycle lasted 10 days. After 2 treatment cycles, ACA titers were measured. If they became negative, the patient was allowed to attempt conception. If it was still positive, a 3 rd treatment cycle was attempted.	N/A
26	30	31.3	≥ 3	T cell activity-Cluster of Differentiation CD4 and CD8	X ₁ - Herbal Formula Yi Qi Gu Shen Tang (Benefit the Qi and Fortify the Kidney Decoction) administered before pregnancy for 1-3 months. After pregnancy was achieved, the herbs were continued intermittently until after the 3 rd month of pregnancy was reached. Before treatment and 70 days into pregnancy, CD (cluster of differentiation) cell levels were measured.	N/A
29	30	21-35	≥ 3	Unexplained	X ₁ - Modified form of Sang Qi Tang herbal formula used. Duration of treatment, and directions on how to decoct herbs were not explained.	N/A

* APA/ACA – Antiphospholipid Antibody/Anticardiolipin Antibody

LA – Lupus Anticoagulant

NK cells – Natural Killer cells

ANA – Antinuclear Antibody

APTT – activated partial thromboplastin time

Appendix D: Summary of Chinese Herbs plus Western Medicine Studies

Appendix D: Summary of Chinese Herbs plus Western Medicine Studies

Study #	# of Subjects	Age Range (years)	# of previous miscarriages ($\geq x$)	Observed Immunological Markers (APA/ACA, LA, NK cells, ANA, APTT, etc)*	Treatment Intervention(s) X ₁ , X ₂ , X ₃ ...	Control Group (non-Chinese medicine) Intervention X ₀
24	4	29-34	≥ 2	Anticardiolipin β_2 Glycoprotein and/or APA/ACA	X ₁ = 1) Herbal Formula: Sairei-to (Chai Ling Tang)- 9 grams per day started before pregnancy and continued throughout prenatal course, 2) Low-dose Aspirin 81mg/day throughout prenatal course, 3) Prednisolone 30-40mg/day during first trimester and reduced to 5-10mg/day during the rest of prenatal course.	N/A
25	1	29	≥ 2	APA/ACA	X ₁ - Tx administered when patient was pregnant and experiencing light spotting, 49 days since her last period. Intramuscular injection of 1000 Units hCG, once per day. After half month, hCG given every other day for one week, and every week thereafter, dosage was cut in half. 3 weeks later, hCG shots were discontinued. The patient also had an upper respiratory infection at the time of her pregnancy, so 6.4 million Units of penicillin was injected intravenously for 3 days. After that, an herbal formula was administered everyday for the first 4 months of pregnancy. Then the herbal decoction was taken every other day for one month. After 5 months of pregnancy, the formula was taken twice a week and continued until the 9 th month of pregnancy.	N/A
27	45	25-35	≥ 2	APA/ACA (18/30); the rest did not test positive for ACA.	X ₁ - After pregnancy was confirmed, human chorionic gonadotropin (hCG) and progesterone levels were measured. If hCG levels and/or progesterone levels were below normal, then 1) 1000 U hCG and/or 20mg Progesterone were administered via intramuscular injection, once per day. Progesterone and hCG levels were monitored regularly. If hCG or Progesterone levels measured at normal levels two times in one week, then hCG and/or Progesterone injections were decreased to every other day. If after the 2 nd week of treatment, Progesterone levels were still within normal range, then medication was discontinued. 2) At the same time, an I.V. injection of 20	N/A

					<p>ml Dan Shen extract + 500 ml saline solution was administered for 10 days. Another 2 rounds of 10-day injections were given, with 10 days of rest between each round.</p> <p>X₂. 1) Except for the Dan Shen/saline solution injection, all treatment with western medication was the same in this group. Dan Shen/saline solution was not given. 2) Shou Tai Wan herbal formula was administered, cooked once per day and divided into two doses, morning and evening. Duration not mentioned.</p>	
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- * APA/ACA – Antiphospholipid Antibody/Anticardiolipin Antibody
- LA – Lupus Anticoagulant
- NK cells – Natural Killer cells
- ANA – Antinuclear Antibody
- APTT – activated partial thromboplastin time

