The Effect of Traditional Chinese Medicine on the Prevention and Treatment of Threatened Miscarriage

By

Amy DePry, OMD, LAc, Dipl. OM

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Approval Signature Page

This Capstone Project has been reviewed and approved by:

_____2/18/2015
Harley Ramsey, Ph.D., Capstone Project Advisor   Date

_____2/18/2015
Daoshing Ni, L.Ac., Specialty Chair   Date

_____2/18/2015
Andrea Murchison, D.A.O.M., L.Ac., Program Director   Date

Abstract

This systematic review of literature examined the effectiveness of Traditional Chinese Medicine on the prevention and treatment of threatened miscarriage. Twenty-five articles that fit the inclusion criteria were reviewed and analyzed. Evidence-based research on acupuncture and Chinese herbal medicine demonstrated statistically significant improvements in pregnancy and live birth rates, intercellular communication, immune-system modulation, and IVF outcomes. Data revealed that when Chinese herbal medicine is administered properly, there are minimal adverse effects on pregnant women.

Data was also synthesized and analyzed to determine the most frequently utilized acupuncture point and most frequently researched Chinese herb that resulted in beneficial effects on the treatment and prevention of miscarriage. This synthesis indicated Spleen 6 to be the most commonly used acupuncture point. It is frequently selected as a preventative treatment before and directly after IVF transfers. This point is selected for the included articles because it affects afferent nerve innervation of the uterus. Huang Qin (*Radix Scutellariae*) was the most researched Chinese herb and research demonstrated its vast beneficial effect on immune-system regulation.

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Chapter 1: Introduction

Miscarriage can be a devastating event. It causes physical distress and can lead to long-lasting negative psychological effects including depression, guilt, anxiety, stress, and anger. (Griebel, Halvorsen, Golemon, and Day, 2005). Some losses are inevitable, but for those that are preventable, it is important to gain a deeper understanding of how Traditional Chinese Medicine can help.

Achieving a successful pregnancy is a challenging process from the initial conception to the final day of delivery. In general, fertilization between two healthy partners can only occur 25% of every 28-day cycle and only one third of these conceptions end in a live birth (Regan and Rai, 2000; Larsen, Christiansend, Kolte, and Macklon, 2013). The threat of miscarriage is greatest in early pregnancy. Within the first trimester, 30% to 60% of all conceptions result in fetal loss (Fritz and Speroff, 2011).

Women with threatened miscarriage present with vaginal bleeding while the cervical os still remains closed, and the fetus is deemed viable via appropriate fetal heart beat and crown to rump length. Bleeding may or may not be accompanied by associated abdominal and back pain. Vaginal bleeding is the most common complication of pregnancy and occurs in 20% to 25% of all clinically recognized pregnancies (Carp, 2013; Qureshi, 2009; Cunningham et al., 2005). Women who experience vaginal bleeding in a viable pregnancy have an increased risk of perinatal death, prematurity, and small for gestational age births (Johns and Jauniaux, 2006; Cunningham et al., 2005; Devalseelan, Fogarty, and Regan, 2010). If vaginal bleeding occurs, a comprehensive evaluation of the patient's history, a thorough physical examination, laboratory testing, including quantitative hCG and fetal ultrasound, are needed to determine the likelihood of a threatened versus an inevitable miscarriage. Several variables contribute to threatened and

inevitable miscarriages, such as fetal factors, placental factors, and maternal factors. Chromosomal abnormalities account for 50% to 70% of all miscarriages during the first trimester (Griebel, Halvorsen, Golemon, and Day, 2005; Cunningham et al., 2005; Betts, 2012). As women and men age, the gamete quality declines and there is an increased risk of fetal chromosomal abnormalities and neural tube defects (Regan and Rai, 2000).Miscarriage is inevitable for approximately half of all pregnant women who present with vaginal bleeding and/or lower abdominal pain (Maciocia, 2010; Li et al., 2012). For the other half of women who present with threatened miscarriage, treatment is an option.

Early utilization of fetal and maternal monitoring, preventative measures, and prompt initiation of affective therapeutic interventions in women who present with a threatened miscarriage can result in favorable pregnancy outcomes. There are many Western medical treatment methods for threatened miscarriage. These include progesterone and synthetic progesterones, Human Chorionic Gonadotrophin (hCG), uterine muscle relaxants and nonpharmacological treatments (Murtaza, Ortmann, Mando-Vandrick, and Lee, 2013). Mixed results are found in research-based literature on pharmacologic therapies for the treatment of threatened miscarriage, and very few Western medical treatments have been shown to be effective. There still remains a need for a reliable form of treatment.

Traditional Chinese Medicine (TCM) stimulates the natural self-healing abilities of the body with acupuncture, Chinese Herbal Medicine, Moxibustion, Electro-Acupuncture and other modalities. The treatment of womens reproductive health issues became specifically addressed in TCM during the Song Dynasty from 960 to 1279 CE, and the administration of TCM for reproductive health still continues to be practiced with much success.

In a meta-analysis regarding the effect of acupuncture on fertility, researchers named four potential mechanisms for increased pregnancy rates as a result of acupuncture treatments as shown in research: Acupuncture may mediate the release of neurotransmitters, which stimulates the secretion of gonadotrophin releasing hormones, which would have an effect on the menstrual cycle, ovulation, and fertility (Mayer et al., 1977; Ferin et al., 1984); Acupuncture may inhibit uterine central sympathetic nerve activity and stimulate blood flow to the uterus and increase endometrial receptivity (Stener-Victorin, Waldenstrom, Anderson, and Wikland, 1996); Acupuncture may inhibit the biological stress response and the central nervous system outflow by stimulating the production of endogenous opioids (Cho et al., 1998); Acupuncture may also regulate the function of the hypothalamic-pituitary-ovarian axis via the central sympathetic system (Paulus et al., 2002).

Chinese Herbal Medicine (CHM) has been studied for its pharmacological effects. In reproductive health, CHM has shown to have a wide variety of benefits. The herb Dang Gui (*Radicis Angelicae Sinensis*), for example, can have a vasoactive effect on the smooth muscle of the uterus, can act as an anti-platelet, can increase phagocytic activity, and can have analgesic and anti-inflammatory effects (Chen and Chen, 2001).

Given this information, it is important to understand the evidence-based research on TCM prevention and treatment strategies in women with threatened miscarriage so that treatment options can be offered and effectively utilized during pregnancy. While there have been several studies examining specific therapeutic modalities, no comprehensive systematic review has been performed.

Research Objectives

There are three objectives for this systematic review. They are:

- To examine the effects of acupuncture and Chinese herbal medicine for the prevention and treatment of threatened miscarriage as measured by the number of miscarriages, live birth rates, and other factors applicable to healthy implantation and gestation

- To analyze the most frequently studied acupuncture point and the most frequently studied Chinese Herb for the prevention and treatment of threatened miscarriage

- To provide a foundation for further research into the prevention and treatment of threatened miscarriage with Traditional Chinese Medicine

Glossary of Relevant Terms

The following is a glossary of terms and definitions that provide a common understanding of the topics discussed in this project:

Biochemical pregnancy: (also known as an Early Pregnancy Loss, Chemical Pregnancy) A pregnancy that fails to progress to ultrasound or histological confirmation, in spite of a positive urinary human chorionic gonadotropin (hCG) test or serum B-hCG test (Annan et al., 2013, European Society of Human Reproduction and Embryology, 2005)

Blastocyst: a thin-walled structure in early embryonic development that contains cells (inner cells mass, ICM) that eventually develop into an embryo

Cervical Os: the opening of the cervix that dilates during childbirth to allow the passage of the baby

Clinical miscarriage: a pregnancy loss occurring after ultrasound examination or histological evidence has confirmed an intrauterine pregnancy; may be subdivided into early clinical loss (before 12th week of gestation) and late clinical pregnancy loss (between weeks 12 and 21) (Larsen, Christiansen, Kolte, and Macklon, 2013)

Complete Miscarriage: all of the products of conception have been passed without the need for surgical or medical intervention (Griebel, Halvorsen, Golemon, and Day, 2005)

Decidua: the endometrial lining of a woman that changes during decidualization from the fibroblastic epithelial cells of the uterine stroma when she is pregnant that becomes the maternal aspect of the placenta

Early Miscarriage: a miscarriage that occurs in the first 12 weeks of pregnancy; woman may have pain without vaginal bleeding, heavy vaginal bleeding without pain, or light vaginal spotting of blood for three or more days before pregnancy loss (Betts, 2006)

Incomplete Miscarriage: when some but not all products of conception are discharged following a miscarriage; woman may experience continued vaginal bleeding, associated abdominal pain and possible fever; surgical dilation and curettage is recommended to remove the remaining products (Betts, 2006; Griebel, Halvorsen, Golemon, and Day, 2005)

Inevitable Miscarriage: a miscarriage that is imminent or in the process of happening; the cervix has dilated but the products of conception have not been expelled; there is heavy vaginal bleeding with cramping pain; a cervical cerclage (surgical stitch to close the cervix) may be performed in an attempt to maintain pregnancy (Griebel, Halvorsen, Golemon, and Day, 2005; Betts, 2006)

Late Miscarriage: a miscarriage that occurs between 12 weeks and fetal viability (between 20-24 weeks depending on country, or fetal weight is below 500g); symptoms leading up to may include pink vaginal discharge for several days or scant brownish vaginal discharge for several weeks (Betts, 2006)

Miscarriage: (also known as Spontaneous Miscarriage) Pregnancy involuntarily terminated before 20 weeks of gestation, if the fetal weight is below 500g, or before a live birth is possible; Definitions vary widely according to state laws

Missed Miscarriage: a pregnancy in which there is fetal demise but no uterine activity to expel the products of conception; potentially there are no warning signs of vaginal bleeding or pain; women are usually given 2 weeks to miscarry naturally, afterwards labor may be induced, or a dilation and curettage (D&C) may be performed (Griebel, Halvorsen, Golemon, and Day, 2005; Betts, 2006)

Recurrent Pregnancy Loss (RPL): (also known as Habitual Miscarriage, Recurrent Miscarriage, Recurrent Pregnancy Failure, Recurrent Spontaneous Miscarriage): Three or more spontaneous miscarriages not necessarily consecutive (Fritz and Speroff, 2011); two or more failed clinical pregnancies documented by ultrasound or histopathological examination (American Society for Reproductive Medicine)

Septic Miscarriage: a spontaneous miscarriage that is complicated by an intrauterine infection (Griebel, Halvorsen, Golemon, and Day, 2005)

Stillbirth: a miscarriage that occurs after fetal viability, when it is deemed possible that the fetus could have survived on its own (after 24 weeks of gestation or fetal weight more than 500g) (Betts, 2006)

Syntiotrophoblast: The cytoplasmic layer of the trophoblast that invades the uterine wall and forms the outermost layer of the placenta

Threatened Miscarriage: vaginal bleeding during pregnancy, and/ or lower back pain, and/ or abdominal cramps while the cervical os remains closed and there is evidence of a viable fetus inside the uterine cavity via ultrasound or Doppler device; a pregnancy complicated by bleeding before 20-24 weeks gestation (Cunningham et al., 2005; Griebel, Halvorsen, Golemon, and Day, 2005)

Trophoblast (trophoderm): The peripheral cells of the blastocyst that attach the fertilized ovum to the uterine wall to become the placenta and membranes that nourish and protect the embryo

For fluidity and to avoid confusion, the term "miscarriage" will be used to describe involuntary loss. This is also to avoid the potential distraction of the social stigma of the term "abortion." Although technically interchangeable, the word "abortion" has become stigmatized with voluntary termination.

Traditional Chinese Medicine Diagnoses for Threatened Miscarriage

In order to be in a state of proper health, the body needs to be in a state of balance. Kidney Essence (Jin, Yin, Yang, Qi, and Blood provide the direction, energy and substance of the reproductive system.

Threatened miscarriage can be diagnosed as a weakness in the Ren Channel, which influences the fetus, and in the Chong Channel, which is the Sea of Blood. Weaknesses in these channels are associated with a deficiency of the Kidneys (Yin or Yang). When the Kidneys are deficient, they can't gather blood and nourish the fetus. This then results in a weakness of the Original Qi of the fetus and improper fetal growth or "fetal restlessness." Once conception occurs, the focus shifts from Kidney Yin to Kidney Yang so that the Uterus remains warm.

