

**Effectiveness of Acupuncture and/or Moxibustion for Fertility  
Treatment in Women with Autoimmune Thyroid Dysfunction.  
A Literature Review**

By

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A Capstone Project

Presented in partial fulfillment of the requirements for the  
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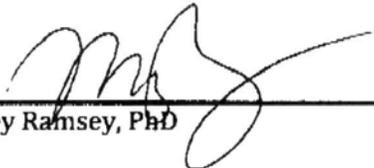
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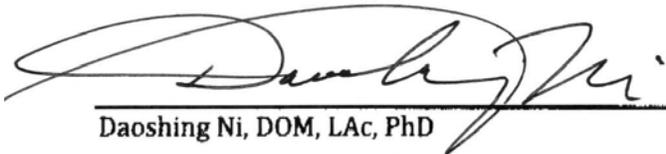
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### **Abstract**

Immune related infertility refers to an inability of conception or to sustain a live-birth due to some aspect of immune dysfunction. Thyroid dysfunction with immunological factors increase the risk of miscarriage, premature labor, or low birth weight as compared to a normal pregnancy in women with normal thyroid function. However there is no specific western treatment for Hashimoto's Thyroiditis besides thyroid medication. The purpose of this research is to maximize the effects of alternative fertility treatments for women who are dealing with autoimmune thyroid dysfunction. After a thorough review, Acupuncture can be used as a treatment of thyroid dysfunction induced infertility, where by anti-inflammatory treatment has shown modulation of Th1 and Th2 balance. Some studies have shown that Moxibustion also has an effect on immunomodulation in normal condition and autoimmune status by elevating CD3+ and CD4+ T-lymphocytes in normal patients and decreasing CD8+ T-lymphocytes. This Literature review may show the possible effectiveness of Acupuncture and/or Moxibustion to reduce possible miscarriage due to Autoimmune Thyroid condition and increase pregnancy rate. However, studies about Acupuncture and/or Moxibustion treatment for autoimmune related female infertility were limited. Therefore, further case studies about Acupuncture and/or Moxibustion for infertility due to Autoimmune Thyroiditis will be helpful to confirm the hypothesis.

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## Chapter 1: Introduction

According to the World Health Organization (WHO) declares infertility as a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse (Brazdova et al., 2014).

Regardless of age, Infertility has been reported to be one of the most universal chronic disorder (Brazdova et al., 2014). Fertility dysfunction is affecting couples worldwide as many as 186 million people (Inhorn & Patrizio, 2015). Female fertility dysfunction has become a major medical issue in Gynecological clinics although male infertility contributing to about half of all cases (Inhorn & Patrizio, 2015). Estimates on the number of couples having fertility issues vary from one in six to one in ten, with 9% currently cited as the probable global average (Cochrane *et al.*, 2016).

In women's menstrual cycle and in achieving fertility affecting the actions of follicle-stimulating hormone and luteinizing hormone is controlled by specific triiodothyronine on oocytes affecting reproduction (Medenica *et al.*, 2015). Also Pregnant women who affected by Subclinical Hypothyroidism or Autoimmune Thyroid antibodies have an increased risk of preeclampsia, perinatal mortality, and miscarriage (Sarkar, 2012). Throughout the last twenty years, Thyroid disease related to pregnancy dysfunction has rapidly increased. Thyroid dysfunction interferes with human reproductive physiology and it reduces the possibility of pregnancy while adversely affecting pregnancy outcomes (Sarkar, 2012).

Autoimmune Thyroid disease is present in about 4% of young females, and up to 15 % of females are Thyroid antibody positive (Sarkar, 2012). In one

prospective cohort study by Liu *et al.* (2014) screened 3315 women and demonstrated that women with Subclinical Hypothyroidism and Thyroid autoimmunity are found to have the highest risk and earlier gestational ages of miscarriage and at an increased risk of miscarriage between four and eight gestational weeks (Liu *et al.*, 2014).

The worldwide annual incidence of Hashimoto's Thyroiditis is estimated to be 0.3-1.5 cases per 1000 persons (Iddah & Macharia, 2013). Also more women than men and older women than younger women tend to have Hashimoto's Thyroiditis (Iddah & Macharia, 2013). Women who have euthyroid function in early pregnancy and who have asymptomatic autoimmune thyroid disorders are at a significant risk of developing hypothyroidism progressively during gestation (Feldthusen *et al.*, 2015). And the presence of Thyroid Peroxidase antibody (TPO Ab) in pregnant women significantly increases the risk of preterm delivery as an immune dysfunction by dysregulating activity of the immune system at the fetal-maternal interface (He *et al.*, 2012).

As a biomedical response to infertility, In Vitro Fertilization (IVF) has become one of Assisted Reproductive Technology (ART) commonly used to support fertility (Cochrane *et al.*, 2016). However, patients with Thyroid Peroxidase Antibody (TPO Ab) or Thyroglobulin Antibody (TGB Ab) have significantly lower fertilization rate, implantation rate, pregnancy rate, and higher risk for miscarriage following In Vitro Fertilization-Embryo Transfer (IVF-ET) when compared with women without TPO Ab or TGB Ab (Zhong *et al.*, 2012). Cho (2015) demonstrated that altered thyroid hormone levels are associated

with disturbed folliculogenesis, a lower fertilization rate, and lower embryo quality (Cho, 2015). Also women who plan to undergo Controlled Ovarian Hyper stimulation should be treated with L-thyroxine if they have positive results for serum anti-thyroid antibodies and TSH levels higher than 2.5 mIU/L (Cho, 2015). Another study shows that Ovarian stimulation used in the preparation of an ART procedure is known to increase the need of thyroid hormones in women with TAI and those with Hypothyroidism for risk reduction in the miscarriage rate and premature delivery (Unuane *et al.*, 2012). These studies show that Fertility is related to Thyroid hormones and Thyroid antibodies.

However, due to the unavailability and unaffordability of IVF in majority of the world, Traditional Chinese Medicine (TCM) including Acupuncture, Moxibustion (Moxa), and Chinese Herbal Medicine (THM) has been used to treat fertility dysfunction (Cochrane *et al.*, 2016). Acupuncture is increasingly used as an adjunct to ART and widely accepted in the complementary and alternative health care system (Cochrane *et al.*, 2016). One study resulted in a significantly higher pregnancy rate when undergoing IVF with acupuncture immediately before and after embryo transfer than without acupuncture (White, 2016). In this capstone study will investigate the connection between Infertility and Autoimmune Thyroid dysfunction.

### **Thyroid and Thyroid Hormones**

Thyroid gland is butterfly-shaped gland which is located at the base of the neck in front of the trachea (Ain & Rosenthal, 2011). Physiologically the thyroid gland produces, stores, and releases the hormones: Triiodothyronine with three iodine atoms (T3),

Thyroxine with four iodine atoms (T4), and reverse T3 derived from T4 and T3 (rT3) (Rothfeld & Romaine, 2003).

T4 is converted to T3 by the removal of an iodine atom, which occurs mainly in the liver and also in the brain tissues where T3 is functional (Rothfeld & Romaine, 2003). Controlling the thyroid gland, the pituitary gland makes thyroid stimulating hormone (TSH), which stimulates the thyroid gland to increase hormonal production, if needed. Also, depending on the amount of T4 it recognizes, the pituitary will increase or decrease the amount of TSH it releases into the bloodstream (Rothfeld & Romaine, 2003). If the pituitary sees very little T4, then it produces more TSH to stimulate thyroid gland to produce more T4 as a negative feedback system (Rothfeld & Romaine, 2003). Then once the T4 level in the blood stream reaches a certain level, the pituitary will stop producing TSH (Rothfeld & Romaine, 2003).

T4 and T3 circulate the body almost entirely bound to specific transport proteins, and there are some situations in which these proteins could change their level in the blood whereby altering T4 and T3 levels which happens frequently during pregnancy or women who take birth control pills (Rothfeld & Romaine, 2003). The thyroid also secretes the hormone calcitonin, which regulates the balance of calcium in the blood stream and in the skeletal system (Rothfeld & Romaine, 2003). Calcium is withdrawn from bones and enters the bloodstream as calcitonin levels go up (Rothfeld & Romaine, 2003). When the calcitonin levels decrease, calcium is then deposited into the skeletal tissue (Rothfeld & Romaine, 2003).