Appendix E: Studies Comparing the Use of Chinese Herbs versus Western Medicine

Appendix E: Studies Comparing the Use of Chinese Herbs versus Western Medicine

Study #	# of Subjects	Age Range (years)	# of previous miscarriages ($\geq x$)	Observed Immunological Markers (APA/ACA, LA, NK cells, ANA, APTT, etc)*	Treatment Intervention(s) X_1, X_2, X_3, \dots	Control Group (non-Chinese medicine) Intervention X_0
2	65	24-38	≥ 2	APA/ACA	X_1 = Herbal formula - Xiao Kang Tang: 100 ml, 2 times/day, before breakfast and after dinner. 1 round of treatment was composed of 2 months of treatment, for a total of 3 rounds (6 months) of treatment. Patients were required to wear condoms to prevent pregnancy during that time. Herbs were not taken during menstruation.	X_0 = Aspirin, 50 mg, once per day. 1 round of treatment was composed of 2 months of treatment, for a total of 3 rounds (6 months) of treatment. Patients were required to wear condoms to prevent pregnancy during that time. Medication not taken during menstruation.
3	106	23-35	≥ 2	Endometrial antibody, APA/ACA	X_1 = Herbal formula cooked in an automatic herb cooker, 300 ml/day, 150 ml morning and evening. Herbs were not taken during menstrual phase. Treatment continued for 3 months.	X_0 = 10 mg prednisone, once per day in the evening. Medication not taken during menstrual phase. Herbs were not taken during menstrual phase. Treatment continued for 3 months. Condoms were used during this time period for the control group to prevent pregnancy.
4	82	22-41	≥ 2	NK cells	X_1 = Herbal pill – Yang Xue An Tai Ke Li (Nourish Blood and Calm the Fetus Pill), 8g (decoction was made from 31.35 g raw herbs), 2-3 times/day, for 3 months, during non-pregnant state.	X_0 = 100 mg Vitamin E supplement, 1 time/day, for 3 months, during non-pregnant state.
7	86	28.85 \pm 3.10	≥ 2	APA/ACA	X_1 = Herbal formula – Xiao Kang Di Huang Tang: 150 ml, 2 times per day, for 45 days. Patients were not pregnant. If antibody titers became negative, the herbs were discontinued. If not negative, the herbs were continued for another 45 days.	X_0 = Patients were not pregnant. 50 mg aspirin, 2 times/day, for 45 days. If antibody titers became negative, aspirin was discontinued. If not negative, the herbs were continued for another 45 days.
28	69	21-40	≥ 2	Antisperm antibody (AsAb)	X_1 = 6 grams of patent herbal pill Zhi Bai Di Huang Wan, 2 times per day. Condoms were used to prevent pregnancy during time of treatment. One cycle of treatment consisted of one month, for a maximum of three cycles, depending on whether AsAb levels turned negative. AsAb levels were evaluated at the end of each month. If AsAb test turned out negative at the end of a month, then treatment was discontinued. If it was still positive, then treatment was continued for the 2 nd or 3 rd month.	X_0 = 5 mg Prednisone, 3 times per day. Condoms were used to prevent pregnancy during time of treatment. One cycle of treatment consisted of one month, for a maximum of three cycles, depending on whether AsAb levels turned negative. AsAb levels were evaluated at the end of each month. If AsAb test turned out negative at the end of a month, then treatment was discontinued. If it was still positive, then treatment was continued for the 2 nd or 3 rd month.
30	72	23-38	≥ 2	Maternal blocking antibody	X_1 = Bu Zhong Yi Qi Tang Formula was used, one bag of herbs per day, cooked once and divided into 2 doses. One treatment cycle consisted of 3 months of treatment. Maternal blocking antibodies were	X_2 = In vitro inducing paternal lymphocyte immunotherapy was administered once every 4 weeks. One treatment cycle consisted of 3 treatments. Blocking antibodies were tested at the end of the treatment cycle.

					measured at the end of the treatment cycle. If the patient became pregnant during treatment, Shou Tai Wan herbal formula was added to Bu Zhong Yi Qi Tang.	
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- * APA/ACA – Antiphospholipid Antibody/Anticardiolipin Antibody
- LA – Lupus Anticoagulant
- NK cells – Natural Killer cells
- ANA – Antinuclear Antibody
- APTT – activated partial thromboplastin time

Appendix F: Studies Comparing the Use of Western Medicine Only versus CH/Western

Appendix F: Studies Comparing the Use of Western Medicine Only versus CH/Western*

Study #	# of Subjects	Age Range (years)	# of previous miscarriages ($\geq x$)	Observed Immunological Markers (APA/ACA, LA, NK cells, ANA, APTT, etc)**	Treatment Intervention(s) X ₁ , X ₂ , X ₃ ...	Control Group (non-Chinese medicine) Intervention X ₀
6	42	23-36	≥ 2	Anticardiolipin antibody (ACA/APA)	X ₁ - 1) Salvia Miltiorrhiza (Dan Shen) intravenous injection made of 250 ml of 5% glucose + 30 ml Dan Shen injection solution, administered 1x/day, for 10 days. 2) Chinese herbal decoction was taken after 10 days of Dan Shen injections. Formula was taken for 3 months. If px was already pregnant, the herbal formula was continued for 3 to 6 months. 3) During the whole course of treatment, Vitamin E, 100 mg, 1x/day, and 4) Folic acid, 10 mg, 3x/day, were also taken. Patients who were not pregnant at the time of the study were allowed to attempt conception during treatment.	X ₀ - 1) Vitamin E, 100 mg, 1x/day, 2) Folic acid, 10 mg, 3x/day throughout treatment.
8	60	23-35	≥ 2	Anticardiolipin antibody (ACA/APA)	X ₁ - After confirming a positive pregnancy test by measuring the presence of β HCG in the blood or urine, 1) 2000 U of HCG was intramuscularly injected every other day and 2) Vitamin E was also given (dosage and frequency not reported). 3) If there was bleeding or spotting, 20 mg of progesterone was given by intramuscular injection every other day, alternating with HCG. 4) Herbal pill called An Tai Jiao Nang was taken 3 times/day, 4 pills each time. If fetal heartbeat was detected on ultrasound 50 days after the end of the last menstrual period, then the treatment was continued for another 2 months.	X ₀ - Same procedures done to confirm pregnancy as in treatment group. HCG, Vitamin E, and progesterone (if bleeding present) were administered in same manner as Treatment group. No herbal medicine was administered.
9	56	25-36	≥ 2	Antisperm antibody, anti-ovarian antibody, endometrial antibody, anti-HCG antibody	X ₁ - Patients were instructed to use condoms to prevent pregnancy during pre-pregnancy treatment, for 3 to 6 months. Western Medication: Before pregnancy, 5 mg Prednisone, three times a day for 7 days, starting from cycle day 3 each month. This was continued for 3 to 6 months, during which the patient was instructed to avoid pregnancy through the use of condoms. After the patient stopped taking medication, pregnancy was attempted. Once pregnancy was confirmed, 20-40 mg/day	X ₀ - Only Western medication was used, in same manner as X ₁ treatment group.