Kidney Yang deficiency can be considered the most common cause of early stage pre-clinical miscarriage and pre-implantation loss. The connection of the Heart and Kidney is also emphasized during early pregnancy. The Bao Mai connects the Heart and the Uterus, and the health of the Heart Qi affects the opening and closing of the Uterus. Therefore, if the Heart Qi is affected, there may be an untimely opening of the Uterus. Threatened miscarriage may also be caused by: Kidney deficiency, Spleen Qi deficiency and sinking, deficiency of Qi and Blood, Blood Heat or Blood stasis. Pregnant women who are diagnosed as "high risk," or who have had a previous miscarriage have a tendency towards some type of imbalance in one of the aforementioned areas.

The following is a glossary of relevant terms and definitions used in Traditional Chinese Medicine, as defined by G. Maciocia and S. Weizenbaum:

Duo Tai: "Dropping Fetus; Falling Fetus:" a miscarriage that happens in the first three months

Hua Tai "Slippery Fetus:" habitual miscarriage

Tai Dong Bu An: "Fetal Movement Not Peaceful:" vaginal bleeding during pregnancy, accompanied by backache, low back soreness, abdominal pain and a bearing-down feeling

Tai Lou: "Fetal Dripping; Restless Fetus:" Threatened Miscarriage; scanty vaginal bleeding during early pregnancy, which may start and stop; there is no back soreness or abdominal pain

Xiao Chan: "Small Labor" or *Bai Chan* "Half Labor:" miscarriage that happens after three months

Zao Chan: "Early Birth:" a miscarriage later in pregnancy

Chapter Two: Literature Review

This chapter provides a summary of the articles that were utilized for this systematic review of literature. The topics covered will be the effects of Traditional Chinese Medicine (TCM) on the prevention and treatment of threatened miscarriage, and applicable research. Topics include: the effects of TCM treatment on recurrent pregnancy loss; the effects of TCM on Assisted Reproductive Technology (ART) outcomes; the effects of TCM on cell growth and cell-to-cell communication; the effects of TCM on the immune system modulation; the effects of TCM on miscarriage; the frequency and implementation of TCM on the prevention and treatment of threatened miscarriage in Asia; and the adverse effects of using TCM during pregnancy.

TCM and Recurrent Pregnancy Loss (RPL)

A woman's risk of miscarriage can be quantified by examining her past obstetric history, the single most important predictive factor being a previous miscarriage, as is the case with Recurrent Pregnancy Loss (Regan and Rai, 2000). In an article that reviewed the pathology and etiology of Recurrent Pregnancy Loss (RPL) according to Traditional Chinese Medicine, Zhao (2013), stresses the importance of determining the underlying cause. He advises patients with the RPL diagnosis to receive TCM treatment three months prior to conception and continue through the first trimester of pregnancy. Zhao applies Western Medical diagnoses common to RPL to six TCM diagnoses as follows: Deficiency of Kidney Yang and Spleen Qi with disharmony of the Chong and Ren Vessels is a pattern commonly seen in women with Polycystic Ovarian Syndrome or Luteal Phase Defect; Kidney Qi Deficiency with Blood Stagnation is commonly seen in women with autoimmune disorders or anti-phospholipid syndrome; Kidney Yin

deficiency with Liver Qi Stagnation and Blood Heat is seen in women with anti-sperm antibodies, natural killer cells or hyperthyroidism; Spleen Qi with Blood Deficiency is usually seen in women with hypothyroidism, Luteal Phase Defect, or an incompetent cervix; Dampness with Heat Stagnation in the uterus is commonly seen during the second or third trimester when the mother contracts an infection; and Blood Stagnation is seen following a traumatic injury. Zhao also reports on two successful case studies of patients with RPL who were treated with acupuncture and herbal medicine.

Rubin, Cantor, and Marx (2013), reported a case study of a 42-year old woman diagnosed with diminished ovarian reserve and RPL (G6, P2). The authors diagnosed her as Kidney Yin and Yang Deficient, with Liver Qi Stagnation agitating the Shen. She was on a cyclical acupuncture and Chinese herbal therapy treatment that changed according to her menstrual cycle. After three months of weekly TCM treatments, she conceived but later miscarried for the fifth time at 4.5 weeks. She was instructed to wait a minimum of 2 months before trying to conceive again while still receiving TCM treatments. Treatments at this time focused on supplementing the Kidney, resolving Blood Stasis, regulating the Liver and supporting the Shen. Two months after the miscarriage, the patient began a cyclical protocol of Western Medicine in conjunction with TCM, and conceived the following month. The patient was prescribed Shou Tai Wan (*Fetus Longevity Pill*) for the first eight weeks of pregnancy. She continued to receive weekly acupuncture until her fifth month of pregnancy and delivered a healthy baby at 39.5 weeks gestation.

The Effects of Traditional Chinese Medicine in Addition to Assisted Reproductive Technology (ART) on Pregnancy Outcomes

Although the In Vitro Fertilization (IVF) environment of is highly monitored and controlled, insights into the effect of acupuncture on the reduction of miscarriage rates and the increase of live birth rates, as well as other IVF outcomes may provide insight into treating threatened miscarriage in a natural setting.

Electro-acupuncture. Stener-Victorin, Waldenstrom, Anderson and Wikland (1996), performed a prospective non-randomized study on the effects of electro-acupuncture (EA) on blood flow impedance to the uterine arteries with women undergoing in vitro fertilization. The Pulsatility Index (PI) measures the blood flow impedance, and a reduction of impedance to the uterine arteries is important for endometrial activity and receptivity for healthy implantation. The "Stener-Victorin protocol" was used for a total of eight treatments, twice per week for four weeks. Points were chosen according to afferent nerve innervation of the uterus (T12 - L2, S2 - S3). Electro-acupuncture (100 Hz at the thoracolumbar levels (acupuncture points Urinary Bladder 23 and Urinary Bladder 28) and 2Hz on the calf muscles (acupuncture points Spleen 6 and Urinary Bladder 57)) was used to activate group III muscle-nerve afferents and was administered for 30 minutes duration at low and non-painful intensity. The PI was statistically significantly reduced shortly after the eighth treatment (P< 0.0001), as well as 10-14 days after the EA treatments. Skin temperature on the forehead (STFH) and in the lumbosacral area (STLS) were also measured. The STFH increased significantly during the EA treatments (P = 0.002), and the STLS did not change significantly. Researchers attribute these results to a central inhibition of sympathetic activity.

Acupuncture. In a prospective randomized study, Paulus et al. (2002) studied the effect of acupuncture before and after embryo transfer in ART (IVF, n = 101; intra-cytoplasmic sperm

injection, (ICSI): n = 59). One-hundred sixty patients with good embryo quality and a mean age of 32.5 were split into one group of 80 patients who received acupuncture 25 minutes before (acupuncture points: Ren 6, Spleen 8, Liver 3, Du 20, and Stomach 29; Auricular: Shenmen, Uterus, Endocrine and Brain) and after embryo transfer (acupuncture points: Stomach 36, Spleen 6, Spleen 10, and Large Intestine 4; same auricular points), and one group of 80 patients who did not receive acupuncture. Clinical pregnancy (as defined by the presence of a fetal sac during an ultrasound examination 6 weeks after embryo transfer) was measured. Clinical pregnancies were recognized in 34 out of 80 of the acupuncture group, and only 21 out of 80 of the control group. This was a statistically significant increase in clinical pregnancy rates (P = 0.03).

In 2004, Magarelli, Cridennda, and Cohen studied the effects of electro-acupuncture in combination with acupuncture pre- and post- embryo transfer on IVF outcomes. These results were compared with outcomes of IVF patients who did not receive acupuncture. Researchers noted statistically significant improvements in pregnancy rates (P< 0.05), and a significant decrease in the rates of miscarriage (P< 0.05) and Ectopic Pregnancies (P< 0.05).

In 2009, Magarelli, Cridennda, and Cohen took their previous work one step further and measured the effects of acupuncture on IVF outcomes and stress indicators (blood cortisol and prolactin levels). The Stener-Victorin protocol (9 electro-acupuncture treatments before egg retrieval), and the Paulus protocol (1 acupuncture treatment within 24 hours before the transfer, and 1 acupuncture treatment 1 hour after embryo transfer) for a total of 11 treatments were administered to the treatment group and compared with a control group who did not receive acupuncture. Pregnancy rate (biochemical and clinical) and live birth rates were both statistically increased compared to the control (P< 0.05). Miscarriage rates were also statistically decreased compared to the control group (P < 0.05), and the number of ectopic pregnancies were reduced.

There were statistically significant improvements in patients who were treated with acupuncture for miscarriage rates, and number of births per pregnancy. The decrease in clinical pregnancies from biochemical pregnancies was less in the acupuncture group than the control group, which shows a reduced early pregnancy loss rate. The results of the study also showed an increase in Prolactin levels with the acupuncture group before the hCG trigger during the IVF cycle. The levels of cortisol were also increased overall for the acupuncture group, most notably towards the end of the electro-acupuncture treatments until the day before the IVF transfer. Although both cortisol and prolactin are associated with stress, improvements in the IVF outcomes indicate the increases in these hormones have a beneficial influence on IVF results.

In a prospective randomized controlled clinical trial, Manca di Villahermosa et al. (2013), evaluated the effectiveness of acupuncture and moxibustion on clinical pregnancies in women undergoing IVF procedures when 2 prior embryo implantations have failed. There were 84 patients diagnosed with embryo implantation failure who were placed into three even groups of 28: one control group, one sham group and one acupuncture group. The acupuncture group received four treatments: one on day one of the ovulation induction, and one on day seven; one on the day before ovarian puncture and one on the day after embryo transfer. For the acupuncture group, moxibustion was first applied unilaterally to Urinary Bladder 18, Urinary Bladder 22, Urinary Bladder 23, Urinary Bladder 52, Ren 3, Ren 4, Ren 5, Ren 7, and Du 4 for five minutes. The following points were then needled unilaterally: Pericardium 6, Kidney 3, Kidney 6, Kidney 7, Kidney 10, Liver 3, Spleen 4, Spleen 6, Spleen 10, Stomach 40 and Lung 7. Zi Gong Xue was needled bilaterally. All needles were retained for 20 minutes. The sham group was needled in eight areas that did not correspond to known acupuncture point locations and no moxibustion was performed. Results showed the rate of clinical pregnancy was significantly higher in the

acupuncture group than in the control or sham groups (P< 0.03). Results also indicated

endometrial thickness was increased compared to both control and sham groups (P< 0.0002)

Manheimer et al. (2008) performed a systematic review and meta-analysis on the effects

of acupuncture with women undergoing in vitro fertilization. The analysis suggested that

acupuncture given within one day of embryo transfer improved clinical pregnancy rates (as

determined by fetal heart beat confirmed by transvaginal ultrasound or gestational sac), ongoing

pregnancies (beyond 12 weeks with ultrasound confirmation of fetal heart activity), and numbers

of live births. The meta-analysis included seven randomized controlled trials with 1366 women

with good embryo quality. Acupuncture administered within one day of embryo transfer was

compared with sham acupuncture or no adjuvant treatment. All trials used a fixed selection of

acupuncture points for the studies, and the selection of points were similar in all but one trial. All

three measured outcomes of clinical pregnancies, ongoing pregnancies and live births were

reported to have an improvement. The clinical pregnancy rate improvement was statistically

significant (P= 0.04). Investigators confirmed no losses to follow up for all trials but two. Three

trials used sham acupuncture and the mean age across trials was homogenous.