Additionally thyroid hormones help the body regulate homeostasis by regulating energy use, body temperature and sustain brain, heart, muscle, and other organs function. Therefore when the thyroid function properly, the metabolism is well maintained for the female and for the potentially pregnant female. Subsequently, normal thyroid function is required for normal fetal brain and somatic tissue development in newborn (Beers *et al.*, 2006). Also protein, carbohydrate, and fat metabolism in the fetus is regulated by the mother's thyroid function (Beers *et al.*, 2006).

Thyroid promotes growth hormone production, which regulates growth in infants and children. Thyroid also has a role in the healthy aging of adults (Rothfeld & Romaine, 2003). Thyroid is responsible for cell differentiation, reproduction function, intelligence, and brain development (Ryan, 2015). Also protein, carbohydrate, and fat metabolism in the fetus is regulated by the mother's thyroid function (Beers *et al.*, 2006). According to Rao *et al.* (2008), Hypothyroidism is significantly correlated with growth and metabolism of the fetus (Rao *et al.* 2008). Early in pregnancy, the mother supplies the fetus with thyroid hormones (Rao *et al.* 2008). Thus thyroid hormones for the fetus become deficient because the mother has Hypothyroidism (Rao *et al.* 2008). Women with high but in normal range TSH with lack of thyroid hormones during pregnancy can cause fetal brain damage resulting in intellectual impairment, and fertility problems are frequently caused by underactive thyroid (Rothfeld & Romaine, 2003). One study suggests that maternal thyroid underfunction may be associated with an impairment of fetal brain development (Poppe and Glinoe, 2003)

### **Autoimmune thyroid dysfunction**

The annual incidence of Hashimoto's thyroiditis worldwide is estimated in Clinical Endocrinology (1995) to be more than 14 million in the states. In recent years, there has been a significant increase in the rates of patients having autoimmune thyroid disorders according to the American Autoimmune related Diseases Association, Inc. Autoimmune thyroid disease occurs due to autoreactive lymphocytes escaping tolerance as a result of a complex interaction between genetic and environmental factors (Iddah & Macharia, 2013). Cell mediated and humoral responses injures the thyroid tissue (Iddah & Macharia, 2013).

The word autoimmune means self-immune or self-attacking. With an autoimmune disorder, body's immune system makes some mistakes when it tries to distinguish foreign antigens like viruses and bacteria from normal parts of your body. It confuses and recognizes specific healthy body parts as foreign antigens. Then the immune system attacks parts of your own body. The reasons of the autoimmune dysfunction can be genetic, stress-related, environmental including deficiency in vitamins and antioxidants, smoking, and infections. These factors can cause thyroid imbalance by acting on the immune system to trigger specifically Thyroid gland.

Hashimoto's thyroiditis and Graves' disease are the leading causes of thyroid imbalance and both conditions represent reactions of the immune system to the thyroid gland. According to Maciocia (1998), Immunological disorders [dysfunction of the immune system such as lupus, antiphospholipid antibody syndrome (APS or APLS), rheumatoid arthritis, multiple sclerosis, myasthenia gravis, thyroid disease, and diabetes mellitus] have

been known to be associated with decreasing pregnancy rates and increased miscarriage rates (Maciocia, 1998).

Hashimoto's disease is a chronic inflammatory autoimmune thyroid disease in which the immune system attacks and destroys the thyroid gland. Thyroid produces too little hormone causing slow metabolism. Most diagnoses occur between the ages of 30-50 and prevalence increases with age in both women and men. It is the most common of all the thyroid conditions in the US and women are often affected than men are. Hashimoto's disease symptoms often develop gradually. The symptoms may include weight gain, cold sensitivity, tingling in the hands and feet, fatigue, hair loss, dry hair, fertility problems, and difficulty concentrating.

### **Thyroid Dysfunction and fertility dysfunction**

Thyroid dysfunction is the most common endocrine disorder in women of reproductive age causing infertility due to menstrual irregularities and anovulation (Weghofer *et al.*, 2016). Thyroid autoantibodies are found in 5-18 % of female child-bearing age, and the main cause of hypothyroidism during pregnancy is chronic autoimmune thyroiditis (AITD) (Klubo-Gwiedzinska, 2011). In June 2012 at The Endocrine Society's 94<sup>th</sup> Annual Meeting in Houston, Jubbin Jagan Jacob, M.D. presented a study based on a 1000 pregnant women in their first trimester Ludhiana in Punjab, India (Jacob, 2012). The study found that even mild thyroid dysfunction could greatly increase the risk of serious problems (Jacob, 2012). Women with mild thyroid dysfunction had double the risk of miscarriage, premature labor or low birth weight as compared to

pregnant women with normal thyroid function (Jacob, 2012). They also had seven times greater risk of stillbirth (Jacob, 2012). As a result, the study recommended that all pregnant women undergo thyroid screening in the first trimester of pregnancy (Jacob, 2012). Pregnant women with thyroid dysfunction should be monitored for balanced thyroid hormones since low thyroid function can affect the development of the fetus (Jacob, 2012). Women who are having trouble conceiving or who have had repeated miscarriages also have their thyroid levels checked as thyroid hormone levels can affect ovulation and increase the risk of a miscarriage (Jacob, 2012).

Pregnancy is a time of immune suppression so that the condition tends to be improved as pregnancy progresses. During pregnancy, both T-cell and B-cell functions are diminished, and the rebound from this immunosuppression may contribute to the development of postpartum thyroid disease (Iddah & Macharia, 2013). However, women stay at risk of infertility if the thyroid does not function well. In other words, the Thyroid and Infertility may be closely related as imbalances of this organ can challenge a conception. For women who try to get pregnant, Hypothyroidism can prevent ovulation or create irregular cycles, including shortened luteal phase which can prevent implantation of a fertilized egg into the uterine wall.

According to Ni (2008), immunological challenges can be associated with not being able to get pregnant as well as with recurrent miscarriages (Ni, 2008). Graves' disease or Hashimoto's thyroiditis is most likely to manifest during the first trimester of pregnancy, the postpartum (right after childbirth) phase, or the first six months after delivery. Hashimoto's Thyroiditis or chronic lymphocytic thyroiditis is a common cause of

Hypothyroidism. In Hashimoto's Thyroiditis, the immune system attacks the thyroid gland and causes inflammation which results an underactive thyroid. Goiter or enlargement of the thyroid gland can also result in Hypothyroidism. Graves' disease is a common cause of hyperthyroidism, where antibodies produced by the immune system attack the thyroid gland and cause it to overproduce hormones. Hyperthyroidism commonly affects women aged 20 to 40, just when fertility is of peak concern. However, Grave's disease is uncommon during pregnancy even though hyperthyroidism is associated with reduced fertility and increased pregnancy loss. And according to the study by Nazarpour *et al.* in 2015, Hypothyroidism and Hyperthyroidism have impacted on pregnancy and fetus health outcomes (Nazarpour *et al.*, 2015). Another study demonstrated that Anti-TPO positive euthyroid females may have a higher prevalence of infertility, anemia as well as preterm delivery (Meena *et al.*, 2016). The study recommended anti-TPO screening in pregnancy may aid in early identification of the women at risk of miscarriage, or preterm delivery (Meena *et al.*, 2016). In one meta-analyses showed that the thyroid antibodies was associated with an increased risk of unexplained subfertility, miscarriage, recurrent miscarriage, preterm birth, and maternal postpartum thyroiditis compared with the no thyroid antibodies (Van den Boogaard *et al.*, 2011).

### **Autoimmune Thyroid Dysfunction and Traditional Chinese Medicine**

Traditional Chinese Medicine is an ancient health care system including Acupuncture, Chinese Herbs, Moxibustion, Cupping, Qi gong, Tuina, and diet with lifestyle advice which have practiced more than 2000 years. Acupuncture is the

insertion of ultra-thin, sterile needles into specific acupuncture points on the channels or meridians of the body. The channels or meridians of the body are energy pathways in both the exterior and interior of the body. These points can be stimulated by inserting needles to regulate the body function. Moxibustion is an incense therapy which contains mugwort (*Artemisia Argyi*) on specific acupuncture points of the body. It can warm the acupuncture points or stimulate circulation of Blood and Qi.

According to Maciocia (1998), Auto-immune dysfunction in Traditional Chinese Medicine indicates deep energetic etiological factor than normal pathogenic factors (Maciocia, 1998). Even though most of the immune dysfunction is due to the Yin deficiency in Blood or Kidney, the autoimmune dysfunctions vary in causes and roots of the disease which have little in common (Maciocia, 1998). The only common among the immune dysfunction is latent heat etiologically (Maciocia, 1998). Therefore, treatment of autoimmune disorders with Traditional Chinese Medicine is the concepts of clearing Heat, reinforcing Yin, supporting Qi and resolving Blood stasis (Maciocia, 1998).