					<p>intramuscular injection of progesterone was administered, along with 2000 IU intramuscular injection of HCG once every other day. After 3 months of pregnancy, the patient was gradually tapered off of the medication.</p> <p><u>Chinese Medicine</u> <u>Pre-pregnancy Tx:</u> 1) Patients diagnosed with Kidney deficiency: modified version of Yu Ling Zhu herbal formula used, 1 bag per day. 2) Patients diagnosed with Liver Qi Stagnation: modified Jia Wei Xiao Yao San used, 1 bag per day.</p> <p><u>Pregnancy Tx:</u> Herbs were take for 3-5 months during pregnancy. 1) Kidney deficiency: modified Bu Shen Gu Tai Yin, 1 bag per day. 2) Qi and Blood deficiency: modified Yang Xue An Tai Tang.</p>	
11	41	23-35	≥ 2	Anticardiolipn antibody (ACA/APA)	<p>X₁- Before attempting pregnancy, the following were administered: 1) Chinese herbal formula taken for 2-3 months, until ACA titers became negative. 2) 10 mg folic acid, 3 times per day, 3) 0.2 g Vitamin C, 3 times per day, 4) “Gold Theragran” (Jin Shi Er Kang) multi-vitamin or “21-Super Vita” (21-Jin Wei Ta) multivitamin, 1 pill, 1 time per day. Supplements and vitamins were taken for at least 3 months. Once the ACA titers became negative, pregnancy was attempted. When BBT was elevated for 16-18 days and pregnancy was confirmed via urine or blood βHCG test, the following were prescribed: 1) Same Chinese herbal formula for 5-10 days, 2) 20 mg intramuscular injection of Progesterone, once per day for 1 week, 3) 2000 Units intramuscular injection of human chorionic gonadotropin (HCG) once per day for 2 weeks, then decreased to 1500 Units daily for 1 week, then 1000 Units. If fetal heartbeat was detected via ultrasound 50 days into pregnancy, 1000 Units of HCG was continued until the end of 12 gestational weeks.</p>	X ₀ – only administered f/olic acid, Vitamin C, and multi-vitamins throughout treatment.
12	89	25-39	≥ 2	Anti-sperm antibody (AsAb), Endometrial antibody (EmAb), Anticardiolipin antibody (ACA/APA)	<p>X₁- Patients were instructed to avoid pregnancy through the use of condoms use condoms to prevent pregnancy during treatment.</p>	X ₂ - Only Western medication was taken during pre-pregnancy period. Treatment during pregnancy was identical to

					<p><u>Pre-pregnancy Tx</u> Western medication: 20 mg Prednisone, once a day for 7 days; then 15 mg, once a day for 7 days; then 10 mg, once a day, for 7 days; then 5 mg, once a day for 7 days. One treatment cycle consisted of 28 days. Medication was to be taken in the morning between 6 and 8 a.m. on an empty stomach. After 28 days, blood and vaginal mucous samples were taken, and AsAb, EmAb, and ACA levels measured. If the results were still positive, the patient continued treatment for another cycle, for a maximum of 3 cycles.</p> <p>Chinese Medicine: At the same time as taking western medication, a Chinese patent herbal pill formula Liu Wei Di Huang Wan was also taken, 10g 3 times a day, on an empty stomach. One treatment cycle lasted one month.</p> <p><u>Tx During Pregnancy</u> After pregnancy was established, 1) the Chinese herbal formula Shou Tai Wan was administered, 1 bag of herbs every 2 days and drunken 1-2 times per day, 2) 100 mg Vitamin E, 3 times a day until the end of the 12th week of pregnancy.</p>	the X ₁ Treatment group.
13	90	23-35	≥2	Anticardiolipin antibody (ACA/APA)	X ₁ - 1) 50-80 mg aspirin per day. 2) Herbal formula administered until ACA levels tested negative two consecutive times with one month between each testing. Patients were pregnant in 1 st trimester and experiencing symptoms of threatened miscarriage at start of tx.	X ₀ - 50-80 mg aspirin per day. Patients were pregnant in 1 st trimester and experiencing symptoms of threatened miscarriage at start of treatment.
14	60	22-36	≥2	Anticardiolipin antibody (ACA/APA)	X ₁ - 1) 25 mg aspirin, twice per day, 2) Herbal formula cooked once per day and divided into two dosages, morning and evening. Herbs and medication were not taken during menstruation. Condoms were used throughout treatment to prevent pregnancy. Treatment was continued for 1 to 3 months, depending on whether ACA levels returned to normal at the end of each month.	X ₀ - 1) 25 mg aspirin, twice per day, 2) 5 mg oral prednisone, once per day. Medication not taken during menstruation. Condoms were used throughout treatment to prevent pregnancy. Treatment was continued for 1 to 3 months, depending on whether ACA levels returned to normal at the end of each month.

*CH/Western – Chinese Herbs plus Western Medicine

**APA/ACA – Antiphospholipid Antibody/Anticardiolipin Antibody

LA – Lupus Anticoagulant

ANA – Antinuclear Antibody

NK cells – Natural Killer cells

APTT – activated partial thromboplastin time

**Appendix G: Summary of Studies Comparing CH Only versus CH/Western versus
Western Medicine Only**

Appendix G: Summary of Studies Comparing CH* Only versus CH/Western versus Western Medicine Only