Chinese Herbal Medicine. In a study of 280 women who received IVF and embryo

transfer (IVF-ET) Liu and Wu (2006) measured the effects of Gutai Decoction on the rate of

miscarriage. Gutai decotion consists of Dang Shen, Shu Di Huang, Bai Shao, Shan Yao, Shan

Zhu Yu, Xu Duan, Du Zhong, Tu Si Zi, Gou Qi Zi, Gan Cao, and Sang Ji Sheng. Progesterone

was administered daily beginning two days before the transfer and continued until the 9th week

of pregnancy, and Pogynova was administered as needed. Group A (n=109) began Gutai

Decoction at the second day of transfer, Group B (n=22) began Gutai Decoction beginning the

14th day after transfer, and a control group (n=116) received no Gutai Decoction. Ten patients

from the control group chose to move to one of the treatment groups because they were

diagnosed with threatened miscarriage. Some modifications to the formula were made according

to the patient's condition, and if a patient presented with threatened miscarriage symptomatic

treatment (not specified) was administered. The formula was taken twice a day for 12 weeks

following the transfer. There was a statistically significant decrease in the rate of miscarriages in

the groups that were treated with Gutai decoction in addition to Western Medicine. The rate of

miscarriage rates for Group A was 12.8%, for Group B was 13.64% and for the control group

was 23.28% (P< 0.05). Liver and kidney function tests were performed on 30 of the treatment

subject for adverse effects from Gutai Decoction, and no abnormalities were shown.

The Effects of Traditional Chinese Medicine on Cellular Growth, Cell-to-Cell Communication, and Immune System Modulation

Acupuncture. Huang, Zheng, Wu and Wang (2010), researched the effects of

acupuncture on the pregnancy rate and number of implantation sites in pregnant rats that were

also treated with Mifepristone, a medication used to end early pregnancy. Researchers also

measured the amount of Cx43, which is one of the main components of gap junctions. Gap

junctions assist with cellular communication that allows cell growth, multi-cell organ

coordination and homeostasis. The study used the acupuncture points Stomach 36, "*Zusanli*",

Spleen 6, "*Sanyinjiao*", and Liver 3 "*Taichong*". Rats that were treated with acupuncture still

had a 75% pregnancy rate when compared to rats that only received the Mifepristone (50%). The

number and quality of the implantation sites in the acupuncture group were also improved

compared to the control. Results revealed a correlation between the acupuncture treatments and

increased expression of Cx43.

Chinese Herbal Medicine. In a study that examined the effects of the formula Dang Gui

Shao Yao San (Dang Gui, Chuan Xiong, Bai Shao, Bai Zhu, Fu Ling, and Ze Xie) and Chai Ling

Tang (Chai Hu, Ze Xie, Ban Xia, Fu Ling, Zhu Ling, Bai Zhu, Huang Qin, Ren Shen, Gan Cao,

Gui Zhi, Sheng Jiang, and Da Zao) in the treatment of recurrent abortion and intrauterine growth

restriction, Nagamatsu et al. (2007) studied granulocyte-macrophage colony-stimulating factor

(GM-CSF) in decidual stromal cells (DSCs). GM-CSFs were selected due to their role as

mediators in intercellular communication in embryonic development. Human DSCs were

cultured with different concentrations of Dang Gui Shao Yao San or Chai Ling Tang.

Researchers measured the effects on cell proliferation, the quality of release of GM-CSFs into

the culture medium, and the GM-CSF mRNA expression in DSCs. Results showed Chai Ling

Tang inhibited the proliferation of cultured DSCs at doses 100 times the recommended amount.

Dang Gui Shao Yao San had no effect on cellular proliferation. The release of GM-CSF into the

cultured medium was increased by both formulas ($P < 0.05$). The amount of GM-CSF mRNA

into cultured DSCs was also upregulated by Dang Gui Shao Yao San and Chai Ling Tang (10

micro g/mL $P < 0.05$; 100 micro g/mL $P < 0.01$).

Ma, You, and Wang (2008), performed a study that evaluated the effect of Tu Si Zi

(*Cuscuta chinensis*) on rats with induced abortion. Researchers measured the expression of

FAS/FASL, PCNA, and HB-EGF four to six days after abortion was induced. Fas Ligand (FasL)

is a protein known to induce apoptosis. The expression of FAS on trophoblasts and deciduas was

significantly lower than the control. Proliferating cell nuclear antigen (PCNA) is a protein fold in

DNA that is a catalytic factor in cell replication. The expression of PCNA on trophoblasts and

deciduas was significantly increased compared to the control. Heparin binding EGF-like growth

factor (HB-EGF) is a protein that plays a role in embryonic-maternal communication during

implantation, and is a potent mitogen for certain cells. The expression of HB-EGF was significantly increased on trophoblasts in the treatment group compared to the control group. Pregnancy rates and progesterone levels were also increased in the treatment group. Data was in the form of an abstract from an article in Chinese, and more details of the study are not known.

Liu and Luo (2009) studied the effect of Zhuyun III on 30 women diagnosed with threatened abortion and measured Interleukin-2 (IL-2), Interleukin-10 (IL-10), progesterone, and B-hCG levels. These levels were compared to the control group which was a normal group of pregnant women with no diagnosis of threatened miscarriage. Zhuyun III includes Tu Si Zi (*Semen Cuscutae*), Sang Ji Sheng (*Ramulus Loranthi*), Xu Duan (*Radix Dipsaci*), Huang Qi (*Radix Astragali*), and Dang Shen (*Radix Codonopsis*). The prescription was administered for four weeks. The administration of the pill format was for "three times a day 6g each time combined with a ZYIII decodtion taken twice every day." Results showed the treatment group had a miscarriage prevention percentage of 86.67%. There was a decrease in IL-2 ($P < 0.01$), an increase in IL-10 ($P < 0.05$), an increase in progesterone ($P < 0.01$) and an increase in b-hCG levels ($P < 0.01$) when compared to the control group.

Zhang et. al. (2004), studied an ethanol extraction of Fu Ling (*Poria cocos wolf*). Fu Ling is known for its ability to maintain pregnancy in the treatment of RPL. Rats were treated with an ethanol extract of Fu Ling (25 mg.kg/day or 50 mg/kg/ day) after a cardiac allograft implantation. The percentages of CD3+, CD4+, and CD8+ lymphocytes and the CD4+/CD8+ ratio in peripheral blood and pathological lesions were assessed on the seventh day after the implantation. Researchers noted a decrease in severity of pathological lesions, and decreased percentages of all lymphocytes measured, as well as a decrease in the CD4+/CD8+ ratio when compared to the control group with no treatment. Results also showed a prolonged survival time

in the two groups who were administered Fu Ling compared to the control. The higher dose increased survival time by thirty days. Data was in the form of an abstract from an article in Chinese, and more details of the study are not known.

Zhong et al. (2002) measured the effects of Bai Zhu (*Rhizoma Atractyodis*) and Huang Qin (*Radix Scutellariae)* on natural killer (NK) cells and interleukin-2 (IL-2) when abortion was induced by Lipopolysaccharide (LPS) in mice. NK cell activity is associated with recurrent pregnancy loss. IL-2 is also known to be detrimental to pregnancy. Pregnant rats were administered Huang Qin and Bai Zhu day 5, 6, and 7 of gestation. LPS was administered at day 7 of gestation, and the uterus was examined at day 9. Results demonstrated a reduction in the number of NK cells in the decidua ($P< 0.01$), and decrease in IL-2 contents in the uteri ($P< 0.05$) when Huang Qin and Bai Zhu were administered.

In a similar study Zhong et al. (2008), measured the effect of Huang Qin and Bai Zhu on Interleukin-10 (IL-10) when abortion was induced by LPS in mice. IL-10 is suggested to improve fetal survival and facilitate placenta growth (Wegmann et al., 1993). Pregnant mice were injected with Huang Qin and Bai Zhu on days five, six, and seven of gestation, and injected with LPS on day seven to induce abortion. Uterine contents were dissected on day nine. The levels of IL-10 were significantly increased in the Huang Qin and Bai Zhu groups ($P< 0.01$), and fetal resorption was decreased ($P< 0.01$). There was no significant difference between the treatment and control group in regards to miscarriage rates.

Ma et al. (2009) observed the effects of Huang Qin on Interferon-y (IFN-y), Interleukin-10 (IL-10), and progesterone in abortion induced mice. IFN-y is a cytokine that may lead to pregnancy failure, and IL-10 is an anti-inflammatory cytokine that inhibits pro-inflammatory cytokines. The flavonoid of Huang Qin, Baicalin, was extracted and administered. Group 1, the

control group, was injected with an ethanol mix from day 5 to day 7 of gestation, and water day

1 to day 7 of gestation; Group 2 was injected with Bromocriptine to induce abortion from day 5

to day 7 of gestation; Group 3 was treated with Bromocriptine from day 5 to day 7, and distilled

water which also contained 10mg/kg body weight of Baicalin from day 1 to day 7; Group 4 was

treated identical to Group 3 with 20 mg/kg body weight of Baicalin instead; and Group 5 was

treated identical to Group 3 but with 50 mg/kg body weight of Baicalin instead. Mice were

sacrificed on day 3, 5, 7, 10 and 12 of gestation. Results revealed statistically significant lower

miscarriage rates at Day 10 and 12 of the mice treated with 20mg/kg ($P< 0.05$) and 50mg/kg

Baicalin ($P< 0.05$). Contents of IFN-y were significantly reduced on Day 12 with 20 mg/kg ($P<$

0.05) and 50 mg/kg Baicalin ($P< 0.01$). There was no significant effect on IL-10. Progesterone

was significantly increased after 20 mg/kg on GD 10 and 12 ($P< 0.05$) and 50 mg/kg Baicalin

treatment on gestation day 5, 10 and 12 ($P< 0.05$).

The Effects of Traditional Chinese Medicine on the Prevention and Treatment of Miscarriage

Chinese Herbal Medicine. Zhang, Zhang and Liu (2000), performed a double-blind

study that evaluated the effect of Yunnan Bai Yao granule on threatened miscarriage. Abortion

was induced on 680 pregnant rats. The effects of Yunnan Bai Yao were compared with

Progesterone treatment and Shou Tai Wan (Tu Si Zi, Sang Ji Sheng, Xu Duan, E Jiao). Results

indicated a statistically significant decrease in the miscarriage rates with Yunnan Bai Yao

treatment compared to Progesterone and Shou Tai Wan ($P< 0.05$). Results also indicated a fetus

protective effect on induced threatened abortion on rats. Increased mean weight of the placenta

and mean weight of the baby rats were both shown to be statistically significant (($P < 0.05$), and

uterine contractions were inhibited. Data was in the form of an abstract from an article in

Chinese, and more details of the study are not known.

        In a study on the treatment of threatened abortion with Jiao Ai Si Wu Tang (E Jiao, Ai

Ye, Shu Di Huang, Dang Gui, Chuan Xiong, Bai Shao, Gan Cao, and Huang Jiu) Ushiroyama et

al. (2006) studied 72 women who were diagnosed with threatened miscarriage. One group was

administered 7.5g/day of granular Jiao Ai Si Wu Tang, and the control group received human

chorionic gonadotropin (hCG). Patients in the treatment group were given 2.5g of the granular

formula three times a day for 8 weeks. The control group was administered 5,000 IT of hCG

intramuscularly three times per week. There was no significant difference in the rate of

miscarriage between the two groups. Jiao Ai Si Wu Tang showed statistically significant

improvements over the hCG group in the following areas: decreased time for uterine

homeostasis($P< 0.0001$), a decreased size of the retro-placental hematoma at day 7 ($P< 0.0001$),

and a decreased time for resolution of retro-placental hematoma in the vicinity of the gestational

sac ($P< 0.0001$).