Hashimoto Thyroiditis as Hypothyroidism which usually manifests with the classic symptoms of Kidney Yang deficiency is often seen mostly in obese female with symptoms like infertility, lethargy, swelling of the ankles, feeling cold and amenorrhea (Maciocia, 1998). Most important time to develop the fetus is at the time of early placental development which needs warm and flourishing Kidney Yang (Maciocia, 1998). Kidney Yang and Wei Qi deficiency is thought to cause the immune disorders in Traditional

Chinese medicine (Maciocia, 1998). Grave's disease as Hyperthyroidism which is related to Blood Heat affecting the Liver and Heart may also be associated with female infertility (Maciocia, 1998). However female infertility in Grave's disease rate is lower than the rate of female infertility in Hashimoto's Thyroiditis and also there are more researches in Hashimoto disease. Therefore Hashimoto's Thyroiditis related female infertility was the main focused issue to research if Acupuncture and/or Moxibustion treatment may be effective for the condition.

### **Definition Key Terms and Glossary of Abbreviations**

**ACTH:** Adrenocorticotrophic hormone. The hormone of the anterior lobe of the hypophysis that governs the nutrition and growth of the adrenal cortex and stimulates it to functional activity. (Stegman, 2005)

**Acupuncture:** Acupuncture is insertion of thin stainless-steel disposable needles into points on the surface of the skin, causing an exchange of electrons within the body, similar to the flow of electricity. (Lewis, 2004)

**APS or aPLS:** Antiphospholipid Antibody Syndrome. A tendency for recurrent thrombosis together with recurrent abortion, thrombocytopenia, and neurologic disease, and elevated blood counts of antibodies against certain negatively charged phospholipids. (Stegman, 2005)

**ART:** Assisted Reproduction Technology. ART is a term used to include a variety of medical procedures used to bring eggs and sperm together without sexual intercourse. (Lyttleton, 2013)

**Autoimmune:** Arising from and directed against the person's own tissues, as in autoimmune disease which includes any disorder in which loss of function or destruction of normal tissue arises from humoral or cellular immune responses of the person to her or his own tissue constituents. (Stegman, 2005)

**B-cells:** Immune cells that make antibodies against antigens in order to remember the antigen. (Kharrazian, 2010)

**Electro-Acupuncture:** Acupuncture in which needles are attached to a source of electric current. (Stegman, 2005)

**Infertility:** Diminished or absent ability to produce offspring. (Stegman, 2005)

**Grave's Thyroiditis:** Graves' disease. Toxic goiter characterized by diffuse hyperplasia of the thyroid gland, a form of hyperthyroidism. An organ specific autoimmune disease of the thyroid gland. (Stegman, 2005)

**Hashimoto's Thyroiditis:** Hashimoto Disease. Chronic autoimmune disease of thyroid resulting from antibodies to thyroglobulin and microsomes, most common cause of hypothyroidism in the U.S. (Stegman, 2005)

**Hyperthyroidism:** An abnormality of the thyroid gland in which secretion of thyroid hormone is usually increased and is no longer under regulatory control of hypothalamic-pituitary centers ; characterized by a hypermetabolic state, usually with weight loss, tremulousness, elevated plasma levels of thyroxin and/or triiodothyronine. (Stegman, 2005)

**Hypothyroidism:** Diminished production of thyroid hormone, leading to clinical manifestations of thyroid insufficiency, including somnolence, slow mentation, dryness and loss of hair, subnormal temperature, hoarseness, muscle weakness, delayed relaxation of tendon reflexes, and sometimes myxedema. (Stegman, 2005)

**Inflammation:** A fundamental, stereotyped complex of cytological and chemical reactions that occur in affected blood vessels and adjacent tissues in response to an injury or abnormal stimulation caused by a physical, chemical, or biologic agent. (Stegman, 2005)

**IVF:** In Vitro Fertilization. IVF involves drugs to stimulate many follicles to ripen – process called controlled ovarian hyper stimulation. (Lyttleton, 2013)

**LE:** Lupus Erythematosus. An illness that may be characterized by skin lesions alone or systemic with antinuclear antibodies present and usually involvement of vital structures. (Stegman, 2005)

**Mifepristone:** Used for first and second trimester medical abortions followed by the prostaglandin analog misoprostol according to the American College of Obstetricians and Gynecologists (ACOG) recommendation (2014) and mifepristone alone results in abortion within two weeks of 54% to 92% of pregnancies (Wikipedia, 2017).

**Moxibustion:** Herbal incense that is burned close to the acupoint. (Lewis, 2004)

**NK cell (Natural Killer Cell):** Immune cells sent to destroy an antigen. (Kharrazian, 2010) Large granular lymphocytes that do not express markers of either T- or B-cell lineage. These cells kill target cells using antibody-dependent cell-mediated cytotoxicity. NK cells can also use perforin to kill cells in the absence of antibody. Killing may occur without previous sensitization. (Stegman, 2005)

**Qi or Chi:** The force of energy existing in all life forms. Qi manifests as five different elements. (Stegman, 2005)

**rT3 (Reverse T3):** A form of thyroid hormone the body cannot use. (Kharrazian, 2010)

**T3 (Triiodothyronine):** A thyroid hormone named for its three molecules of iodine, and the most predominate and active form of thyroid hormone the body can use. (Kharrazian, 2010)

**T4 (Thyroxine):** A thyroid hormone named for its four molecules of iodine. (Kharrazian, 2010)

**TCM:** Traditional Chinese Medicine. An ancient system of healing; based on the concepts of balance, moderation, and harmony, from Taoism. Network of 12 channels carry life energy (Qi) to organs. Symptoms represent disharmony in the balance of the flow of energy. Techniques used to restore harmony include herbal remedies, qi gong, massage, cupping, acupuncture, and acupressure. (Stegman, 2005)

**TGB (Thyroglobulin):** A protein that contains thyroid hormone, usually stored in the colloid within the thyroid follicles; biosynthesis of thyroid hormone entails iodination of the L-tyrosyl moieties of this protein. A defect in thyroglobulin will lead to hypothyroidism. (Stegman, 2005)

**TGB Ab (Thyroglobulin Antibodies):** Immune cells that indicate the immune system in attacking TGB in the thyroid gland. (Kharrazian, 2010)

**Th1:** T-helper cells involved in an innate, or immediate, immune response. (Kharrazian, 2010)

**Th2:** T-helper cells involved in a humoral, or delayed, immune response. (Kharrazian, 2010)

**T-helper cells:** Immune cells that help direct immune activity. (Kharrazian, 2010)

**Thyroid Antibodies:** Antibodies from white blood cells that target the thyroid gland, causing an autoimmune disease. (Ain & Rosenthal, 2010)

**Thyroid binding globulins:** Proteins that transport thyroid hormones through the bloodstream. (Kharrazian, 2010)

**Thyroid Follicles:** Small spheres of hormone-producing cells within the gland. (Kharrazian, 2010)

**Thyroid Gland:** An endocrine gland which secretes thyroid hormone and calcitonin, consisting of irregularly spheroid follicles, lying in front and to the sides of the upper part of the trachea, of horseshoe shape, with two lateral lobes connected by a narrow central portion, the isthmus; occasionally an elongated offshoot, the pyramidal lobe, passes upward from the isthmus in front of the trachea. (Stegman, 2005)

**Thyroiditis:** Inflammation of the thyroid gland. (Stegman, 2005)

**Thyrotoxicosis:** The state produced by excessive quantities of endogenous or exogenous thyroid hormone. (Stegman, 2005)

**TNF $\alpha$  (Tumor necrosis factor alpha):** The primary role of TNF is in the regulation of immune cells. A cell signaling protein (cytokine) involved in systemic inflammation and is one of the cytokines that make up the acute phase reaction. It is produced chiefly by activated macrophages, although it can be produced by many other cell types such as CD4+ lymphocytes, NK cells, neutrophils, mast cells, eosinophils, and neurons (Wikipedia, 2017).