Study #	# of Subjects	Age Range (years)	# of previous miscarriages ($\geq x$)	Observed Immunological Markers (APA/ACA, LA, NK cells, ANA, APTT, etc)**	Treatment Intervention(s) X ₁ , X ₂ , X ₃ ...	Control Group (non-Chinese medicine) Intervention X ₀
10	90	23-38	≥ 2	APA/ACA, LA	<p>All patients were not pregnant at the start of treatment.</p> <p>X₁- Chinese + Western Medicine group: Patients diagnosed with Kidney Yin deficiency were prescribed 1) Xiao Kang #1 herbal formula, 100 ml twice a day, 2) 25-50 mg aspirin once a day, and 3) 5 mg prednisone, three times a day. Patients diagnosed with Kidney Yang deficiency were prescribed Xiao Kang #2 formula plus the same dosage of aspirin and prednisone as stated above.</p> <p>X₂- Chinese medicine only group: Patients diagnosed with Kidney Yin deficiency were prescribed Xiao Kang #1 herbal formula. Kidneys diagnosed with Kidney Yang deficiency were prescribed Xiao Kang #2 herbal formula. 100 ml twice a day.</p>	<p>All patients were not pregnant at the start of treatment.</p> <p>X₀- Western medicine only group: 1) 25-50 mg Aspirin, once a day, plus 2) 5 mg prednisone, 3 times per day.</p>
15	87	23-41	≥ 2	APA/ACA	<p>X₁- (CH Only group): Tai Min Ling concentrated patent herbal granules, 1 packet dissolved in water and drunk every other day starting from around 30 days into pregnancy and ending ½ month before expected due date.</p> <p>X₂- (CH + Western group): Combined use of Tai Min Ling herbal granules and Western medicine treatment minus the heparin shots. Same usage as X₁ and X₃ group.</p>	<p>X₃ (Western medicine group): 1) 5 mg Prednisone, once a day, 2) 50 mg Aspirin once a day, 3) intramuscular injection of 6125 Units Heparin every other day, and 4) 2.5 grams of Intravenous Gammaglobulin every 21 days starting from around 30 days into pregnancy and ending ½ month before expected due date.</p>

* CH – Chinese Herbs

** APA/ACA – Antiphospholipid Antibody/Anticardiolipin Antibody

LA – Lupus Anticoagulant

NK cells – Natural Killer cells

ANA – Antinuclear Antibody

APTT – activated partial thromboplastin time

Appendix H: Summary of Observed Outcome Measures

Appendix H: Summary of Observed Outcome Measures

Type of Outcome Measure	Studies Which Observed This Outcome(Listed by Study Number)	Total Number of Studies
O1*- % Live births/Pregnancies	1, 5, 10, 11, 12, 13, 15, 16, 17, 18, 19, 20, 21, 24, 25, 26, 27,	17
O2* - % of patients who experienced decrease in antibody titers after treatment	1, 3, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 19, 22, 23, 24, 28	18
O3* – Change in immunomodulatory activity	4, 15, 16, 20, 21, 26, 29, 30	8
O4*- Number of weeks of sustained pregnancy	8, 9, 10, 21, 27	5
O5 – Change in trophoblast cell activity	4	1

*O1 – Outcome 1

O2 – Outcome 2

O3 – Outcome 3

O4 – Outcome 4

O5 – Outcome 5

Appendix I: Outcomes and Conclusions

				(P>0.05).														
4	O3	Change in immunomodulatory activity	Treatment group: Decrease in natural killer (NK) cell activity from 17.52 ± 5.71 to 13.28 ± 5.09 after 3 months of treatment. Control group: Decrease in NK cell activity from 18.04 ± 5.34 to 16.99 ± 5.73. “Normal” group – 12.74 ± 4.91.	C4-3- Natural killer (NK) cell activity significantly decreased in the treatment group post-treatment (P<0.001), but not in the control group (P>0.05).									X					
				C4-4 – There was no significant difference in NK cell activity between the treatment group post-treatment and the “normal” group (p>0.05).								X						
	O5	Change in trophoblast cell activity	Treatment group: Increase from 53.39± 9.67 to 61.85 ± 11.73 after 3 months. Control group: Increase from 52.76 ± 10.13 to 54.27 ± 8.92. “Normal” comparison group – 64.59 ± 11.	C4-1 – The trophoblast stem (TS) cell activity significantly increased in the treatment group (p<0.001), but not in the control group (p>0.05).									X					
				C4-2 – There did not appear to be a significant difference between the treatment group’s TS cell activity post-treatment and the “normal” group’s TS cell activity.								X						
5	01	Pregnancy Rate % (Pregnancies/Total Subjects)	The pregnancy rate was not available for this study.	C5-1- The herbal formula Bao Chan Shen Xiao Fang was effective in preventing miscarriage and achieving live birth in a majority of patients.	X													
		Live Birth Rate % (Live Births/Pregnancies)	ABO group: 89.5% (17/19) Rh group: 66.7% (2/3) Antiphospholipid antibody group: 85.7% (6/7) In total, pregnancy was preserved successfully in 86.2% of patients (25/29). (The number of patients in the APA/ACA group was stated as n=6 in one section of the article, and then as n=7 in the results graph, so the # of total patients in the study was not consistent -															

		treatment	(28/36) Control group: 25.% (5/20)	returned to normal/negative levels was significantly greater in the treatment group than in the control group after treatment (P<0.01)														
	04	Number of weeks of sustained pregnancy	Percentage of patients who made it through > 15 weeks of pregnancy and whose ultrasound findings showed a viable, healthy fetus: Treatment group: 52.8% (19/36) Control group: 10% (2/20)	C9-2- The percentage of patients who made it through >15 weeks of pregnancy was significantly higher in the treatment group than in the control group (P<0.01).					X									
10	01	Pregnancy Rate% (Pregnancies/Total Subjects)	The pregnancy rate was not available for this study.	C10-1- The X ₁ treatment group had higher live birth rates than either the X ₂ treatment group or the Western medicine only control group (p<0.05).					X	X								
		Live Birth Rate % (Live Births/Pregnancies)	X ₁ Treatment group (CH/Western): 33.3% (10/30) X ₂ Treatment group (CH Only): 13.3% (4/30) Control Group (Western Only): 10% (3/30)	C10-2- A greater percentage of patients in the X ₁ Treatment group experienced a decrease to normal/negative values in either ACA or LA by the end of treatment (p < 0.05).						X	X							
	02	% of px who experienced decrease in antibody titers after treatment	<u>Anticardiolipin (ACA/APA) or Lupus Anticoagulant (LA) (% that decreased to normal levels after treatment)</u> X ₁ Treatment group: 73.3% (22/30) X ₂ Treatment group: 30% (9/30) Control group: 30% (9/30)	C10-3- The percentage of pregnancies that were still viable at >28 weeks into pregnancy was greatest in the X ₁ Treatment group. The difference was significant (p < 0.05).					X	X								