The Prevalence of Chinese Herbal Medicine and the Treatment of Threatened Miscarriage in Asia and Adverse Effects

        A meta-analysis was performed by Li, Leung, Chung, and Wang, (2014), on the use of

Traditional Chinese Medicine during pregnancy in China. Of the facets of Traditional Chinese

Medicine (Chinese Herbal Medicine, Acupuncture, Dietary therapy, Qi Gong, Tui Na, Tai Chi,

Cupping, Die Da, and Gua Sha), CHM was the most common therapeutic approach at 56.2%,

followed by acupuncture at 40.8%. The review included only human studies, and excluded

animal studies, chemical studies, genetic studies, and microbiology studies. Of all of the

literature regarding TCM and pregnancy collected, the most common clinical indication for

CHM was for miscarriage, and the most common type of miscarriage was threatened

miscarriage. The Shou Tai Pill, *Fetus Longevity Pill*, was the most frequently used formula. This

formula enhances the function of the Kidney and regulates the Qi in the human body to benefit

the mother and the fetus. According to the synthesis, the top three most commonly used single

herbs are Bai Zhu *(Atractylodis, Macrocephalae)* to prevent miscarriage, Tu Si Zi *(Chinese*

Dodder Seed) to prevent miscarriage and prelabor*,* and Xu Duan *(Dipsaci Radix)* to stop vaginal

bleeding and prevent miscarriage. The effective rate for the CHM was recorded for each clinical

trial and ranged from 75% to 100%. Of the studies that reported on the adverse effects, most

reported that there were none. In the few studies that reported adverse effects, nausea, dry mouth,

anorexia, and constipation were noted. Adverse pregnancy outcomes were not studied. The

authors note that because of the wide variation of CHM in the literature reviewed, and the

potential of most of the studies to be flawed, the effectiveness of the studies could only represent

the general effects of CHM, not the effects of specific formulas or herbs, nor could meaningful

conclusions be made.

   In a population-based survey, Chuang et al. (2007) reviewed the prevalence of Chinese

herbal medicine taken during pregnancy. Authors used data from 1783 pairs of postpartum

women from 29 towns in Taiwan. An interview questionnaire was given to women six months

after their deliveries. The overall percentage of these women who took Chinese herbal medicine

during their pregnancy was 24.1%, and 19.9% of those women used CHM for threatened

abortion. The most common formula was An Tai Yin (Huang Qi, Tai Zi Shen, Bai Zhu, Dang

Gui, Sheng Di Huang, Bai Shao Yao, Sang Ji Sheng, Du Zhong, Tu Si Zi, Huang Qin, Zhu Ma

Gen) at 13.9%.

Yang, Luo, Liao and Liu (2013) performed a systematic review of 41 randomized clinical trials with a total of 3660 women that summarized the evidence of Chinese herbal medicine for the treatment and prevention of Recurrent Pregnancy Loss (RPL) as well as its safety. Inclusion criteria were females who had at least two miscarriages and were trying to conceive or were pregnant. There were a variety of outcomes measured and variables tested. The trials included patent medicinals, and practitioner-prescribed herbal formulas. The most frequently used decoction was modified Shou Tai Wan at 21.9%. Modified Shou Tai Wan demonstrated a positive effect and safety for recurrent miscarriage in improving the developmental state of the embryo, as well as live birth rates. The most commonly used singe herb was Dang Gui (*Radix Angelicae Sinensis)* and Dan Shen (*Radix et Rhizoma Salviae Miltiorrhizae).* None of the trials reported a negative outcome in terms of live birth rate or status of embryonic development. Eleven trials reported no adverse effects of CHM, and two reported nausea in the CHM group. A high risk of bias for a majority of the trials was reported.

Further results of this meta-analysis were three trials indicated a superior effect of CHM over conventional medicine for healthy embryonic development. Four trials reported a higher live birth rate with CHM when compared to progesterone-based treatment, and one trial found a higher live birth rate with CHM over when compared with hCG-based treatment. Two trials found a higher rate of live births with CHM over other conventional medicine, and three stated uncertain effect. Both live birth rates and embryonic developmental states were measured with CHM and Western Medicine and compared to Western Medicine alone. Results showed that four trials found a higher live birth rate of treatments with CHM in addition to progesterone-based treatment when compared with progesterone based treatment alone, and two showed better embryonic developmental state with the same treatment comparison. One trial found live birth

rates to be higher with hCG and CHM in combination for treatment as opposed to hCG treatment

alone, and four trials favored CHM with hCG-based treatments.

A systematic review was performed to measure the adverse effects of toxicity,

intervention failure, and adverse pregnancy and perinatal outcomes of Chinese medicinals that

are used to treat threatened miscarriage. Li et al. (2012) reviewed and analyzed 32 clinical

studies for their research. These studies were all from China, the earliest date was 1987, and

included RCT studies, a quasi-RCT study, non-randomized controlled trials, and case series.

There were a variety of outcomes measured and variables tested. Over 90% of the identified

studies did not include adverse effects, and due to the heterogeneity and poor designs of studies,

authors note the results may be questionable. Articles that compared Western medicine as a

control or in combination with CHM were included.

Researchers from this study analyzed the rate of intervention failure of CHM and

Western Medicine on the treatment of threatened miscarriage. Results showed Chinese Herbal

Medicine had 3.1% to 18.5% rate of intervention, and Western Medicine showed a 15% to

56.9% rate of intervention failure. When a meta-analysis of RCTs was performed that included

the comparison of treating threatened miscarriage with Western Medicine against treating with

Western Medicine in combination with CHM, results showed a significantly lower incidence of

intervention failure of Western Medicine in combination with CHM. A meta-analysis of the

articles that researched CHM compared to combination of CHM and Western medicine and

compared to Western medicine alone showed no significant difference between any of the

groups.

Adverse pregnancy outcomes including preterm labor, postdate delivery, and diabetic

pregnancy were also analyzed across the data. Meta-analysis was inconclusive due to insufficient

quantity and homogeneity of data. In one RCT study, 1.8% of CHM and 7.4% Western medicine treatments reported neurodevelopment morbidity. No significant differences were found in perinatal outcomes. Data results of all measurements suggest CHM for the treatment of miscarriage may not be associated with an increased risk for neonatal mortality, congenital malformation, or preterm delivery. Dry mouth, constipation and insomnia were reported in 2-8% of women with CHM treatment alone. No adverse effects of CHM were reported in the other studies.

In a study by Li et. al. (2011), the reproductive toxicity of Bai Zhu (*Atractylodes Rhizoma)* was measured in rats, mice, and rabbits. Bai Zhu was administered at different doses and at various gestational periods. No significant adverse outcomes were found in rats. Malformation in rabbits occurred at 3x the normal dose, as well as hydrous fetalis and fetal resorption. In mice there was a significant increase in post-implantation loss with 2 and 3 times the normal dose ($P< 0.001$). Decreases in fetal growth parameters in mice showed to be statistically significant in the gastrulation period at 1x dose ($P< 0.001$), but increased during the Oraganogenesis period at 1x normal dose with early gestational exposure to Bai Zhu ($P< 0.05$). Late gestational exposure resulted in pre- and postnatal mortality at 2 and 3 times normal dose in mice ($P< 0.05$). There were no statistically significant differences in congenital malformations in mice, reproductive toxicity in rats or rabbits.

Acupuncture. In a debate article discussing the potential benefits of using acupuncture for threatened miscarriage, Betts, Smith, and Hannah, (2012), presented the idea of providing supportive care and acupuncture to reduce perceived stress levels during early pregnancy. In early pregnancy, overstimulation of the hypothalamic-pituitary-adrenal axis can be caused by stress, which reduces progesterone. Until the placenta takes over the production of progesterone

at 10-12 weeks, this suggests a risk with lower progesterone levels. Authors reviewed three studies for their article. One was a randomized control trial on the effectiveness of acupuncture for reducing infertility-related stress. Women in the acupuncture group reported significant decrease in social and relationship concern as measured by the Fertility Problem Inventory (FPI). The second article was a qualitative study of eight women on the emotional effects of receiving acupuncture treatments for fertility. They reported a better ability to cope with infertility issues and viewed acupuncture as providing supportive care. Lastly, was a review of Magarelli, Cridennda and Cohen (2009), on the beneficial changes in serum cortisol and prolactin levels as previously reviewed.

Literature Review Integration

Prior research has shown the addition of TCM in a natural environment as well as to an IVF protocol has been beneficial. Results demonstrate a decrease in the numbers of miscarriages, including early pregnancy loss, when compared to non-treatment control groups. In IVF settings, the use of acupuncture, moxibustion, electro-acupuncture, and CHM have shown to improve IVF results, increase blood flow in uterine arteries, and modulate stress hormones for favorable IVF outcomes. Research also suggests TCM can have a beneficial effect on cellular growth, cell-to-cell communication, and immune system modulation. The goals of this research is to synthesize studies that reviewed the effects of TCM on the prevention and treatment of threatened miscarriage, to analyze the most common acupuncture point and herb used in the treatment and prevention of miscarriage with this data, and to provide a foundation for future research on the topic, which has not been done before.

Chapter Three: Methodology

Human Subjects Research Ethical Considerations

This research did not involve gathering of new data, and all data that were used were pre-existing and extracted from archived patient charts, so the current study is exempt from Institutional Review Board (IRB) consideration. The proposal for the current study was still submitted to and reviewed by the Yo San University IRB Director in March of 2013. Subsequent to that submission the researcher received a letter from the IRB Director affirming the exempt status of the study. A copy of the IRB letter is included in Appendix A.

Procedures/ Sampling

The data was collected and analyzed using research synthesis techniques. This includes data sources of peer reviewed articles and textbooks. A systematic review of literature was conducted using twenty-five peer reviewed articles. The peer reviewed articles consisted of research on Traditional Chinese Medicine and threatened miscarriage, or closely related and applicable subject matter. Articles were researched online using the Pub Med, Cochrane Library and Google Scholar databases. Bibliographies of the selected articles were also screened. The search terms used included: Chinese Medicine, Chinese herbs, Traditional Chinese Medicine, acupuncture, herbal medicine, miscarriage/ abortion, threatened miscarriage, spontaneous abortion, miscarriage predictor, miscarriage prevention. The search parameters initially only included studies from the past five years, human studies, and studies that were in English. Search parameters were broadened to collect more data. The final search parameters included dates from 1996 to 2014, animal studies, studies that were in English, and translated abstracts of studies in Chinese. Case studies were not considered initially because quantitative data was preferred for

reliability and homogeneity, but later included for more data. Articles involving herbal medicine not used in Traditional Chinese Medicine were not included.

Secondary analysis and content analysis of data was conducted using articles and published source texts. Applicable data from the peer reviewed articles were entered into three different tables for analysis: one for acupuncture points used in each study; one for Chinese Herbal formulas used in each study; and one for herbs used in each study. The most frequently used herb and acupuncture point in the articles were noted and their physiological and pharmacological effects were studied from source texts.

In the Acupuncture Points Table, the points used in each study were listed on the vertical "y" axis and the study numbers were listed across the horizontal "x" axis. An "X" was marked in the vertical column of the study when a needle was inserted. If further differentiation was used with the acupuncture points, it was noted. Differentiation included: side of administration ("U" indicates unilateral) and method of stimulation ("MB" indicated Moxibustion; "E" indicates electro-acupuncture). Two tables included Chinese Herbs and Chinese Formulas used in each study. The herb or formula used in each study were listed on the vertical "y" axis and the study numbers were listed across the horizontal "x" axis. An "X" was marked in the vertical column of the study when an herb or formula was used. If further differentiation was used with the herbs, it was noted. Each source was labeled for reference. A reference list naming sources by chart number is included in the appendix.

The articles were analyzed and information was input into a table summary of the sources. The table summarized information from each article. Article source, cohort size, whether the article data studied an aspect of treatment or prevention of miscarriage, the independent variable, the dependent variable, results and a grade based on the quality of evidence were all noted. The

level of evidence for each study was assessed using the Strength of Recommendation Taxonomy

(SORT) scale published by Ebell et al. (2004). The quality of each study is rated as level 1, 2, or

3. The definition and explanation of the Strength of Recommendation Taxonomy report is

included on page 63.

This information will be reported on in the form of a Capstone Project and presented for

doctoral course credit as well as used for presentation.

Inclusion Criteria

For the current systematic review of literature, inclusion criteria was:

- Studies and articles that involve the use of acupuncture and Chinese Herbal Medicine on

  the prevention and treatment of threatened miscarriage

- Studies and articles that involve the use of acupuncture and Chinese Herbal Medicine

  concurrently with in vitro in fertilization that measure miscarriage rates, live birth rates, or

  factors affecting conception, implantation and gestational health

- Studies and articles involving the use of acupuncture and Chinese Herbal Medicine in

  threatened miscarriages as a result of Recurrent Pregnancy loss

Exclusion Criteria

For the current study, exclusion criteria was:

- Studies involving ectopic pregnancy

- Studies involving non-Chinese herbal medicine in the prevention and treatment of

  Miscarriage

- Cases involving treatment for emotional issues as a result of recurrent pregnancy loss

Chapter Four: Results

Twenty-five studies met the inclusion criteria for the current research project, including three abstracts of articles translated from Chinese. Articles included five systematic reviews and/ or meta-analyses, two case studies, one debate article, and seventeen clinical studies. Seven of the studies included animals as test subjects, and one included a cell culture. Seven of the clinical studies evaluated the effect of acupuncture on the prevention and treatment of miscarriage, and eleven evaluated the use of CHM. Dependent variables were heterogenous and widespread.