**TPO (Thyroid Peroxidase):** An enzyme in the thyroid responsible for thyroid hormone production. (Kharrazian, 2010)

**TPO Ab (Thyroid Peroxidase Antibody):** Immune cells that indicate the immune system is attacking TPO in the thyroid gland. (Kharrazian, 2010)

**TRH (Thyrotropin Releasing Hormone):** A hormone sent from the hypothalamus to the pituitary gland to stimulate thyroid activity. (Kharrazian, 2010)

**TSH (Thyroid Stimulating Hormone):** A glycoprotein hormone produced by the pituitary gland, anterior lobe of the hypophysis that stimulates the growth and function of the thyroid gland. (Stegman, 2005)

## Chapter 2: Literature Review

In this literature review of Thyroid dysfunction in relation to infertility, a correlation can be seen in autoimmune dysfunctions inhibiting a successful pregnancy or birth rate. Thyroid dysfunction and TPO Ab in female are related to subfertility and early pregnancy loss (Vissenberg *et al.*, 2015). Immune related infertility refers to an inability to conceive or maintain a pregnancy because some aspect of the immune system prevents it. Autoimmune diseases are common in women and pregnancy is a common trigger (Kharrazian, 2006). Hashimoto's Thyroiditis is an autoimmune condition with imbalance of immunity, T helper 1 cells (Th1) and T helper 2 cells (Th2) (Lyttleton, 2013). Correcting this Th1/Th2 balance has been a key strategy in the treatment of various immune disorders (Lyttleton, 2013). And another research shows that the activation of thyroid specific T-cells leads to the recruitment of autoreactive B-cells and the mounting of thyroid stimulatory immune response via anti-thyroid antibodies (Iddah & Macharia, 2013).

T helper cells (CD4+) subdivided into Th1 and Th2. Th1 produces the pro-inflammatory cytokines such as Interferon gamma (IFN- $\gamma$ ) and tumor necrosis factor alpha (TNF- $\alpha$ ) to eliminate invaders that occur inside our cells like virus and intracellular bacteria. Th2 secretes anti-inflammatory cytokines such as interleukin 4 (IL-4), IL-10, and IL-13. Th2 attacks pathogens outside our cells like extracellular bacteria and parasites. Cytokines play a critical role in the early stages for blastocyst implantation and placental development (Gui *et al.*, 2012). Women are Th1 dominant in the first half of pregnancy while women are Th2 dominant during the second half of pregnancy (Kharrazian, 2006).

During pregnancy excessive pro-inflammatory Th1 can lead to uncontrolled tissue damage and pregnancy complication while anti-inflammatory Th2 can reduce the risk of miscarriage.

Another contributing factor to the observed hypothyroidism in Hashimoto's thyroiditis patients could be the circulating TSH inhibitory antibodies (Iddah & Macharia, 2013). Graves' disease on the other hand represents the other end of spectrum wherein the patients suffer from hyperthyroidism (Iddah & Macharia, 2013). Lyttleton (2013) in her book explains some autoimmune diseases which makes antibodies to own cells and some alloimmune diseases which makes antibodies to foreign cells are associated with increased incidence of miscarriage. The presence of various immune factors such as natural killer cells, antiphospholipid antibodies, thyroid antibodies, etc increase the likelihood of an immune reproductive disorder (Lyttleton, 2013). Antiphospholipid antibodies in acquired thrombophilia prevent the placental cells from properly attaching to the uterine lining. These antibodies prevent the formation of the syncytiotrophoblasts which have an important role in the establishment and function of the placenta (Lyttleton, 2013). With each pregnancy loss, there is an increased chance that the mother will develop antibodies to phospholipid molecules (Lyttleton, 2013).

There is no method to reduce thyroid antibodies but thyroid hormone will be given when Autoimmune is diagnosed with elevated TSH (Lyttleton, 2013). Although thyroid function appears to be normal, antibodies to the thyroid gland can be increased. Increased antibodies can cause higher chances of miscarriage (Lyttleton, 2013). Some recent reviews of Acupuncture on the immune system have shown that appropriate and frequent applied

acupuncture treatment can provoke sustained anti-inflammatory activity without stimulation of pro-inflammatory cells (Lyttleton, 2013). It is thought that the immunomodulatory effect of acupuncture may result from the increase in levels of endogenous opioids such as endorphin, met-enkephalin, leu-enkephalin, and serotonin with acupuncture (Lyttleton, 2013). Stress affects the immune system by elevating levels of activated T cells which can reduce implantation rates of embryos and elevating inflammatory processes in the body which might affect the implantation of the embryo (Lyttleton, 2013). Fortunately, acupuncture has been shown to exert a beneficial modulatory effect on such immune imbalances caused by anxiety and stress (Lyttleton, 2013).

According to Quintino *et al.* (2014), the prevalence of infertility was 52.3% in Grave's Disease and 47.0% in Hashimoto's Thyroiditis (Quintino *et al.*, 2014). Feldthusen *et al.* (2015) found that women with higher TSH levels experience less number of children born and the less number of pregnancies (Feldthusen *et al.*, 2015). And also women with higher TPO Ab levels indicates the less number of children born (Feldthusen *et al.*, 2015). In the study, mild Hypothyroidism was associated with higher age of first child born and higher risk of not having children and not getting pregnant (Feldthusen *et al.*, 2015). Thyroid hormones are critical and essential for developing and nourishing fetal and neonatal brain, as well as for many other aspects of fetal growth (Feldthusen *et al.*, 2015). Hence pregnant women with thyroid issue need to be checked and treated more than non-pregnant women because T4 must be sustained for women and the developing fetus (Feldthusen *et al.*, 2015). The thyroid in fetus is fully functional around 12 weeks of

pregnancy (Feldthusen *et al.*, 2015). If the mother does not have sufficient thyroid hormones, she may be at increased risk of miscarriage (Feldthusen *et al.*, 2015).

Ain and Rosenthal (2011) stated that studies indicate a 32 percent risk of miscarriage in women with anti-thyroid antibodies, or subclinical Hashimoto's disease or Graves' disease, compared to a 16 percent risk in women without them (Ain & Rosenthal, 2011). The risk of miscarriage also rises because of age. In general population of healthy pregnant women under thirty-five, one in six pregnancies ends in miscarriage with risk at its highest point during the first trimester (Ain & Rosenthal, 2011). Given these statistics, it's important to be alert to signs of miscarriage with symptoms like bleeding and cramping between second month and third month (Ain & Rosenthal, 2011). It is normal to have slightly enlarged thyroid gland during pregnancy because the placenta makes a human chorionic gonadotropin (HCG) which stimulates the mother's thyroid gland (Ain & Rosenthal, 2011). Pregnant women who have antibodies for autoimmune thyroid disease are at an increased risk for miscarriage, postpartum thyroiditis, Grave's disease, and hypothyroidism (Ain & Rosenthal, 2011). Children born to mothers with Hypothyroidism or high TSH levels are at higher risk of intellectual or motor impairment (Ain & Rosenthal, 2011). This is why any pregnant women need to do the routine thyroid function tests, TSH tests and thyroid antibody tests (Ain & Rosenthal, 2011).

In normal pregnancy, TPO Ab and TGB Ab levels as autoantibodies decline and in the postpartum, TPO Ab and TGB Ab increase as a normal physiologic changes (Balucan *et al.*, 2013). To reduce the risk of miscarriage or any fetus development defect, screening for antibodies in pregnancy will be necessary

(Balucan *et al.*, 2013). Because the detection of thyroid antibodies before or early in pregnancy can predict the development of pregnancy loss, the need for thyroxine replacement therapy during pregnancy, and the onset of postpartum thyroiditis (Balucan *et al.*, 2013).

### **Western Diagnosis by American Thyroid Association**

#### **Blood Test for Thyroid Stimulating Hormone (TSH)**

Measuring TSH level in a blood test is the most sensitive test to assess Thyroid hormone status. Most healthy individuals, a normal TSH value means that the thyroid is functioning normally. A high TSH level can indicate that the thyroid gland is failing to make Thyroid hormone because of a problem that is directly affecting the thyroid which is Hypothyroidism. Occasionally, a low TSH may result from an abnormality in the pituitary gland, which prevents it from making enough TSH to stimulate the thyroid. In the other hands, the low TSH level usually indicates that the person has an overactive thyroid that is producing too much thyroid hormone which is Hyperthyroidism (see Table 1).

#### **Blood Test for T4**

T4 circulates in the blood in two forms as the T4 bound to proteins that prevent the T4 from entering the various tissues that need thyroid hormone and the Free T4 which enters the various target tissues to exert its effects. The Free T4 fraction is the most important to determine how the thyroid is functioning, and tests to measure this are called the Free T4(FT4) and the Free T4 index(FT4I or FTI). Individuals in Hyperthyroidism will

have an elevated FT4 or FTI, whereas individuals in Hypothyroidism will have a low level of FT4 or FTI.