				C10-4- It appears that there was no significant difference between the X ₂ Treatment group (CH Only) and the Control group (Western Only) in the number of weeks of sustained pregnancy for each group.										X		
	04	Number of weeks of sustained pregnancy	<p>1) <u>Pregnancy still viable > 28 weeks into pregnancy:</u> X₁ group: 40% (12/30) X₂ group: 16.7% (5/30) Control group: 20% (6/30)</p> <p>2) <u>Pregnancy still viable >20 weeks into pregnancy:</u> X₁ group: 20% (6/30) X₂ group: 53.3% (16/30) Control group: 53.3% (16/30)</p> <p>3) <u>Pregnancy lasted <18 weeks and resulted in miscarriage:</u> X₁ group: 6.6% (2/30) X₂ group: 13.3% (4/30) Control group: 16.7% (5/30)</p>													
11	01	Pregnancy Rate% (Pregnancies/Total Subjects)	The pregnancy rate was not available for this study.	C11-1 – The total percentage of live births was significantly greater in the treatment group than in the control group (P<0.01).					X							
		Live Birth Rate % (Live Births/Pregnancies)	Treatment group – 82.6% (19/23) Control group – 16.7% (3/18)													
	02	% of px who experienced decrease in antibody titers after treatment	Anticardiolipin antibody (ACA) (+) to (-): Treatment group - 86.9% (20/23) Control group – not indicated.	C11-2 – A conclusion cannot be drawn regarding decrease in antibody titers between the two groups because a value/percentage for the Control group was not available.												X
12	01	Pregnancy Rate% (Pregnancies/Total Subjects)	The pregnancy rates were not available from this study.	C12-1- The live birth rate in the treatment group was significantly higher than in the control group (P<0.05).					X							
		Live Birth Rate % (Live Births/Pregnancies)	Treatment group: 38.3% (18/47) Control group: 28.6% (12/42)													
	02	% of px who experienced decrease in antibody titers after treatment	Percentages include those who became pregnant and had live births (but whose changes in antibody titers can only be assumed to have become negative) plus those whose antibody titers became negative but did not have live births.	C12-2- The overall percentage of decrease in antibody titers in the Treatment group was significantly higher than the Control group after treatment						X						

			Treatment group: 74.5% (35/47) Control group: 52.4% (22/42)	(P<0.05).														
13	O1	Pregnancy Rate% (Pregnancies/Total Subjects)	The pregnancy rates were not available for this study.	C13-1 – Although none of the patients experienced full-term pregnancies, but the percentage of premature deliveries resulting in live births among patients in the treatment group was significantly higher than patients in the control group (P < 0.05).					X									
		Live Birth Rate % (Live Births/Pregnancies)	X ₁ group (CH/Western) - 92.3% (42/45) had premature deliveries resulting in live births. X ₂ group (Western Only) – 75.6% (34/45) had premature deliveries resulting in 1 live births.															
14	O2	% of px who experienced decrease in antibody titers after treatment	Change in Anticardiolipin levels from (+) to (-) after 3 months of treatment: Treatment group – 86.7% (26/30) Control group – 66.67% (20/30)	C14-1- Anticardiolipin antibody (ACA) levels decreased significantly more in the Treatment group after 3 months of treatment than in the Control group (P<0.05).					X									
15	O1	Pregnancy Rate% (Pregnancies/Total Subjects)	All groups had 100% pregnancy rate: X ₁ group (CH Only)- 24/24 X ₂ group (CH/Western)– 35/35 X ₃ group (Western Only) – 28/28	C15-1- The percentage of patients who experienced live births or whose ultrasound at 20 weeks showed a healthy, viable fetus was highest in X ₂ treatment group (Chinese medicine + Western medicine) and lowest in the Chinese medicine only group (p>0.05)				X	X	X								
		Live Birth Rate % (Live Births/Pregnancies)	Percentage of patients who experienced live birth or whose ultrasound at 20 weeks showed a healthy, viable fetus: X ₁ group (CH Only): 41.7% (10/24) X ₂ group (CH/Western): 94.3% (33/35) X ₃ group (Western Only): 75% (21/28)															
	O3	Change in antibody levels after treatment	Antiphospholipid antibodies (APA/ACA): All 3 groups experienced a drop in ACA titers after treatment, but in varying degrees: X ₁ group (CH Only) – ACA titers dropped from 32.25 ±	C15-2- ACA/APA levels dropped significantly more in the X ₂ (CH + Western) group compared to the CH Only					X	X								

		<p>births/pregnancies)</p>	<p>ultrasound or had already experienced live birth by the time the study was written. The live birth rate apart from viable pregnancy rate was not available for this study.</p>	<p>birth rate amongst women with recurrent miscarriage due to immunological causes.</p>													
				<p>C20-2- There was a significant increase in BE, AIA, and CTA after treatment in patients with Blocking Antibody Deficiency (BAD) whose pregnancies continued to be viable or who delivered live offspring (P<0.05 ~ P<0.01) compared to before treatment.</p>													<p>X**</p>
<p>03</p>		<p>Change in immunomodulatory activity</p>	<p><u>Change in Blocking Effect (BE), Anti-idiotypic Antibody (AIA), and Cytotoxic Antibody (CTA) levels in patients with Blocking Antibody Deficiency (BAD)</u></p> <p><u>1. Blocking effect (BE):</u> 1) In patients whose pregnancies continued to be viable or who delivered live offspring: Increase from -101.89 ± 180.11 before treatment to -8.13 ± 54.36 after treatment. 2) In patients whose pregnancies were not viable and which resulted in miscarriage: BE increased from -270.90 ± 292.61 to -150.30 ± 67.01</p> <p><u>2. Anti-idiotypic Antibody (AIA):</u> 1) In patients whose pregnancies continued to be viable or who delivered live offspring: Increase from -74.41 ± 104.71 before treatment to 3.84 ± 41.57 after treatment. 2) In patients whose pregnancies were not viable and which resulted in miscarriage: AIA decreased from -42.23 ± 31.69 pre-treatment to -47.83 ± 77.27 post-treatment.</p> <p><u>3. Anti-paternal Cytotoxic Antibody (CTA):</u> 1) In patients whose pregnancies continued to be viable or who delivered live offspring: Increase from 10.29 ± 4.81 before treatment to 19.04 ± 10.83 after treatment.</p>	<p>C20-3- In the group with patients whose pregnancies were not viable and which resulted in miscarriage despite treatment, there was no significant difference in BE, AIA, and CTA levels before and after treatment (P>0.05).</p>												<p>X**</p>	
				<p>C20-4- In the comparison “normal” group who had normal blocking antibody levels (BAN) and whose pregnancies were viable or which resulted in live births, there was no significant difference in antibody levels pre- and post-treatment. (P>0.05).</p>												<p>X**</p>	