The Effects of Acupuncture and Chinese Herbal Medicine for the Prevention and Treatment of Threatened Miscarriage

Four of the twenty-five studies that met the inclusion criteria measured the effectiveness of Chinese Herbal Medicine on the treatment of Threatened Miscarriage. The meta-analysis showed an increased effective rate with Chinese Herbal Medicine when compared with the control. Zhuyun III indicated a positive outcome on pregnancy rates. Gutai Decoction was compared with hCG treatment and there was no significant difference between the two in regards to pregnancy rates, and Yunnan Bai Yao indicated a statistically significant decrease in miscarriage rates as a treatment for threatened miscarriage when compared to Shoutai Wan and progesterone treatment.

Of the twenty-five studies that met the inclusion criteria, twelve measured the effects of TCM (Acupuncture or CHM) on the rate of pregnancy, rate of miscarriages, and/ or live birth rates on humans or animals. Five out of five of the studies reported an increase in the rate of pregnancy and four were statistically significant. Of the studies that reported on live birth rate, all reported an increase. In regards to the seven articles that reported on the rate of miscarriage,

all were decreased, and five were statistically significant. Both case studies of patients who were diagnosed with Recurrent Pregnancy Loss reported live births following the treatment of TCM.

Other variables were measured across studies of human and animal subjects, and included both acupuncture and CHM treatments. Improvements in cell communication markers increased (three studies), quality of implantation increased (two studies), Interleukin-2 decreased (two studies), Interferon-y decreased (one study), Interleukin-10 increased (one study, and one study showed no significant difference), Natural Killer cells decreased (one study), Progesterone levels increased (three studies), b-hCG increased (one study), the rate of ectopic pregnancies decreased (two studies), the rate of multiple births decreased (one study), number of oocytes for IVF retrieval increased (one study), endometrial thickness increased (one study), there was no significant difference in the number of embryos transferred for IVF procedure (one study), Pulsatility Index of uterine artery blood flow was decreased (one study), there was a shorter time to return to uterine homeostasis (one study), shorter time to resolve a retroplacental hematoma (one study), baby and placenta weight increased (one study), and contractions were inhibited (one study). Details of results from each study are listed in the Article Summary Chart (Appendix C).

Three of the studies reported on the potential adverse effects of CHM. Two of the studies were meta-analyses. One meta-analysis reported no statistical significance in regards to toxicity, failure of intervention, adverse pregnancy outcomes and adverse perinatal outcomes. The other meta-analysis reported no statistical significance of adverse effects. The third study measured the adverse effects of Bai Zhu when administered to mice, rats, and rabbits. Most adverse outcomes (n = 8) resulted from administration of Bai Zhu at two and three times its normal dosage. There were five reports of unfavorable outcomes on mice during different gestational periods with the

recommended dose of Bai Zhu (weight, crown to rump length, head length), most of which were

balanced out by the delivery date and insignificant to birth rates. The majority of the

measurements across animals and dosages resulted in no significant changes.

The Most Frequently Used Acupuncture Point in the Clinical Studies for the Prevention and Treatment of Threatened Miscarriage

The most frequently used acupuncture point in the reviewed articles was Spleen 6, *San*

Yin Jiao located about three inches above the tip of the medial malleolus and posterior to the

border of the tibia. All five of the clinical studies (four human studies and one animal study) that

used acupuncture as their independent variable implemented Spleen 6 along with other

acupuncture points. The human studies were in an In Vitro Fertilization environment, and all

studies used Spleen 6 before implantation occurred. Four of the clinical trials reported reduced

miscarriage rates, improved pregnancy rates and/or improved IVF outcomes. One study used

electro-acupuncture on Spleen 6, and reported an increase in uterine blood flow.

The acupuncture points for the prevention and treatment of miscarriage from the articles

reviewed were recorded in Table 1. The reference guide for articles included in the tables can be

found in Appendix B.

Table 1

Point	A.2	A.3	A.4	A.5	A.6
Du 4					MB
Du 20	X		X		
Kidney 3					X U
Kidney 6					X U
Kidney 7					X U
Kidney 10					X U
Large Intestine 4	X		X		
Liver 3	X		X	X	X U
Lung 7					X U
Pericardium 6	X		X		X U
Spleen 4					X U
Spleen 6	X	X E	X, XE	X	X U
Spleen 8	X		X		
Spleen 10	X		X		X U
Stomach 29	X		X		
Stomach 36	X		X	X	
Stomach 40					X U

Table 1 (Continued)

Point	A.2	A.3	A.4	A.5	A.6
Urinary Bladder 18					MB
Urinary Bladder 22					MB
Urinary Bladder 23		X E	XE		MB
Urinary Bladder 28		X E	XE		
Urinary Bladder 52					MB
Urinary Bladder 57		X E	XE		
Ren 3					MB
Ren 4					MB
Ren 5					MB
Ren 7					MB
Ear Shen Men	X		X		
Ear Uterus	X		X		
Ear Endocrine	X		X		
Ear Brain	X		X		

Key: MB: Moxibustion; **X:** Acupuncture Needle Inserted; **U:** Unilateral Insertion; **XE:** Acupuncture Needle Inserted with Electro-Stimulation

The Most Frequently Studied Single Herb Studied in the Clinical Studies for the Prevention and Treatment of Threatened Miscarriage

The single herbs studied for the prevention and treatment of miscarriage from the articles reviewed were recorded in Table 2. The reference guide for articles included in the tables can be found in Appendix B.

Table 2

Herb	A.1	A.8	A.9	A.10
Bai Zhu, *Rhizoma Atractylodis macrocephalae*		X	X	
Huang Qin, *Scutellariae Radix*		X	X	X
Tu Si Zi, *Cuscutae Semen*	X			

The most commonly studied single herb in the reviewed articles was Huang Qin (*Radix Scutellariae*). Of the four studies that involved Chinese single herbs as the independent variable, Huang Qin was utilized in three. All three articles were clinical studies that measured the effects of Huang Qin on immunological markers in pregnant mice. Huang Qin was administered before, during and after induced abortion in all studies. Results indicated a statistically significant difference in the following immunological variables: decreased in Interleukin-2, a decrease in Natural Killer Cells, an increased amount of Interleukin-10 (one study reported no significant difference), and a decreased amount of Interferon-y. The administration of Huang Qin also resulted in statistically significant differences in the following variables: increased progesterone levels, and a decrease in the miscarriage rates (one study showed no significant difference).

Formulas used in the reviewed articles were also noted in chart format, but no formula was studied for its effects on the treatment and prevention of threatened miscarriage more than once. Data from this research synthesis is illustrated in Table 3.

Table 3

Formula	A.7	A.11	A.12	A.13	A.14
Chai Ling Tang, *Bupleurum and Poria Decoction*				X	
Dang Gui Shao Yao San, *Angelica Peonia Powder* modified				X	
GuTai Decoction			X		
Jiao Ai Si Wu Tang, *Gelatinum Asini Artemesia Four Substances Decoction,* modified	X				
Yun'an Granule, Yunnan Bai Yao					X
Zhuyun III		X			

The Quality of Evidence

Evaluation of the articles for their quality of evidence based on the Strength of Recommendation Taxonomy (Appendix D) resulted in seven articles of "good quality evidence," thirteen articles of "limited quality," and five articles as "other evidence." The quality of evidence for each article is included in the Article Summary Table (Appendix C), and the Strength of Recommendation Taxonomy Guide may be found in Appendix D.

Chapter Five: Discussion

From conception to delivery, pregnancy is a multi-faceted event, and there are many

factors that need to be in place for favorable outcomes. This systematic review has demonstrated

that Traditional Chinese Medicine can be effectively therapeutic for some of these factors.

Research suggests that Acupuncture and Chinese Herbal Medicine improve implantation rates,

improve intercellular communication, modulate the immune system response, improve IVF

outcomes, and improve outcomes for the treatment of threatened miscarriage.

The Effect of Traditional Chinese Medicine on the Treatment and Prevention of Threatened Miscarriage

In the studies reviewed, the implementation of Traditional Chinese Medicine resulted in

an increase in the rates of pregnancy and live birth rates. The five studies that evaluated the

effect of acupuncture in conjunction with the IVF protocol all showed statistically significant

improvements in pregnancy rates, decreased miscarriage rates, and/ or live birth rates when

compared to non-treatment control. Five additional studies that included animals, case studies,

Huang Qin, and Gu Tai Decoction showed significant improvements in pregnancy rates and/ or

decreases in miscarriage rates, and increases in the qualities of implantations.

Implantation. The loss of a pregnancy can be caused by a failure of the blastocyst to

implant. The results from this review have demonstrated that when acupuncture is added to the

IVF protocol, there is a statistically significant improvement in implantation rates, and

statistically significant decreases in miscarriage rates compared to non-treatment controls.

Acupuncture outside of the IVF setting has shown to improve the quality and number of

implantations in rats.

One reason for implantation failure is a disadvantageous uterine lining, which may be due to decreased uterine blood flow. Research indicated the administration of electro-acupuncture can result in reduced blood flow impedance in the uterine arteries. Furthermore, the results of this study lasted up to two weeks after treatment, which also showed the lasting effect of electro-acupuncture treatments. Not only can this be beneficial for proper embryo implantation, but healthy uterine blood flow is very important for placental and fetal growth and development.

Implantation failure may also be due to decreased progesterone levels. Progesterone induces secretory changes in the endometrium, promotes smooth muscle relaxation of the uterus, and helps to support successful uterine implantation. It also modulates the maternal immune response by activating lymphocytes that synthesize Progesterone Induced Blocking Factor (PIBF) to promote a shift away from Th-1 cytokines towards protective Th-2 cytokines, blockade the natural killer cell degranulation, and increase asymmetric non-cytotoxic blocking antibodies. Research suggests that serum progesterone measured in early pregnancy is the most powerful single predictor of pregnancy outcome in natural conceptions (Abdelazim, Belal, and Maklouf, 2013). Extensive prior research has shown no significant difference between women treated with high-dose progesterone for threatened miscarriage and non-treatment control groups (Murtaza, Ortman, Mando-Vandrick, and Lee, 2013). In addition, vaginal administration with vaginal bleeding is unreliable. Also, oral micronized progesterone bioavailability is poor, so high doses are needed. This may result in side effects such as drowsiness and liver toxicity.

This systematic review has indicated that Traditional Chinese Medicine has a favorable effect on progesterone levels. The herbs Tu Si Zi and Huang Qin were both shown to be beneficial towards levels of progesterone levels when abortion was induced in rats. The herbal formula Zhuyun III also showed to increase progesterone levels as a treatment for women who

were diagnosed with threatened miscarriage, and the majority of those women were able to continue on to a healthy pregnancy.

The glycoprotein hCG stimulates the production of progesterone from the corpus luteum during pregnancy in order to maintain the pregnancy and prevent it from regression (Larsen, Christiansen, Kolte, and Macklon, 2013). Subnormal values of hCG are associated with abnormal pregnancies or miscarriage. Research on the treatment of threatened miscarriage with hCG has shown no significant difference than in non-treatment control groups (Devaseelan, Fogarty, and Regan, 2010). The levels of hCG were shown to be statistically significantly increased when Zhuyun III was administered to women who presented with threatened miscarrige.

Intercellular Communication. In order for the complexity of conception, implantation and gestation to be successful, there needs to be proper cell-to-cell communication. Intercellular communication is significant in cell growth, multi-cell organ coordination, and homeostasis. Research indicated acupuncture has a beneficial effect on increased intercellular communication in pregnant rats as revealed by measurement of a main component of gap junctions. Huang, Zheng, Wu and Wang suggest the mechanical stimulation (one method in which cells communicate) of acupuncture points may enhance intercellular communication by activating gap junctions between cells to increase intracellular transfer of molecules.