### **Blood Test for T3**

T3 tests is not a marker to evaluate hypothyroid patients since it is the last test to become abnormal. For example, patients can be severely Hypothyroid with a high TSH and low FT4, but have a normal T3. However in some pregnant women or birth control pill taking women, the test will show high level of total T4 and T3 because the estrogens increase the level of the binding proteins. In these cases, it is better to see both of TSH and the FT4 for Thyroid evaluation. Patients with hyperthyroidism will have an elevated T3 level. In some individuals with a low TSH, only T3 is elevated while FT4 is normal.

### **Blood Test for Thyroid Antibody**

The immune system of the body normally attack and destroy foreign invaders like bacteria and viruses with substances lymphocytes to protect itself. In many patients with Hypothyroidism or Hyperthyroidism, lymphocytes make antibodies which stimulate or damage the Thyroid gland. Two common antibodies are Thyroid Peroxidase (TPO) and Thyroglobulin (TGB). They cause Thyroid problems by directed against thyroid cell proteins. Positive anti-thyroid peroxidase and/or anti-thyroglobulin antibodies in a patient with hypothyroidism make a diagnosis of Hashimoto's Thyroiditis which is autoimmune thyroid disease (See Table 2). A test for TPO antibodies (TPO Ab) is most important as Hashimoto's Thyroiditis's most commonly occurs when the immune system

attacks TPO (Kharrazian, 2006). Thyroglobulin Antibodies (TGB Ab) test is necessary, since Hashimoto's Thyroiditis can follow a TGB attack (Kharrazian, 2006). However the test result can show negative antibodies because the immune system fluctuates and the immune system is not attacking the Thyroid gland (Kharrazian, 2006). Positive antibody test confirms an Autoimmune Thyroid condition and indicates that the immune system is the target for therapy (Kharrazian, 2006) (See Table 3).

**Table 1 Thyroid conditions and Appropriate Thyroid blood tests**

Thyroid condition	Free T4	T3 Or Free T3	TSH	Thyroglobulin
Normal thyroid function(euthyroidism) in a person with a normal thyroid gland	Normal	Normal	Normal	Normal
Normal thyroid function(euthyroidism) in a person without a thyroid gland	Normal	Normal	Normal	Very low or none
Early or subclinical hypothyroidism	Normal or low	Not used	Slightly High	Not used
Hypothyroidism	Low	Not used	High	Not used
Mild or subclinical thyrotoxicosis	Normal or high	Normal Or high	Slightly low but greater than 0.2	Not used
Thyrotoxicosis	High	High	Low(less than 0.2)	Not used
Thyrotoxicosis from thyroid pills	High	High	Low	Low
Thyrotoxicosis from hyperthyroidism (Graves' disease or toxic thyroid nodule)	High	High	Low	High

**Table 2. Typical thyroid function test results: Hyperthyroidism and Hypothyroidism**

Cause	Test				
	TSH	T3/T4	TSI	Antithyroid Antibody	Radioactive Iodine uptake test
Graves' Disease	↓	↑	+		↑
Thyroiditis with Hyperthyroidism	↓	↑	-		↓
Hashimoto Disease (Thyroiditis Early Stage)	↑		↓ or Normal	+	
Hashimoto Disease (Thyroiditis Later Stage)	↑		↓	+	
Thyroid Nodule (Hot or toxic)	↓	↑	-		↑ or Normal
Pituitary Abnormality	↓		↓	-	

Key: ↑ = Above Normal ↓ = Below Normal + = Positive - = Negative

**Table 3. Lab tests used to measure Thyroid function by Kharrazian, (2010)**

Laboratory tests	Functional Range/ Laboratory Range	How it's used (Condition)
TSH (Thyroid Stimulating Hormone)	(F) 1.8-3.0 mU/L (L) 0.5-5.5 mU/L	Thyrotropin released by the pituitary gland. Most sensitive measure of thyroid function. TSH increases when T4 drops, and TSH decreases when T4 rises.
TT4 (Total Thyroxine)	(F) 6-12 ug/d (L) 5.4-11.5 ug/d	Bound and unbound T4. Measuring along T3 uptake can be calculated the activity of fT4.
FTI (Free Thyroxine Index)	(F) 1.2-4.9 mg/dl (L) 4.6-10.9 mg/dl	Total T4 and T3 uptake. Measured by multiplying TT4 levels by the T3 uptake and determines how much active T4 is available. Even when drugs impact thyroid binding, the

		FTI should be within normal range if the thyroid is functioning properly.
Free T4 (Free Thyroxine)	(F) 1.0-1.5 ng/dL (L) 0.7-1.53 ng/dL	Measures thyroid hormone available to enter cells (hypothyroidism, thyrotoxicosis) High ft4 also be caused by taking heparin or by an acute illness that causes binding protein levels to suddenly fall
Resin T3 uptake	(F) 28-38 md/dl (L) 24-39 md/dl	The amount of sites for active or unbound T3 to bind with proteins. High testosterone can cause low T4, by reducing the binding sites. High estrogen or birth control pills can cause high total T4 and low T3 uptake by raising the binding sites.
Free T3, ft3 (Free Triiodothyroxine)	(F) 300-450 pg/mL (L) 260-480 pg/mL	The best marker for measuring active thyroid hormones available to thyroid receptor sites. Ordered when a patient has hyperthyroid symptoms and ft4 is normal.
Reverse T3 , rT3	(F) 90-350 pg/mL (L) 90-350 pg/mL	Measures reverse T3 which usually produced when having major trauma, surgery, or severe chronic stress. Increased T3 is due to an inability to clear rT3 from elevated cortisol
Thyroxine-binding globulin(TBG)	(F) 18-27ug/dL (L) 15-30 ug/dl	Measures the amount of proteins in the blood that transport thyroid hormones to the cells. Elevated Testosterone can cause low TBG, elevated estrogen can raise TBG
Thyroglobulin(TGB)	Less than 35 ng/mL	Measures thyroglobulin, a unique protein from thyroid cells
TPO Ab (Thyroid peroxidase antibodies)	0-70 IU/mL	Measures TPO (the enzyme responsible for the production of thyroid hormones) antibodies
TGB Ab (Thyroglobulin antibodies)	0-2.2 IU/mL	Measures TGB (made in thyroid gland and used to produce thyroid hormone) antibodies
TSI or TSH Ab (Thyroid stimulating immunoglobulin, Thyroid stimulating hormone antibodies)	Less than 130% of basal activity	Measures autoimmune antibody to TSH receptor (Graves' disease)

### **Traditional Chinese Medicine Diagnosis**

Traditional Chinese Medicine as a comprehensive alternative medicine, the diagnosis considers general health, pulse and tongue examination, menstrual health including blood color, texture, and flow, duration and frequency, temperature variation and pain for women (Alfred & Ried, 2011). Thyroid imbalance in Traditional Chinese Medicine can be explained by Yin and Yang (Rothfeld & Romaine, 2003). In life, Yin and Yang constantly change into each other like day and night, rising and falling and hot and cold. Yin and Yang change means that each exists within a dynamic relationship to the other (Rothfeld & Romaine, 2003). From this perspective, underactive Thyroid results from an imbalance in which Yin dominates and Yang is deficient because there is less activity and less heat (Rothfeld & Romaine, 2003). Autoimmune related diseases need long term treatment strategies because the diseases need to be directed away from the Yin interior which is the blood, fluids or Yin viscera towards the Yang which is exterior (Arsovska *et al.*, 2016).

In Western Medicine, Autoimmune Thyroid Disease has been associated with Neoplasm and Kidney disorders (Iddah & Macharia, 2013). Patients with Kidney diseases have Endocrine abnormality (Iddah & Macharia, 2013). Thyroid dysfunction causes remarkable changes in glomerular and tubular functions, and in electrolyte and water homeostasis (Iddah & Macharia, 2013). From a clinical practice viewpoint, it should be mentioned that both Hypothyroidism and Hyperthyroidism are accompanied by remarkable alterations in the metabolism of

water and electrolyte, as well as in cardiovascular function (Iddah & Macharia, 2013).