				levels.															
30	O3	Change in immunomodulatory activity	<p>Blocking Effect</p> <p>Treatment group:</p> <p>1) Blocking Effect of Blocking Antibody 1 (BE-Ab1): Before treatment: -64.08 ± 38.58 After treatment: -9.17 ± 7.77</p> <p>2) Blocking Effect of Anti-Idiotypic antibody to blocking antibody (BE-Ab2): Before treatment: -34.81 ± 29.86 After treatment: -5.67 ± 8.19</p> <p>3) Blocking Effect (BE) against CD3 (cluster of differentiation 3): Before Treatment: -0.68 ± 2.48 After treatment: -0.03 ± 2.41</p> <p>4) BE against CD4: Before treatment: -0.33 ± 0.53 After treatment: -0.06 ± 1.75</p> <p>5) BE against CD8: Before treatment: -0.35 ± 1.99 After treatment: -0.33 ± 0.43</p> <p>Control group (paternal lymphocyte immunotherapy):</p> <p>1) BE-Ab1: Before treatment: -59.61 ± 43.47 After treatment: -7.06 ± 4.49</p> <p>2) BE-Ab2: Before treatment: -42.13 ± 33.05 After treatment: -3.53 ± 8.90</p> <p>3) BE against CD3: Before treatment: 1.68 ± 0.25 After treatment: 0.55 ± 0.20</p> <p>4) BE against CD4: Before treatment: 1.16 ± 0.42 After treatment: -0.22 ± 1.4</p> <p>5) BE against CD8: Before treatment: 0.61 ± 0.73 After treatment: 0.53 ± 0.88</p>	<p>C30-1- There was a significant increase in both BE-Ab1 and BE-Ab2 ratios in the Treatment and Control group after treatment, thus indicating an increase in maternal blocking antibody efficiency. (P<0.05). There was no significant difference between the immunotherapy control group and the Chinese medicine treatment group results.</p>															

*O1 – Outcome 1
O5 – Outcome 5

O2 – Outcome 2

O3 – Outcome 3

O4 – Outcome 4

** “Other” conclusions:

C20-2, C20-3, C20-4, and C20-5: Increased maternal blocking antibodies, antiidiotypic antibodies, and cytotoxic antibodies are associated with successful pregnancy outcomes, and a deficiency in any of these antibodies are associated with increased risk of miscarriage.

C27-1, C27-2: One type of Chinese medicine treatment (Dan Shen Saline Solution) was more effective than the other Chinese medicine treatment (Shou Tai Wan).

C30-2- Both CH alone and Western medicine alone were not effective.

Appendix J: Outcome 1 – Live Birth Rates

Appendix J: Outcome 1 – Live Birth Rates

Study #	Live Birth Rate: CH Only (%)	Live Birth Rate: CH + Western (%)	Live Birth Rate: Western Only (%)
1	ANA: 62.5% (10/16) ACA IgG: 100% (1/1) ACA IgM: 76.9% (10/13) ANA & ACA positive: 0% (0/5)		
5	ABO group: 89.5% (17/19) Rh group: 66.7% (2/3) APA group: 85.7% (6/7)		
10	13.3% (4/30)	33.3% (10/30)	10% (3/30)
11		82.6% (19/23)	16.7% (3/18) (only administered folic acid, vitamin C, and multi-vitamins throughout treatment)
12	38.3% (18/47)		28.6% (12/42)
13		92.3% (42/45)	75.6% (34/45)
15	41.7% (10/24)	94.3% (33/35)	75% (21/28)
16	100% (9/9)		
18	86% (37/43)		
19	100% (10/10)		
20	88.2% (60/68)		
21	87.5% (49/56)		
26	70% (21/30)		
27		X ₁ group (Dan shen saline solution + HCG, Progesterone): 70% (21/30) X ₂ group (Shou Tai Wan + HCG, Progesterone): 40% (6/15)	
Mean	1188.9/17= 69.9%	329.9/5= 66.0%	205.9/5= 41.2%
Range	0% - 100%	33.3% - 94.3%	10% - 75.6%

**Appendix K: Outcome 2 – Percentage of Patients Experiencing Decrease in Antibody
Titers After Treatment**

Appendix K: Outcome 2 – Percentage of Patients Experiencing Decrease in Antibody Titers After Treatment