The administration of Dang Gui Shao Yao San and Chai Ling Tang also resulted in improved cellular communication markers in the feto-placental unit. Dang Gui Shao Yao San and Chai Ling Tang are known empirically for their ability to treat intrauterine growth restriction and treat recurrent pregnancy loss. Tu Si Zi was shown prevent spontaneous abortions, to have a modulatory effect on cell apoptosis and the proliferation of deciduas and cytotrophoblasts.

Recent research suggests women with a higher amount of decidualized endometrial stromal cells have an increased ability to sense and reject unviable embryos (Larsen, Christiansen, Kolte, and Macklon, 2013). Endometrial stromal cells migrate around the embyo approximately the same time as implantation. Women with no history of miscarriages showed the inhibition of endometrial stromal cells in the presence of a low-quality embryo, while women with RPL showed similar migration patterns of endometrial stromal cells with embryos of both low and high quality. Women with RPL may be allowing embryos of poor viability to implant inappropriately, instead of rejecting them. The result would present as a pre-clinical loss. This is another example of potential miscarriages being caused by a failure of the cells to communicate appropriately.

Immune System Regulation. Pregnancy can be viewed as a type of immunological paradox- one body growing and developing inside of another. Many women with autoimmune disorders may find it challenging to have a successful pregnancy. In addition, the natural progression through a pregnancy is a shift from in the Th-1 cytokines towards the protective T-helper (Th-2) dominated cytokine balance. This review has shown Traditional Chinese Medicine is beneficial for modulation of the immune response. Huang Qin, Bai Zhu, and the formula Zhuyun III all decrease the Th1 response and/ or increase the Th2 response.

Zhang et al., 2004 applied the idea of a fetus growing inside of a uterus to an allograft implantation setting, linking the idea of foreign tissue functioning in another. The research of Fu Ling on a cardiac allograft implantation resulted in a decreased number of lymphocytes as well as decrease in the severity of pathological lesions when compared to the control. Fu Ling is known empirically for its ability to maintain pregnancy in the treatment of recurrent pregnancy loss.

Retroplacental Hematoma. The diagnosis of a retroplacental hematoma during the first

trimester is shown to increase the risk of miscarriage. Jiao Ai Si Wu Tang was administered as a

treatment for women who were diagnosed with threatened miscarriage and compared with a

control group treated with hCG. Results indicated a decreased time to return to uterine

homeostasis, and a decreased time for the retroplacental hematoma to resolve in the threatened

miscarriage group treated with Jiao Ai Si Wu Tang.

Secondary Findings

Preventative Treatment. Of the fourteen studies that specifically measured the rates of

miscarriages or number of clinical pregnancies with the use of Traditional Chinese Medicine, ten

of the studies were preventative measures. Traditional Chinese Medicine was administered

before implantation occurred (IVF setting), or before and during induced abortion in rodents. All

of these studies resulted in improved pregnancy rates and decreased miscarriage rates, but it is

important to note that these were all preventative measures as opposed to treatment of the

condition of threatened miscarriage when it presents. Secondary findings indicate a preventative

healthcare approach to pregnancy, before implantation takes place, may help prevent fetal and

embryonic loss.

TCM in Combination with Western Medicine. Most of the articles reviewed that

indicated positive pregnancy outcomes when Traditional Chinese Medicine was administered

were in a highly controlled IVF environment, in which the patients are also on a Western

pharmaceutical regimen. In addition, all three meta-analyses mentioned that Traditional Chinese

Medicine in conjunction with Western biomedicine may potentially be the most effective

therapeutic approach to the treatment of threatened miscarriage, rather than Western Medicine or

Traditional Chinese Medicine alone. In order to responsibly care for women with vaginal

bleeding during pregnancy, proper diagnostics with a thorough examination is essential. This

includes confirmation of fetal viability. Laboratory tests including complete blood count, blood

typing with Rh testing, a pelvic examination to determine whether the cervix is effaced or

dilated, and a transvaginal ultrasound are all important in order to diagnose threatened

miscarriage and to determine the plan of patient care. Testing is crucial to rule out any other

reasons for vaginal bleeding during pregnancy, including cervical lesions or polyps, ectopic

pregnancy, cervical cancer, vaginal or cervical infection, molar pregnancy, subchorionic

hemorrhage, or trauma (Griebel et al., 2005; Quereshi, 2009). Early utilization of fetal and

maternal monitoring, preventative measures, and prompt initiation of affective therapeutic

interventions in women who present with a threatened miscarriage can result in favorable

pregnancy outcomes. In order to implement the most responsible and accountable patient care for

a patient who presents with vaginal bleeding during pregnancy, proper diagnostic testing from

Western medical practitioners is needed. An integrative approach to patient care is essential and

has shown in this review to potentially be the most therapeutic approach, rather than either

paradigm in isolation.

The Most Frequently Used Acupuncture Point in the Prevention and Treatment of Threatened Miscarriage

The acupuncture point Spleen 6, *San Yin Jiao,* was used in all five of the clinical studies

that used acupuncture as their independent variable. Interestingly, this point is contra-indicated in

pregnancy because of its strong influence on the uterus. In each of the studies, Spleen 6 was used

as a preventative treatment, before implantation occurred. Four of the five studies were

conducted in the IVF setting. Spleen 6 was utilized in these studies up to four weeks before the

transfer because it affects afferent nerve innervation of the uterus. It was also used for its

relaxation effect on the uterus the day of the transfer and after the procedure. The results of four of the five studies measured the pregnancy outcomes to be statistically significantly improved. The fifth study measured an improvement of blood flow to the uterus with the administration electro-acupuncture on Spleen 6.

Spleen 6 has many functions. *San Yin Jiao,* "Three Leg Yin" is the meeting point of the Spleen, Liver and Kidney channels which together are known empirically to dominate menstruation, conception, and pregnancy. It is the primary point for treating gynecological, sexual and emotional disorders. In addition to inducing labor, Spleen 6 alleviates the pain of childbirth, calms the spirit, and benefits fertility.

The Most Frequently Studied Chinese Herb in the Prevention and Treatment of Threatened Miscarriage

Huang Qin (*Radix Scutellariae*) was the most frequently studied herb in this research synthesis. The current synthesis demonstrated its vast immuno-regulating effects. Among many other functions, it is an herb that is known empirically for its ability to calm a restless the fetus, specifically in combination with Bai Zhu (*Atractylodis Rhizome*). Pharmacologically, Huang Qin has been researched to have antibiotic properties and anti-inflammatory properties (Chen and Chen, 2001).

Although Huang Qin was the most commonly studied herb in the research synthesized, there is not necessarily a correlation between Huang Qin and the frequency of its use for the treatment and prevention of threatened miscarriage. Data from the meta-analysis that were included in the synthesis noted the most common herb used in China for the treatment of threatened miscarriage was was Bai Zhu. This synthesis is the start of an attempt to gather information on the effects of Chinese Herbal Medicine on threatened miscarriage.

Limitations of the Current Study

There are very few studies available documenting the incidence of miscarriage in a normal, representative population of pregnant women (Regan & Rai, 2000). In a systematic review of literature on Chinese medicine administered during pregnancy, Li, Leung, Chung, and Wang (2014), found that 78.6% of pieces of their literature were in Chinese, and 21.4% were published in other languages. This demonstrates the need for translation and integration of studies that have already been conducted on the topic of threatened miscarriage for a more cohesive understanding of treatment approaches available.

The majority of the research used for this systematic review that measured the effects of acupuncture on miscarriage rates and live birth rates are prospective studies that use acupuncture as an adjunct treatment to IVF. Results from studies that involve the highly controlled and monitored IVF procedures cannot be directly applied to an environment of natural conception, implantation and gestation. This is another limitation of the study. However, the positive effects of acupuncture in an IVF setting on pregnancy outcomes may be seen as a foundation for more research on the effects of acupuncture and pregnancy outcomes in a natural conception.

The limited amount of research available also led to a wide heterogeneity of data. Data was extrapolated from results across multiple variables, and the quality of evidence (as demonstrated in Appendix C) is lower than expected for dependable results. The meta-analysis studies mentioned their results to be unreliable, and crossover between these analyses is possible.

The possibility of a hypothesis bias also cannot be excluded. To account for this the inclusion of adverse outcomes of Chinese herbal medicine on the treatment of pregnant women were also included in this systematic review. The possibility of cultural differences among the

origins of the articles cannot be excluded. Many of the studies were in China where Traditional

Chinese Medicine is primary practice. Clinical trials from China are constructed around the

acceptance that acupuncture is an effective treatment. This may be a hindrance in the availability

of research on potentially adverse outcomes of TCM. In the meta-analysis on adverse outcomes

of CHM and threatened miscarriage, there was a significant lack of data, which authors

acknowledge.

Implications and Recommendations for Future Research

The treatment options for threatened miscarriage provided by the standard of care in the

United States are not statistically effective. There still remains a need for an efficient approach.

Analysis of the research articles presented in this synthesis (Article Summary Table, Appendix

C) shows a trend towards preventative care for improved pregnancy outcomes. The practice of

treating a condition before it manifests into its symptomatology is standard for Traditional

Chinese Medicine. Along with the future research that needs to be conducted for the treatment of

threatened miscarriage, emphasis should also be placed on research into preventative care. On

the topic of treating threatened miscarriage, respected authorities in the field of TCM encourage

women to be treated three months before conception, and to continue treatment throughout the

first trimester. For example, Lyttleton (2013), suggests that a pregnant patient should continue to

record her Basal Body Temperature during the first trimester. This is so the practitioner can

monitor her level of Kidney Yang and to prevent it from becoming deficient and causing

miscarriage. Also, when a pregnant woman presents with a history of a miscarriage or is high

risk in any way, she should be treated as if she is presenting with a threatened miscarriage,

regardless of presence of vaginal bleeding or abdominal cramping. This is because she has a

tendency towards a type of imbalance, and preventative and early treatment will result in the most optimal outcome. The practice of preventative approaches should be implemented as a standard of care. It is more effective to treat threatened miscarriage before the symptamotology shows, than after a women presents with vaginal bleeding.

Results from the review of the articles showed acupuncture treatments have a cumulative and lasting effect (Magarelli, Cridennda, and Cohen, 2009; Stener-Victorin, Waldenstrom, Anderson and Wikland, 1996). This is an important implication for practice, and worthy of future investigation.

More evidence-based research following STRICTA guidelines needs to be done to examine the effectiveness and safety of Traditional Chinese Medicine as a preventative measure and as a treatment for threatened miscarriage. TCM is successfully utilized and practiced in other regions of the world, and results show minimal side effects with proper administration of Chinese herbal medicine and acupuncture on treating pregnant women. This systematic review of literature covered a range of topics applicable to threatened miscarriage. It would be beneficial to study each causal factor and potential treatment in much greater depth.

Pregnant women are a delicate population for the topic of research, and larger preliminary studies on animal subjects and cell cultures need to occur before application to this population. Although there is little to do for miscarriages as a result of chromosomal abnormalities and other issues that lead to an inevitable miscarriage, for those that do have a chance to sustain a healthy pregnancy, more research needs to be done for effective treatment options.

In conclusion, I hope this study will be of value to Traditional Chinese Medical practitioners, Western medical physicians, patients, and students and provide them with

information about the effects of TCM on threatened miscarriage. I hope this systematic review of

literature will elucidate and provide a foundation for future research on effective preventions and

treatments for threatened miscarriage, in area where options are currently insufficient.

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Appendix A: Copy of IRB Approval Letter

YO SAN
UNIVERSITY
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MEDICINE
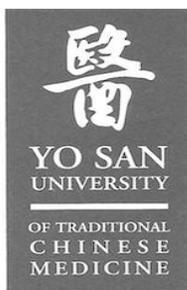
March 28th, 2014

Amy Depry, L.Ac.
2760 Lake Sahara Drive #104
Las Vegas, NV 89117

Dear Amy,

Your revised research proposal has been approved, with no additional recommendations effective through March 31, 2015.