Hypothyroidism slows down the heart, causing a slow pulse, decreased exercise tolerance, and shortness of breath (Ain & Rosenthal, 2011). Prolonged Hypothyroidism will also lead to Lymphedema causing swelling hands and feet seen with congestive heart failure and Hypertension due to lack of thyroid hormone to relax the arteries (Ain & Rosenthal, 2011). This symptoms will lead to misdiagnosis with heart failure but people with heart failure have faster pulse (Ain & Rosenthal, 2011). Hypothyroidism also increase cholesterol levels, which can increase the development of blockages in arteries (Atherosclerosis) leading to a heart attack or stroke as well as congestive heart failure (Ain & Rosenthal, 2011).

To compare with those studies, Hypothyroidism in Traditional Chinese Medicine is also related to Kidney, Heart, and Spleen (Arsovska *et al.*, 2016). It can be categorized by Spleen and Kidney Qi deficiency, Heart and Kidney Yang deficiency, and Kidney Jing deficiency (Arsovska *et al.*, 2016) (See Table 4).

**Table 4. TCM diagnosis for Hypothyroidism**

TCM diagnosis	Indication/Symptoms	TCM treatment principle
Spleen and Kidney Qi deficiency	Subclinical Hypothyroidism, Early stages of an underactive Thyroid, Subacute Hypothyroidism, Hashimoto's Thyroiditis, Elevated TSH, Normal to low T4 and T3. Fatigue, tiredness, depression, mild sensitivity to cold, poor	Tongue: pale and scalloped. Pulse: weak, thready, and deep. Treatment: Strengthen and supplement Spleen and Kidney Qi and resolve the phlegm.

	appetite, constipation, weight gain, weak bladder, irregular cycles	
Heart and Kidney Yang deficiency	Well developed and clinical Hypothyroidism. Cardiovascular complications are common, cold intolerance, puffy face and eyes, depression, weight gain, dry skin and hair, no sweating, poor appetite, frequent urination, constipation, hoarse voice, low basal body temperature.	Tongue: pale, swollen and scalloped. Pulse: weak, slow or imperceptible. Treatment: Nourish Kidney, Spleen and Heart Yang.
Kidney Jing (essence) deficiency	Late stage illness where the Kidneys are severely depleted and the marrow is being affected (usually elder patients). Dizziness, headaches, poor memory, insomnia, tinnitus, hair loss, general weakness, urinary frequency.	Tongue: slightly pale or pink and dry with no coat. Pulse: weak, thread, deep and imperceptible. Treatment: Supplement and enrich Kidney Jing.

### Western Treatments

According to Gary (2011), conventional treatment for Hashimoto's Thyroiditis consists primarily of thyroid hormone replacement when Hypothyroidism develops (Gary, 2011). There is no known medical therapy to treat or arrest the progressive thyroid gland destruction by Hashimoto's Thyroiditis (Gary, 2011). Hypothyroidism is transient but most patients require lifelong thyroid hormone replacement, typically L-thyroxine, 75-150mg once daily (Stegman, 2005). The interrelationships between Thyroid hormone and Estrogen which is essential for maintaining a pregnancy bloodstream (Rothfeld & Romaine, 2003). Thyroid hormone supplement interacts with the estrogen by blocking estrogen to

enter the bloodstream (Rothfeld & Romaine, 2003). This indicate that the patients with Thyroid dysfunction need to consult thoroughly with doctor when to try to be pregnant if taking thyroid medicine. There are some studies indicated that untreated Hypothyroidism women experience miscarriage at a risk (Rothfeld & Romaine, 2003). Before trying to conceive, all Hypothyroidism female patients planning to have a baby should be recommended to address the Thyroid hormone balance. Thyroid hormone supplementation can remove the risks of miscarriages even though not all miscarriages result from Thyroid imbalance (Rothfeld & Romaine, 2003).

Western treatments for autoimmune thyroiditis depend on the type of thyroiditis and the clinical presentation. Thyroid hormone replacement will be initiated for Hypothyroidism as soon as the diagnosis is made if there is an elevated TSH even though there is no symptoms (Ain & Rosenthal, 2011). One study showed that Levothyroxine reduces the incidence of spontaneous abortions in women with high Anti-TPO antibody by decreasing anti TPO antibody levels after 2-3 months of treatment (Mosaddegh, 2012). Enlarged goiter due to scarring in the thyroid gland can obstruct the neck and may require a surgery to remove the thyroid gland (Ain & Rosenthal, 2011). Treatment for Hashitoxicosis which the thyroid gland begins to leak out its thyroid hormone stores causing thyroid home depleting is beta blockers to slow the heart as well as block the adrenaline rush (Ain & Rosenthal, 2011). Beta blocker will decrease palpitations and reduce shakes and tremors (Ain & Rosenthal, 2011). As symptoms improve, the medication is tapered off since the thyrotoxic phase is temporary until it becomes failing (Ain & Rosenthal, 2011). Antithyroid medications are not used for the thyrotoxic phase of

thyroiditis of any kind since the thyroid is not overactive (Ain & Rosenthal, 2011). Mild anti-inflammatory medications such as aspirin or ibuprofen will be used for thyroidal pain, and steroid therapy with prednisone will be used for the occasional severe pain.

Thyroid hormone replacement prescription medicines are Armour Thyroid (natural, non-synthetic thyroid hormone made with desiccated animal thyroid gland), Cytomel (synthetic triiodothyronine, T3, used alone or in combination with thyroxine to treat hypothyroidism), Desiccated Thyroid (includes Armour, Westhroid, Naturthroid, and Proloid with active ingredients of T3 and T4), Levothroid (containing synthetic thyroxine, T4, most common thyroid medication), Levoxyl (containing synthetic thyroxine, T4), Synthroid (containing synthetic thyroxine, T4), and Thyrolar (containing a fixed ratio mixture of synthetic T3 and T4) (Kharrazian, 2010).

### **Acupuncture/Moxibustion for Autoimmune Thyroid dysfunction**

A statistical association of having TPO Ab and having a higher risk of miscarriage, there is nothing that you can do to alter whether you have TPO antibodies or not (Ain & Rosenthal, 2011). There is no way to prevent a miscarriage just because you know you have TPO antibodies (Ain & Rosenthal, 2011). This gives Traditional Chinese Medicine as an alternative way having potential to treat Autoimmune Thyroid dysfunction.

Treatment of autoimmune disorders in TCM is the concepts of clearing Heat, reinforcing Yin, supporting Qi and resolving Blood stasis (Lyttleton, 2013). The most important time to develop the fetus is at the time of early placental development which needs warm and flourishing Kidney Yang (Lyttleton, 2013). Kidney Yang and Wei Qi

deficiency is thought to cause the immune disorders in Traditional Chinese medicine (Lyttleton, 2013). According to Lewis (2004), thyroid hormone is Yang in nature, so Hypothyroidism produces the sensation of cold and sluggish Yang energies (See Table 5).

In Traditional Chinese Medicine, the treatment will be focused on regulating energy levels, restoring hormonal balance, smoothing emotions and helping sleep, emotions and menstrual problems (Arsovska *et al.*, 2016). Acupuncture stimulates the nervous system and causes the release of neurochemical messenger molecules influencing the body's homeostatic mechanisms (Arsovska *et al.*, 2016). Acupuncture regulates on the autonomic nervous system, hormones, and neuropeptide release to control metabolism and acupuncture may regulate the immune system as well as emotional state (Arsovska *et al.*, 2016).

According to Lyttleton (2010), recent reviews on the effect of acupuncture on the immune system have concluded that appropriate and frequently applied acupuncture treatment can provoke sustained anti-inflammatory activity, without stimulation of pro-inflammatory cells (Lyttleton, 2010). Stress affects the immune system and elevating levels of activated T-cells causing reduction of implantation rate of embryos. Women who are diagnosed with immune factors that might contribute to recurrent miscarriages (Lyttleton, 2010). Cases like antiphospholipid antibodies or autoimmune conditions that we associate with poor placentation, has been shown as clotting factors (Lyttleton, 2010). The acupuncture point for recurrent miscarriage related to immune factors will safeguard Kidney function and nourish Qi and Blood (Lyttleton, 2010).