Study #	CH Only (%)	CH + Western (%)	Western Only (%)
1	ANA: 63% (17/27) ACA IgG: 100% (7/7) ACA IgM: 94.3% (25/27)		
2	Anticardiolipin antibody: 63% (29/46)		ACA: 31.6% (6/19) (Aspirin only)
3	Anti-Cardiolipin Antibody: 93.2% (41/44) Endometrial Antibody: 90.2% (37/41)		ACA: 81% (34/42) EmAb: 72.5% (Prednisone)
6		Anti-Cardiolipin Antibody 92.8% (26/28)	ACA: 14.3% (2/14) (Vitamin E and Folic Acid)
7	Anticardiolipin antibody: 91.6% (44/48)		ACA: 63.1% (24/38) (Aspirin)
8		Anticardiolipin antibody: 83.3% (25/30)	ACA: 60% (18/30) (HCG, Vitamin E, and Progesterone)
9		Antisperm Ab, Anti-ovarian Ab, Endometrial Ab, Anti-HCG Ab: 77.8% (28/36)	AsAb, Anti-ovarian Ab, EmAb, Anti-HCG Ab: 25% (5/20) (Prednisone, progesterone, HCG)
10	Anticardiolipin: 30% (9/30)	ACA: 73.3% (22/30)	ACA: 30% (9/30) (Aspirin, Prednisone)
11		Anticardiolipin antibody: 86.9% (20/23)	Not reported. (folic acid, vitamin C, multi-vitamins)
12		Antisperm Ab, Endometrial Ab, anticardiolipin Ab: 74.5% (35/47)	AsAb, EmAb, ACA: 52.4% (22/42) (prednisone)
14		Anticardiolipin antibody: 86.7% (26/30)	ACA: 66.7% (20/30) (aspirin, prednisone)
16	Anticardiolipin antibody: 90.9% (10/11)		
18	Anticardiolipin antibody: 55.8% (24/43)		
19	Anticardiolipin antibody: 75% (9/12)		
22	Anticardiolipin antibodies: 86.1% (31/36).		
23	Anticardiolipin antibodies: 97.2% (35/36)		
28	Antisperm antibodies: 85.7% (30/35)		AsAb: 58.8% (20/34) prednisone
Mean	Among all studies: 1116/14 = 79.7% Among ACA studies: 877.1/11 = 79.7% Among Endometrial Ab, Antisperm Ab studies (only 2): 175.9/2 = 88%	Among all studies: 575.3/7 = 82.2% Among ACA studies: 497.5/6 = 82.9% Among Antisperm Ab, Endometrial Ab, Anti-ovarian Ab, Anti-HCG Ab studies: 152.3/2 = 76.2%	Among all studies: 555.4/11 = 50.5% Among studies using Aspirin only: 94.7/2 = 47.4% Among studies using Aspirin + Prednisone: 96.7/2 = 48.4% Among studies using Prednisone only: 264.7/4 = 66.2%
Range	30% - 100%	73% - 93%	14.3% - 81%

Appendix L: Outcome 4 – Number of Weeks of Sustained Pregnancy

Appendix L: Outcome 4 – Number of Weeks of Sustained Pregnancy

Study #	Pregnancy viable at > 15 weeks			Pregnancy viable at > 20 weeks			Pregnancy viable at ≥ 28 weeks			Pregnancy lasted <18 weeks and resulted in miscarriage		
	CH Only	CH + Western	Western Only	CH Only	CH + Western	Western Only	CH Only	CH + Western	Western Only	CH Only	CH + Western	Western Only
8								93.3% (28/30)	73.3% (22/30)			
9		52.8% (19/36)	10% (2/20)									
10				53.3% (16/30)	20% (6/30)	53.3% (16/30)	16.7% (5/30)	40% (12/30)	20% (6/30)	13.3% (4/30)	6.6% (2/30)	16.7% (5/30)
21							98.2% (55/56)					
27	X1 group (Dan Shen Saline solution, HCG, Progesterone: 70% (21/30) had full term live birth, 23.3% (7/30) were 26-31 weeks pregnant at time article was published, 6.6% (2/30) miscarried at <60 days of pregnancy. X2 group (HCG, Progesterone, Shou Tai Wan): 40% (6/15) had full term live birth, 33.3% (5/15) were 20-26 weeks pregnant at time the article was published, 26.7% (4/15) did not last > 60 days of pregnancy.											

Appendix M: Quality Assessment of Research Methodology

Appendix M: Quality Assessment of Research Methodology

Study #	Research design made clear?	Randomized? (Yes/No)	Variables clearly described? (Yes/No)	Control Group? (Yes/No)	Inclusion/Exclusion Criteria clearly stated? (Yes/No)	Description of Tx was sufficient enough in detail that it could be repeated on my own(Replicability)? (Yes/No)	Researcher Derived Quality Measure (1-4) *
1	Yes	No	Yes	No	Yes	No	2
2	Yes	Yes	Yes	Yes	Yes	Yes	4
3	Yes	Yes	No	Yes	Yes	No	3
4	No	No	Yes	Yes	Yes	No	2
5	Yes	No	No	No	No	Yes	2
6	Yes	Yes	Yes	Yes	Yes	Yes	4
7	Yes	Yes	Yes	Yes	Yes	Yes	4
8	Yes	Yes	Yes	Yes	Yes	Yes	4
9	Yes	Yes	Yes	Yes	Yes	Yes	4
10	Yes	Yes	Yes	Yes	Yes	No	3
11	Yes	Yes	Yes	Yes	Yes	Yes	4
12	Yes	No	Yes	Yes	Yes	Yes	3
13	Yes	Yes	Yes	Yes	Yes	No	3
14	Yes	Yes	Yes	Yes	Yes	Yes	4
15	Yes	Yes	Yes	Yes	Yes	Yes	4
16	Yes	No	Yes	No	No	Yes	2
17	No	No	Yes	No	No	No	1
18	Yes	No	Yes	No	Yes	No	2
19	Yes	No	Yes	No	Yes	Yes	3
20	Yes	No	No	No	Yes	Yes	2
21	Yes	No	Yes	No	Yes	Yes	3
22	No	No	No	No	Yes	No	1
23	Yes	No	Yes	No	No	No	2
24	Yes	No	Yes	No	Yes	Yes	3
25	Yes	No	Yes	No	No	Yes	2
26	Yes	No	Yes	No	Yes	No	2
27	Yes	Yes	Yes	Yes	Yes	No	3
28	Yes	Yes	Yes	Yes	Yes	Yes	4
29	Yes	No	Yes	No	Yes	No	2
30	Yes	Yes	Yes	Yes	No	Yes	3