Should there be any significant changes that need to be made which would alter the research procedures that you have explained in your proposal, please consult with the IRB coordinator prior to making those changes.

Sincerely,

Penny Weinraub, L.Ac.
IRB Coordinator

Appendix B: Reference Guide for Articles Included in the Charts

A.1 Ma, H.X., You, Z.L., and Wang, X.Y. (2008) Effect of total flavones from Cuscuta chinensis on expression of Fas/FasL, PCNA and HB-EGF in SD rats model with bromocriptine-induced abortion. Zhong Yao Cai, 31 (11) 1706 - 1709.

A.2 Paulus, W., Zhang, M., Strehler, E., El-Danasouri, I., and Sterzik, K. (2002) Influence of acupuncture on the pregnancy rate in patients who undergo assisted reproduction therapy. Fertility and Sterility, 77 (4) 721-724.

A.3 Stener-Victorin, E., Waldenstrom, U., Anderson, S., and Wikland, M. (1996) Reduction of blood flow impedance in the uterine arteries of infertile women with electro-acupuncture. Human Reproduction, 11 (6), 1314 - 1317.

A.4 Magarelli, P.C., Cridennda, D. K., Cohen, M. (2009) Changes in serum cortisol and prolactin associated with acupuncture during controlled ovarian hyper stimulation in women undergoing in vitro fertilization- embryo transfer treatment. Fertility and Sterility, 92 (6), 1870 - 1879. SV: Stener-Vicroin Protocol; P: Paulus Protocol

A.5 Huang, G. H., Zheng, C. H., Wu, Y. X, and Wang, W. (2010) Involvement of connexin 43 in the acupuncture effect of improving rat blastocyst implantation. Fertility and Sterility, 93 (5), 1715 - 1717.

A.6 Manca di Villahermosa, D., Guercio dos Santos, L., Nogueira, M., Vilarino, F., and Barbosa, C. (2013) Influence of acupuncture on the outcomes of in vitro fertilization when embryo implantation has failed: a prospective randomized controlled clinical trial. British Medical Journal, 31 157-161.

A.7 Ushiroyama, T., Araki, R., Sakuma, K., Nosaka, S., Yamashita, Y., and Kamegai, H. (2006) Efficacy of the Kampo Medicine Xiong-Gui-Jiao-Ai-Tang, a Traditional Herbal Medicine, in the Treatment of Threatened Abortion in Early Pregnancy. The American Journal of Chinese Medicine, 34 (5) 731-740.
        Xiong-Gui-Kiao-Ai-Tang (Jiao Ai Si Wu Tang): Chuan Xiong, Ai Ye, Bai Shao, E Jiao, Gan Cao, Dang Gui, Sheng Di Huang

A.8 Zhong, X.H., Zhou, Z.X., Li, T.S., Wang, E.Q., Shi, W.Y., and Chu, S.M. (2002) Anti-Abortive Effect of Radix Scutellariae and Rhizoma Atractylodis in Mice. The American Journal of Chinese Medicine, 30 (1) 109-117.

A.9 Zhong, X.H., Shi, W.Y., Ma, A. T., Gong, X.C., Zhai, X.H., Zhang, T., and Wang, X.D. (2008) Effects of Radix scutellariae and Rhizoma atractulodis on LPS-Induced Abortion and the Uterine IL-10 Contents in Mice. The American Journal of Chinese Medicine, 36 (1) 141-148.

A.10 Ma, A.T., Zhong, X.H, Liu, Z.M., Shi, W.Y., Du, J., Zhai, X.H., Zhang, T. and Meng, L.G. (2009) Protective Effects of Baicalin against Bromocriptine Induced Abortion in Mice. The American Journal of Chinese Medicine, 37 (1) 85 - 95.

A.11 Liu, F., and Luo, S. (2009) The effect of Chinese herbal treatment on Th1- and Th2Type Cytokines, Progesterone and B-Human Chorionin Gonadotropin in early pregnant women with threatened abortion. Chinese Journal of Integrative Medicine, 15 (5) 353-358.

A.12 Liu, Y., and Wu, J. (2006) Effect of Gutai Decoction on the Abortion Rate of In Vitro Fertilization and Embryo Transfer. Chinese Journal of Integrative Medicine, 12 (3) 189 - 193.
> Gutai Decoction: Dang Shen, Shu Di Huang, Bai Shao, Shan Yao, Shan Zhu Yu, Xu Duan, Du Zhong, Tu Si Zi, Gou Qi Zi, Gan Cao, Sang Ji Sheng

A.13 Nagamatsu, T., Fujii, T., Matsumoto, J., Kanai, T., Hyodo, H., Yamashita, T., Kozuma, S., and Takentani, Y. (2007) Theoretical Basis for Herbal Medicines, Tokishakuyaku-San and Sairei-To, in the Treatment of Recurrent Abortion: Enhancing the Production of Granulocyte-Macrophage Colony-Stimulating Factor in Decidual Stromal Cells. American Journal of Reproductive Immunology, 57, 287-293.
> Tokishakuyaku-San (Dang Gui Shao Yao San): Dang Gui, Chuan Xiong, Bai Shao, Bai Zhu, Fu Ling, Zi Xie
> Chai Ling Tang: Chai Hu, Zhi Ban Xia, Huang Qin, Ren Shen, Gan Cao, Gai Zhu, Zhu Ling, Fu Ling, Ze Xie, Gui Zhi, Da Zao, Sheng Jiang

A.14 Zhang, J., Zhang, Y., and Liu, G. (2000) Clinical and experimental study on yun'an granule in treating threatened abortion. Zhongguo Zhong Xi Yi Jie He Za Zhi, 20 (4) 251-254.
> Yunnan Bai Yao: Specific ingredients remain obscure, but most compositions include the following herbs:
> San Qi, Lao Guan Cao, Bing Pian, She Xiang

Appendix C: Article Summary

Cohort demographics and clinical characteristics – Information regarding the entire cohort in the 25 selected studies listed by alphabetical order of last name of researcher. Quality of evidence of each study according to the SORT (Strength of Recommendation Taxonomy included in Appendix D) criteria published by Ebell et al., 2004.

SOURCE	COHORT SIZE*	PREVENTION TREATMENT	INDEPENDENT VARIABLE	DEPENDENT VARIABLE	RESULTS OF IV GROUP^	QUALITY OF EVIDENCE
Betts, Smith, and Hannah, 2012	N/A	N/A	N/A	N/A	N/A	3
Chuang, Hsieh, Guo, Tsai, Chang, Lin, and Chen, 2007	1783	Treatment	Population based survey of CHM used during pregnancy	1: Most common reason for using CHM	1: Threatened Miscarriage	3
Huang, Zheng, Wu, and Wang, 2010	40 Female Rats	Treatment	Acupuncture	1: mRNA Cx43 2: Protein Cx43 3: Quality of implantations 4: PR 5: Number of implantations	1: Increase vs RNAi (P<.05) 2: Increase vs RNAi (P<.01) 3: Higher vs RNAi 4: NS 5: Increase vs RNAi (P<.05)	2
Li, Dou, Neilson, Leung,	3412	Treatment	CHM	1:Toxicity 2: Failure of	1: N/A 2: NS vs	2

| Li, Tang, Man, Yeung, Lau, Leung, and Wang, 2011 | 100 Mice Dams; 191 Mice Pups; 9 Rat Dams; 108 Rat Litters; 6 Rabbit Dams; 68 Rabbit Litters | Prevention and Treatment | Bai Zhu *(Atractylodes Rhizome)* | 1: Maternal Weight Gain in mice 2: Pregnancy Duration in mice 3: Litter Size in mice 4: Post Implantation Loss Rate in mice 5: Early Fetal Resorption Rates in mice 6: Late Resorption Rates in mice 7: Crown Rump Length in mice 8: Head Length in mice 9: Number of Somites in mice 10: Placental Diameters in mice 11: Neonatal Weight Gains in mice 12: Pre-natal mortality in mice | 1: Increased, Oraganosis (P<.05) 2: Increased in 2x dose, Gestational (P<.05) 3: NS (P>.05) 4: Increased in 2x, 3x dose, Implantation (P<.001) 5: NS 6: Increased 1x dose, Organogenesis (P<.05) 7: Shorter Gastrulation (P<.001); Increased 1x dose Organogenesis (P<.05) 8: Decreased 1x, 2x dose (P<.01); Increased 1x dose Organogenesis (P<.05) 9: Decreased 1x, Gastrulation (P<.001) 10: Increased 1x dose Oranogenesis (P<.001) 11: Decreased, Maturation; Decreased, 3x dose Postnatal day 7 (P<.05); Decreased, 1x 3x dose, Post bata; Day 14 (P<.05); Decreased, 1x 3x dose, Post Natal Dat 7, Gestational (P<.05) 12:Increased 2x, 3x | 2 |

				13: Post-natal Mortality in mice 14: Stillborns in mice 15: Congenital Malformations in mice 16: Reproductive Toxicity in Rats 17: Reproductive Toxicity in Rabbits	Maturation (P<.05) 13: Increased 2x, 3x Maturation (P<.05); Increased 1x 2x Gestation (P<.05) 14: Increase before post-natal day 7 (P<.05) 15: NS 16: NS 17: Reproductive Toxicity in Rabbits: NS	
Li, Leung, Chung, and Wang, 2014	211 Clinical Trials	Treatment	Meta-Analysis of CHM	1: Most common reason for using CHM 2: Most common Formula studied for TM 3: Effective rate of CHM for TM 4: Most common herb used for TM	1: Miscarriage 2: Shou Tai Pill 3: 75% - 100% 4: Bai Zhu (Atractylodes Rhizome)	2
Liu and Wu, 2006	280	Prevention	Gutai Decoction (With Varying Modifications	1: Miscarriage Rate	1: Decreased (P<.05)	2

			)			
Liu and Luo, 2009	50	Treatment	Zhuyun III	1: IL-2 2: IL10 3: Progesterone 4: B-hCG	1: Decreased (P<.01) 2: Increased (P<.05) 3: Increased (P<.01) 4: Increased (P<.01)	1
Ma, You, and Wang, 2008 (ABSTRACT)	Rats (number not mentioned)	Prevention	Tu Si Zi (*Cuscuta Chinensis*)	1: PCNA on trophoblasts and deciduas 2: HB-EGF on trophoblast 3: Progesterone	1: Increased 2: Increased 4: Increased	3
Ma, Zhong, Liu, Shi, Du, Zhai, Zhang, and Meng, 2009	80 Mice	Prevention	Huang Qin (*Radix Scutellariae*) a.10mg/kgBW b.20mg/kgBW c.50mg/kgBW	1: Interferon-y 2: Interleukin-10 3: Progesterone 4: MR	1: Decreased b. (P<.05) c. (P<.01) GD 12 2: NS 3: Increased b. (P<.05) GD 10, GD 12; c. (P<.05) GD 5, GD 10, GD 12 4: Decreased	2

					b.c. (P<.05) GD10, GD 12	
Magarelli, Cridennda, and Cohen, 2009	67	Prevention	Acupuncture and Electro-Acupuncture	1: Serum Cortisol Lvl 2: Serum Prolactin Lvl 3: FSH Levels 4: PR 5: MR 6: Ectopic Pregnancy Rate 7: Births per Pregnancy 8: Multiple Births	1: Increased day 7-13 2: Increased day 5-8 3: NS 4: Increase (P<.05) 5: Decrease (P<.05) 6: NS 7: Increase (P<.05) 8: Decrease (P<.05)	1
Magarelli, Cridennda, and Cohen, 2004	114	Prevention	Acupuncture and Electro-Acupuncture	1: PR 2: MR 3: Ectopic Pregnancies 4: Live Birth Rate	1: Increase (P<.05) 2: Decrease (P<.05) 3: Decrease (P<.008) 4: Increase (P< .05)	1