**Table 5. 4 different ways in TCM clinical diagnosis for Hypothyroidism by Tao (2008)**

TCM Diagnosis	Symptoms
Yang insufficiency of the Spleen and Kidney	general weakness, lassitude and drowsiness, dizziness, soreness and weakness of the waist and knee joints, aversion to cold with cold limbs, tinnitus and deafness, general edema, dry hair and skin, decreased food intake and constipation, Tongue : flabby, teeth marks on the border and white-sticky tongue coating, Pulse : deep-thready
Yang insufficiency of the heart and kidney	palpitation and restlessness, chest distress, chilliness with cold limbs Tongue : white-slippery coating Pulse : deep-slow or knotted
Failure of Yang-Qi	commonly seen in coma patients with mucous edema, general lassitude; in severe cases, consciousness with convulsion, shallow breathing, muscular relaxation and forceless, decrease of skin temperature Tongue : pale-flabby Pulse : small-diminishing
Deficiency and loss of Kidney essence	dry mouth, yellow urine, headache and dizziness, insomnia and dreamy sleep Pulse : thready or deep-weak

### Acupuncture/Moxibustion for Autoimmune Dysfunction

The balance of Th1 and Th2 cell responses may be important to reduce a cause of infectious allergic and autoimmune diseases because Th1 and Th2 ratio may shift during pregnancy.

Normally higher serum levels of Th2 cytokines were detected in normal pregnancy compared with unexplained recurrent pregnancy losses and significantly higher serum levels of Th1 cytokine was present in women with recurrent pregnancy losses, compared with normal pregnancy (Gui *et al.*, 2012). In the research found that the average implantation blastocysts number was higher in Acupuncture treatment group (Gui *et al.*, 2012). It showed that Acupuncture could improve the poor receptive state of

endometrium due to mifepristone (RU-486) by promoting Th2 cytokines secretion and inhibiting Th1 cytokines to improve blastocyst implantation (Gui *et al.*, 2012).

Th1 cytokine levels were significantly higher in Thyroid Autoimmunity women than normal function thyroid women. This response during pregnancy and this change may lead to infertility (Huang *et al.*, 2015). Thyroid autoimmunity and thyroid dysfunction adverse conception and pregnancy outcome (Huang *et al.*, 2015). Isolated Thyroid autoimmune dysfunction with normal TSH level may affect the pregnancy with a higher risk of miscarriage treatment of euthyroid pregnancy women with positive thyroid peroxides antibodies is still controversy in Western medicine. Acupuncture can be a possible treatment with Levothyroxine substitution to lower the risk of infertility and miscarriage.

Aoki *et al.* (2008) reported that both Electro-Acupuncture and Moxibustion on DU4 influence macrophages in a way that the Lipopolysaccharide (LPS) reactivity was suppressed by 50% (Aoki *et al.*, 2008). It shows that increased susceptibility to infection as a side effect is not to occur even though it doesn't mean the body's defenses against infection are suppressed completely (Aoki *et al.*, 2008). The anti-inflammation effect of acupuncture may be a very important underlying mechanism of acupuncture in treating disease (Liang *et al.*, 2015)

According to Liu *et al.* (2013), Acupuncture on ST36 may enhance endogenous opioid peptides and elevate  $\beta$ -endorphins significantly by CD4+ T cells in Hypothalamus and in plasma by CD4+ T cells (Liu *et al.*, 2013). According to the study, successive Electro-acupuncture treatment on ST36 may restore the balance to the Th1/Th2/Th17 Treg T

helper cell responses by stimulation the hypothalamus to increase ACTH production and/or  $\beta$ -endorphins (Liu *et al.*, 2013).  $\beta$ -endorphin possibly increased by Electro-acupuncture is an important opioid which has therapeutic effects like alleviation of pain, reduction of inflammation, and improvement of sleep disturbance. It is also used as an analgesic in the body to numb or dull pains.

In the review journal by Kavoussi and Ross (2007), anti-inflammatory actions of acupuncture by mediating via reflexive central inhibition of the innate immune system are presented (Kavoussi and Ross, 2007). In the view of direct or indirect physiological mediation, Electro-acupuncture stimulate the efferent vagus nerve activation and deactivate inflammatory macrophage (Kavoussi and Ross, 2007).

Acupuncture or Electro-acupuncture has been studied to be effective on reducing the elevated serum levels of antigen-specific IgE by suppressing the increases of Th2 cytokines, especially IL-4 (Kim and Bae, 2010). Some clinical reports shows that there is positive effect of acupuncture on rheumatoid arthritis which is Th1 dominant disorders (Kim and Bae, 2010). Therefore Acupuncture is effective on dual immunomodulatory and balancing of Th1 and Th2 by maintaining homeostasis (Kim and Bae, 2010).

### **Acupuncture/Moxibustion for Fertility**

Infertility in women means that something is not working correctly in the process which should result in fertility (De La Vallee, 2007). One of the reason in TCM is emptiness of the Kidneys due to a weak constitution with a basic insufficiency of the Kidneys, or exhaustion of the Kidneys because of having sexual relationships too early, or sexuality not

managed well. And also the emptiness of the Kidney Qi, Chong and Ren Mai can be another reason which means that the circulation cannot warm up and bring the blood to the uterus, so there can be irregularities and disruption in menstruation and possible infertility (De La Vallee, 2007). The tongue will be normally pale with a white coat, and the pulse will be deep and thin, deep and slow, or deep and weak (De La Vallee, 2007). The Acupuncture treatment on REN4, Du4, KD3, SP6, UB23, and GB26 can be applied to regulate and support the Ren Mai and Chong Mai. And Moxibustion on Ren Mai to warm up the whole lower abdomen including uterus will be a good approach (De La Vallee, 2007).

According to Maciocia (1998), constitutional weakness of the Kidney-Essence, overwork causing Kidney Yin Deficiency (Maciocia, 1998). Constitutional weakness of the Kidney-Essence can be caused due to the woman's mother having been too old when conceiving, the parents' health being not good at the time of conception (Maciocia, 1998). The Kidney-Essence in TCM is the basis for the Heavenly Guy, so lack of the Kidney-Essence in women cannot conceive (Maciocia, 1998). Excessive physical work or exercise can cause infertility due to the Spleen and Kidney Yang weakness and also excessive sexual activity at an early age can cause the weakness of the Kidney and the Directing and Penetrating Vessels damage. Invasion of cold into the Uterus also can cause infertility by coldness obstructing the Uterus and the Directing and Penetrating Vessels (Maciocia, 1998). Consumption of cold or greasy diet is an important cause of Infertility (Maciocia, 1998).

### **Chapter 3: Methodology**

Purpose of this study is to find alternative way for infertile women dealing with autoimmune thyroid dysfunction not only to be healthier but also to become fertile. This chapter highlights the research methods used to determine acupuncture points and the clinical procedures utilized to accomplish the objective. This Literature review included the information from published books, classroom notes and lectures, used studies and peer reviewed articles that were of public record and already de-identified. Research and articles were compiled through online searches of medical journals through PubMed, EBSCO, Google Scholar, and BioMed Central using the following key search terms: Thyroid, Hypothyroidism, Autoimmune Thyroiditis, Infertility, Hashimoto's Thyroiditis, Traditional Chinese Medicine, Alternative Medicine, Acupuncture, Moxibustion, Phlegm, Spleen Qi Deficiency, Yin Fire, Kidney Yang Deficiency, Kidney Yin Deficiency, Qi and Blood Deficiency, Yuan Qi, Minister Fire, Latent Heat.

Analysis of the data gathered was conducted by categories demonstrated significant influences and efficacy as a systematic literature synthesis. It focused the intent of the researcher on synthesizing all of the research used in order to test the hypothesis. The researcher primarily utilized a desktop program called Zotero which was a citation management program that helps to collect, organize and cite the research information. However, the sources were manually printed, collected and organized instead of the citation program, Zotero. Upon conducting the search, 75 articles were found. After including those articles and published books which were written in English, and those that were human research and animal research, and excluding all articles older than 1990, male

fertility, Chinese Herbal Medicine, and Grave's Thyroiditis, 57 articles were included in the final search. The articles were organized into different categories : Autoimmunity, Autoimmunity and Miscarriage/Infertility, Autoimmunity and Acupuncture and/or Moxibustion, Infertility/Pregnancy, Infertility/Implantation/Pregnancy and Acupuncture, Thyroid dysfunction and Acupuncture, Thyroid dysfunction and Infertility, Autoimmune Thyroid dysfunction, Autoimmune Thyroid dysfunction and Infertility or Implantation or Pregnancy, and Acupuncture and/or Moxibustion for Auto Autoimmune Thyroid dysfunction and Infertility/Implantation/Pregnancy.

### **Human Research Ethical Considerations**

There was no informed consent needed for this research synthesis was literature review. There was no human subjects enrolled in this study and therefore this is not applicable. Only public record of already de-identified participants will be used.