* Researcher derived quality measure:

1=No relevance

2= Somewhat relevant

3= Relevant

4= Highly relevant

*1= no relevance = ≤ 1 “yes” response

2= somewhat relevant = 2-3 “yes” responses

3= Relevant = 4-5

“yes responses

4= Highly Relevant = 6 “yes” responses

Appendix N: Research Design

Appendix N: Research Design

Research Design		Studies of This Design Type (listed by study number)	Total Number of Studies
Experimental	Experimental*	2, 4, 6, 7, 8, 9, 10, 11, 13, 15, 27, 28, 30	13
	Pre-Experimental**	1, 5, 16, 18, 19, 20, 21, 22, 23, 26, 29	11
	Quasi-Experimental***	12	1
Non-Experimental	Case Study/Series	17, 22****, 23****, 24, 25	5

* Experimental: control group present

**Pre-experimental: no control group present

*** Quasi-Experimental: looks like experimental design because there is a comparison group, but there is no random assignment to groups.

****Studies 22 and 23 were pre-experimental studies; however, each article also presented a case study at the end.

Appendix O: Herbs Used in Each Study

Appendix O: Herbs Used in Each Study

Study #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30			
Al Ye					X																												
Bai Bian Dou																			(X)														
Bai Shao	X			X	X	X		X	X						X			X	X		X		X		X					(X)			
Bai Hua She Cao		X					(x)																							(X)			
Bai Ji Tan		X																		(X)										(X)			
Bai Zhu	X				X			X	X	X	X		X							X	X		(X)	X	X	X			X	X			
Ban Xia	X															X				X					X								
Bo He									X																								
Cang Zhu	X															X				X					X								
Chai Hu	X								X							X				X					X		X						
Chen Pi								X																(X)		X					X		
Chi Shao							(x)			X							X						X								X		
Chuan Bei Mu					X																												
Chuan Jiao									X																								
Chuan Xiong					X				X					X										(X)									
Da Huang						X																			(X)								
Da Zao	X																X			X											(X)		
Dan Shen		X				X	x			X	x		X	X	X		X	X				X	X							X1 (injection)			
Dang Shen		X				(x)	x	X	X	X	x									X		X		(X)		X				X			
Dang Gui				X	X	X		X	X	X									X	X										X			
Di Gu Pi										X					X					X						X					X		
Di Yu Tan																															(X)		
Du Zhong		X							X				X			X					X										X		
E Jiao									X											X									X2	X	(X)		
E Zhu		X																															
Fu Ling	X						X			X		X				X					X		X		X					X			
Gan Cao, Sheng	X			X	X				X	X			X	X	X		X				X		X		X								
Gan Cao, Zhi									X										X											(X)	X		
Go Ji										X															X		X				X		
Gou Qi Zi		X	X	X										X							X						X	X					
Gui Zhi	X															X				X				X	X								
He Shou Wu								X																									
Hong Hua							(x)																										
Hou Pu					X																												
Huang Bai						(x)				X																				X			
Huang Qi				X		X		X	X	X			X						X				X		X		X			X	X		
Huang Qin	X			X		(x)		X	X	X						X	X	(X)	X	X					X	X	X						
Ji Xue Teng								X																									
Jing Jie					X																												
Lian Qiao		X																															
Lian Zi Rou																			(X)			X											
Lu Jiao Jiao		X																															
Lu Jiao Pian																																	
Lu Jiao Shuang									X										(X)					X									
Mai Dong																								(X)									
Mu Dan Pi																								(X)									
Mu Xiang						X																											
Nu Zhen Zi		X						X		X				X																	X		
Pu Gong Ying																															(X)		
Qian Shi																								(X)									
Qiang Huo					X																												
Ren Shen	X		X													X				X			(X)	X									
Rou Gong Rong																															X		
Rou Gui																								(X)									
San Qi																								X									
Sang Ji Sheng		X						X	X	X		X			X				X		X												
Sha Ren																																	
Sha Shen										X																							
Shan Yao		X	X				X						X							(X)			(X)	X	X	X	X	X	X	X			
Shan Zhu Yu		X		X			X						X							X													
Sheng Di Huang		X			X											X								(X)	X								
Sheng Jiang	X					X											X				X												
Sheng Ma																										X							X
Shu Di Huang		X					X		X					X										X		X		X	X	X			
Tao Ren		X																															
Tu Si Zi		X		X	X		X	X	X	X			X	X	X				X	X		X	X	X	X	X	X	X	X2		(X)		
Xian Miao		X																															
Xiang Fu										X																							
Xian He Cao																															(X)		
Xiao Hui Xiang																								(X)									
Xu Duan		X	X		X	X		X	X	X			X		X				X		X				X	X	X2		X	(X)			
Yi Mu Cao		X	X	X	X														X		X		X										
Yin Chen Hao						X				X												X											
Yin Yang Huo	X																																
Yu Jin															X					X													
Ze Lan			X										X																				
Ze Xie	X						X									X	X														X		
Zhi Ke					X																												
Zhi Mu							(x)				X																				X	X	
Zhu Ling	X															X					X												
Zhu Ma Gen								X																									
Zi He Che						(x)																											(X)
Zi Su Geng																																	
Herbal Formula	Sairei-to (CXiao Kang Tang				Bao Chan Shen Xiao Fang				Yu Lin Zhu, Xiao Kang #1 Formula, Xiao Kang #2 Formula					Tai Min Lin Sairei-to (Chai Ling Tang)																			