Manca di Villahermosa, Guercio dos Santos, Nogueira, Vilarino, and Barbosa 2013	84	Prevention	Acupuncture and Moxibustion	1: Biochemical Pregnancy 2: PR 3: Number of Oocytes 4: Endometrial Thickness 5: Number of Embryos Transferred	1: Increase (P=.0327) 2: Increase (P=.0169) 3: Increase (P=.0427) 4: Increase (P=.0002) 5: NS	1
Manheimer, Zhang, Udoff, Haramati, Langenberg, Berman, and Bouter, 2008	1366	Prevention	Acupuncture	1: CP 2: Ongoing Pregnancy 3: Live Birth Rate	1: Increased 2: Increased 3: Increased	2
Nagamatsu, Fujii, Matsumoto, Kanai, Hyodo, Yamashita, Kozuma, and Takentani, 2007	Cultured Decidual Cells from 12 cases of legal abortion of women	Prevention	Dang Gui Shao Yao San Chai Ling Tang	1: Cell Number of Cultured DSCs 2: GM-CSF Production in Cultured DSCs 3: DSCs effect on GM-CSF expression at mRNA level	1: a. NS b. Reduced at > 100x dose 2: a.b. Increased (a. 50 micro g/mL (P<.05); ab 100 micro g/mL (P<.05) ab 200, 400 micro g/mL (P<.01)) 3: a. b. upregulated (ab 10 micro g/mL (P<.05), ab 100 micro	2

					g/mL (P<.01))	
Paulus, Zhang, Strehler, El-Danasouri, and Sterzik, 2002	160	Prevention	Acupuncture	1: CP	1: Increased (P = 0.03)	1
Rubin, Cantor, Marx, 2013 (CASE STUDY)	1	Prevention and Treatment	Acupuncture and CHM	1: Live Birth	1: One miscarriage, One Live Birth, no control group	3
Stener-Victorin, Waldenstrom, Anderson, and Wikland, 1996	10	Prevention	Electro-Acupuncture	1: Pulsatility Index 2: Skin Temp on Forehead 3: Skin Temp on Lumbosacral area	1: Reduced (P<.0001) 2: Increased (P = .002) 3: NS	1

| Ushiroyama, Araki, Sakuma, Nosaka, Yamashita, and Kamegai, 2006 | 72 | Treatment | Jiao Ai Si Wu Tang/ Jiao Ai Tang | 1: Time to reach Uterine Homeostasis 2: Retroplacental hematoma size at Day 7 3: Number of days for retroplacental hematoma to be resolved 4: Rate of miscarriage | 1: Shorter, (P<0.0001) 2: Smaller, (P<0.0001) 3: Shorter, (P<0.0001) 4: No Difference | 1 |

Yang, Luo, Liao, and Liu, 2013	3660	Prevention and Treatment	CHM	1: Live Birth Rate 2:Embryonic Developmental State 3: Adverse Effects	1: Majority Increased 2: Majority Increased 3: Majority NS	2
Zhang, Liu, Xia, Li, Lu, Zang, and Yao, 2004 (ABSTRACT)	80 Rats	Prevention and Treatment	Fu Ling (*Poria*)	1: Survival Time 2: Pathological Lesions 3: Percentages of CD3+, CD4+, and CD 8+ lymphocytes 4: CD4+/CD8+	1: Increased 2: Decreased 3: Decreased 4: Decreased	2
Zhang, Zhang, and Liu, 2000 (ABSTRACT)	1: 580 patients 2: Rats	Treatment	Yunnnan Bai Yao	1: MR on patients 2: Weight of baby rats 3: Weight of rat Placenta 4: Uterine Contractions	1: Decreased (P<.05) 2: Increased (P<.05) 3: Increased (P<.05) 4: Inhibited	3
Zhao, 2013 (CASE STUDY)	2	Prevention and Treatment	Acupuncture and CHM	1: Live Birth	1: 2 Live Births, no control group	3

Zhong, Zhou, Li, Wang, Shi, and Chu, 2002	21 Mice	Prevention	Huang Qin (*Radix Scutellariae*), Bai Zhu (*Rhizoma Atractylodis*)	1: Interleukin-2 2: Natural Killer Cells	1: Decreased (P<.05) 2: Decreased (P<01)	2
Zhong, Shi, Ma, Gong, Zhai, Zhang, and Wang, 2008	26 Mice	Prevention	Huang Qin (*Radix Scutellariae*), Bai Zhu (*Rhizoma Atractylodis*)	1: MR 2: Fetal Resorption 3: Interleukin-10	1: NS 2: Decreased (P< .01) 3: Increased (P< .01)	2

Abbreviations used: **CHM**: Chinese Herbal Medicine; **PR**: Pregnancy Rate (definitions of diagnostics not always specified between Biochemical and Clinical Pregnancy); **FSH**: Follicle Stimulating Hormone; **CP**: Clinical Pregnancy; **MR**: Miscarriage Rate; **NS**: Not Significant (P>0.05); **IV**: Independent Variable; **RNAi**: RNA interference technique + Acupuncture + Mifepristone control group; *****: Human unless stated otherwise; **^**: Compared to Primary Control Group unless stated otherwise; **vs:** in comparison to; **BW:** Body Weight; **GD:** Gestational Day; **PCNA:** Proliferating Cell Nuclear Antigen; **HB-EGF:** Heaparin-binding EGF-like growth factor; **TM:** Threatened Miscarriage; **GM-CSF:** Granulocyte-macrophage colony-stimulating factor; **DSC:** Decidual Stromal Cells

Appendix D: Strength of Recommendation Taxonomy (SORT)

Strength of Recommendation Taxonomy (SORT)

In general, only key recommendations for readers require a grade of the "Strength of Recommendation." Recommendations should be based on the highest quality evidence available. For example, vitamin E was found in some cohort studies (level 2 study quality) to have a benefit for cardiovascular protection, but good-quality randomized trials (level 1) have not confirmed this effect. Therefore, it is preferable to base clinical recommendations in a manuscript on the level 1 studies.

Strength of recommendation Definition

A   Recommendation based on consistent and good-quality patient-oriented evidence.*

B   Recommendation based on inconsistent or limited-quality patient-oriented evidence.*

C   Recommendation based on consensus, usual practice, opinion, disease-oriented evidence,* or
         case series for studies of diagnosis, treatment, prevention, or screening.

Use the following table to determine whether a study measuring patient-oriented outcomes is of good or

Study quality	Diagnosis	Treatment/prevention/screening	Prognosis
Level 1—good-quality patient-oriented evidence	Validated clinical decision rule SR/meta-analysis of high-quality studies High-quality diagnostic cohort study†	SR/meta-analysis of RCTs with consistent findings High-quality individual RCT‡ All-or-none study§	SR/meta-analysis of good-quality cohort studies Prospective cohort study with good follow-up
Level 2—limited-quality patient-oriented evidence	Unvalidated clinical decision rule SR/meta-analysis of lower-quality studies or studies with inconsistent findings Lower-quality diagnostic cohort study or diagnostic case-control study§	SR/meta-analysis of lower-quality clinical trials or of studies with inconsistent findings Lower-quality clinical trial‡ Cohort study Case-control study	SR/meta-analysis of lower-quality cohort studies or with inconsistent results Retrospective cohort study or prospective cohort study with poor follow-up Case-control study Case series
Level 3—other evidence	Consensus guidelines, extrapolations from bench research, usual practice, opinion, disease-oriented evidence (intermediate or physiologic outcomes only), or case series for studies of diagnosis, treatment, prevention, or screening		

limited quality, and whether the results are consistent or inconsistent between studies.

Consistency across studies

Consistent: Most studies found similar or at least coherent conclusions (coherence means that differences are explainable) or if high-quality and up-to-date systematic reviews or meta-analyses exist, they support the recommendation; *Inconsistent:* Considerable variation among study findings and lack of coherence orIf high-quality and up-to-date systematic reviews or meta-analyses exist, they do not find consistent evidence in favor of the recommendation

*—Patient-oriented evidence measures outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life. Disease-oriented evidence measures intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes (e.g., blood pressure, blood chemistry, physiologic function, pathologic findings).
†—High-quality diagnostic cohort study: cohort design, adequate size, adequate spectrum of patients, blinding, and a consistent, well- defined reference standard.

‡—High-quality RCT: allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80 percent).
§—In an all-or-none study, the treatment causes a dramatic change in outcomes, such as antibiotics for meningitis or surgery for appen-dicitis, which precludes study in a controlled trial.

FIGURE 1. The Strength of Recommendation Taxonomy. (SR = systematic review; RCT = randomized controlled trial)

SORT: Level of Evidence for an Individual Study
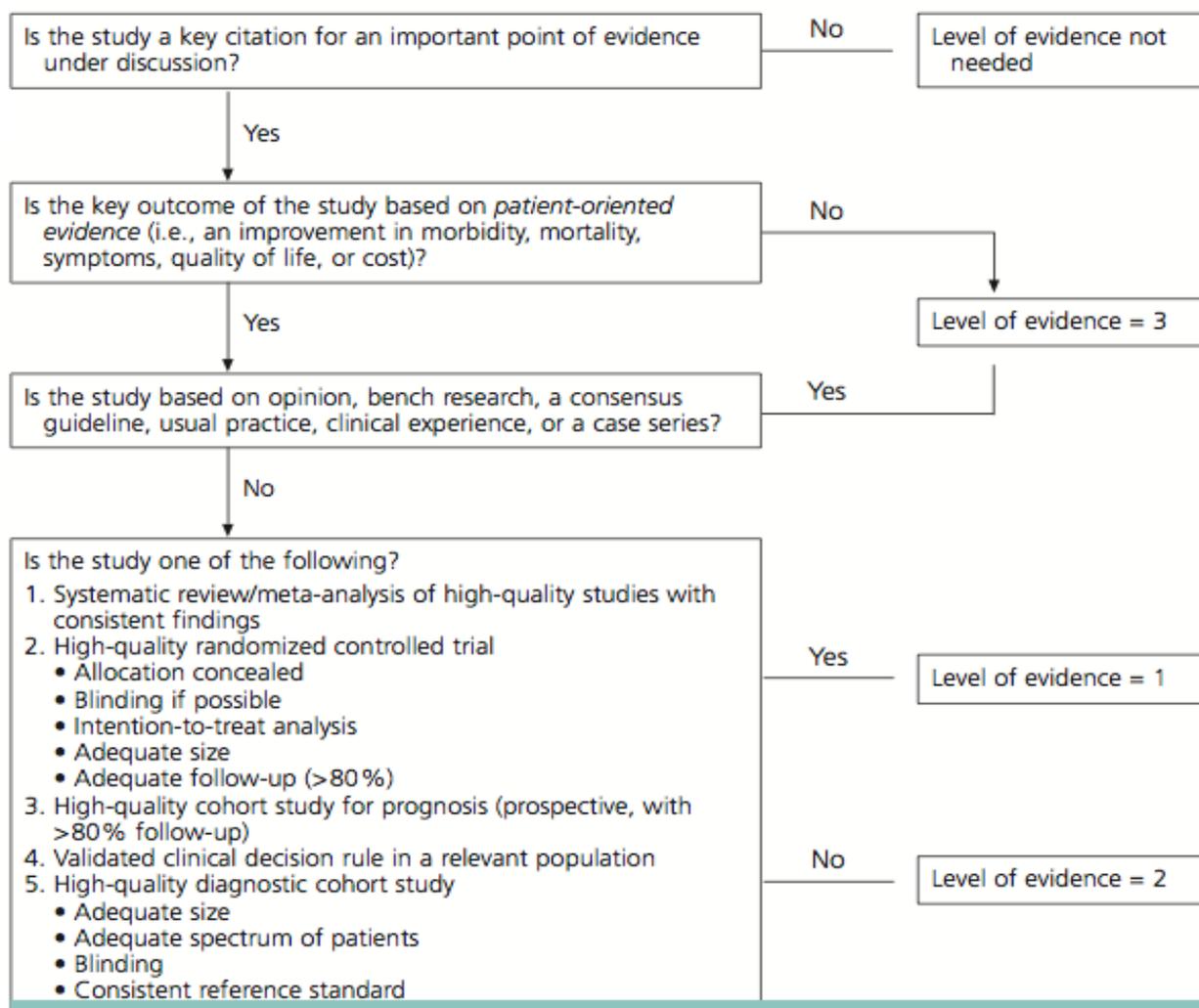
FIGURE 3. Algorithm for determining the level of evidence for an individual study.