## Chapter 4: Result

### Acupuncture for Autoimmune Thyroid Dysfunction and Fertility

Thyroid dysfunction and thyroid peroxidase autoantibodies (TPO Ab) in females are related to subfertility and early pregnancy loss (Vissenberg *et al.*, 2015). Immune related infertility refers to an inability to conceive or maintain a pregnancy because some aspect of the immune system prevents it. Autoimmune diseases are common in women and pregnancy is a common trigger (Kharrazian, 2006).

Infertility in TCM is frequently treated according to the menstrual cycle phases. During the menstruation phase or Atrophy of corpus luteum phase, the treatment is focused on regulating menstruation like stopping bleeding if the period is too heavy or invigorating blood if it is too scanty (Maciocia, 1998). During post-menstrual phase or Follicular development phase, the primary treatment goal is to nourish the blood and Kidney (Maciocia, 1998). During the inter-menstrual phase or Follicular maturity and ovulation phase, the treatment is to nourish Kidneys in order to consolidate the Directing and Penetrating Vessels. Lastly, the pre-menstrual phase or luteal phase is the phase when the corpus luteum develops and secretes progesterone, and the Yang is nourished and Liver Qi is moved (Maciocia, 1998) (See Table 6).

In TCM by Lewis (2004), more than any blood test results or any exam results, our immune system itself can cause the root problems (Lewis, 2004). Immunologic factors can be caused by the body heat and/or dampness, Blood stagnation, too much or too little Yin and Yang imbalance (Lewis, 2004). B-cells in the bone marrow and T-cells in the Thymus gland are the necessary fighters to defend the body against pathogens in the immune

system (Lewis, 2004). Strengthening the Origin, circulation, sustenance, and mobilization of these cells will tonify the immune system such as B-cells and T-cells (Lewis, 2004) (See Table 7).

All autoimmune reactions are body aches, increasing depression, irritability, premenstrual symptoms, early morning insomnia, night sweats, panic attacks, thin uterine lining (less than 8 mm on day 13 or 14), pro-response to high levels of follicle stimulating hormone, and hormone levels crashing in the middle of the cycle (Lewis, 2004). These symptoms correspond to a pattern of Liver Qi stagnation and Yin deficiency with heat in the Heart and Liver (Lewis, 2004). The pituitary and ovarian function imbalance and the Heart symptoms like palpitation, restlessness, and insomnia may be accompanied (Lewis, 2004) (See Table 8).

According to De La Vallee (2007), reasons of infertility in TCM is deficiency of the Kidneys due to a weak body or a basic insufficiency of the Kidneys, or exhaustion of the Kidneys due to early exposure of sexual relationships, or poorly managed sexuality. And also the emptiness of the Kidney Qi, Chong and Ren Mai can be another reason. Kidney deficiency will cause circulation problems which cannot warm up and fail to bring enough blood to the uterus. There may be irregular period or any disruption in menstruation. It can possibly lead the women to infertility (De La Vallee, 2007). The tongue with Kidney deficiency will be normally pale with a white coat, and the pulse will be deep and thin or deep and slow, or deep and weak (De La Vallee, 2007). The Acupuncture points can be REN4, Du4, KD3, SP6, UB23, and GB26 to regulate and support the Ren Mai and Chong Mai.

**Table 6. Infertility Treatment with Acupuncture and/or Moxibustion by Maciocia, 1998 in Obstetrics & Gynecology in Chinese Medicine**

<b>TCM Diagnosis</b>	<b>Clinical manifestations</b>	<b>Tongue (T) / Pulse (P) diagnosis</b>	<b>Treatment principle</b>	<b>Acupuncture / Moxa protocol</b>
Kidney Yang Deficiency	Prolonged menstrual cycle, Either scanty or heavy period, backache, dizziness, cold, depression, frequent urination	T : pale, swollen, wet P : deep, weak	Tonify Kidney Yang, stoke up the Fire of the Gate of Life, strengthen the Uterus	KD13, KD3, UB23, UB52, REN4, DU4, LU7, KD6, REN8. All with reinforcing method. Moxa on REN8 should be used
Kidney Yin Deficiency	Long term infertility, early period, scanty and light colored blood, 5 palm heat, night sweating, dizziness, tinnitus	T : red without coating P : floating-empty or rapid- fine	Nourish Kidney Yin and Kidney Essence	REN4, REN7, KD3, KD13, SP6, LU7, KD6, UB52. No Moxa should be used.
Blood Deficiency	Scanty period, pale blood, delated cycle, tiredness, depression, dizziness, pale complexion, blurred vision	T : pale and thin P : choppy or fine	Nourish Blood and the Essence, strengthen the Liver and Kidneys	REN4, ST36, SP6, KD13, UB20, UB23, UB17, ZI GONG XUE (3 Cun lateral to REN3). All with reinforcing method.

				Moxa is applicable.
Cold in Uterus	Primary infertility, delayed cycle, scanty period, small clots, painful period, better with heat, feeling colder during period, pale face, feeling cold, sore back	T : pale, thick-white coating P : weak, tight	Warm and tonify Kidney Yang, warm the Uterus, scatter cold	REN2, REN4, DU4, KD7, UB23, REN7. All with reinforcing method. Moxa should be used.
Dampness in the lower burner	Irregular periods, delayed cycle, mid-cycle pain, vaginal discharge, long term infertility, adhesions, obesity, feeling of heaviness	T : sticky coating P : slippery	Resolve Dampness, remove obstructions from the Directing and Penetrating Vessels	REN3, ZI GONG XUE, ST28, SP9, SP6, REN9, SU7, KD6, ST30, KD14, UB32. For Damp heat, GB41, SJ5, GB26, UB32, REN4 All with reducing or even method. No Moxa
Blood-Heat	Early periods(short cycle) up to twice a month, heavy flow, feeling hot during period, thirst, mental restlessness	T : red P : rapid, overflowing	Cool Blood, regulate the periods	LI11, SP10, KD2, LV3, SP6, P3, UB17, REN4, LU7, KD6 No Moxa
Stagnation of Qi	Irregular periods, premenstrual tension, painful periods, breast distention, irritability	T : normal color P : wiry or choppy	Move Qi, eliminate stagnation, pacify the	LV3, GB34, SJ6, PC6, REN6, REN4, KD14, SP4, PC6. All with reducing

			Liver regulate the periods	or even method. No Moxa.
Stasis of Blood	Irregular and painful periods, dark blood with clots, irritability, manic behavior, mental restlessness, abdominal pain.	T : purple P : wiry or choppy	Invigorate blood, eliminate stasis, pacify Liver and the Penetrating Vessel, and regulate the periods.	LV3, GB34, UB17, SP10, SP6, PC6, SJ6, REN6, REN4, SP4 (Rt), PC6 (Lt), KD14, ST29, KD6 (Rt), LU7 (Lt). All with reducing or even method

**Table 7. Immune system strengthening by Lewis (2004)**

<b>Components</b>	<b>Defensive forces</b>	<b>Strengthen</b>	<b>Acupuncture protocol</b>
Origin	Ensure a strong foundation by choosing the best soldiers	Tonify Kidney	KD3, KD7, LV14, UB23, UB52, DU4
Circulation	Allow transit of the troops via safe passages	Penetrating meridian	ST30, SP4, PC6
Sustenance	Provide adequate nourishment to keep the forces healthy	Nourish Spleen	ST36, REN6, Ren12
Mobilization	Don't allow the regiment to stagnate or revolt	Remove energetic blockages	UB23, KD16, ST30

**Table 8. Autoimmune Infertility and Miscarriage by Lewis (2004)**

<b>Diagnosis</b>	<b>Symptoms</b>	<b>Treatment</b>	<b>Acupuncture and/or Moxibustion protocol</b>
Spleen Qi deficiency and dampness. Phlegm(condensed dampness) Obstruction	Fatigue, lack of strength, lower back pain, heavy lower legs, heavy dragging feeling, profuse sticky, and thick vaginal discharge, and positive sperm (blood, essence) antibodies. May be overweight. Tongue : thin, white coating Pulse : fine, slippery or viscous	Supplement the Spleen, dry dampness, and transform phlegm	Strengthen the Spleen : SP6, ST36, REN6 Resolve dampness : SP9, ST40
Blood obstruction and stagnation, Blood stasis, Liver Qi stagnation	Abdominal pain associated with menstrual flow, blood clots. Tongue : may be dark, small, flat blemishes or discolorations on the edges of the tongue or darkened papillae (bumps) Pulse : taut or wiry, choppy, coming and going roughly	Move the Qi, invigorate the Blood, and transform stasis	Invigorate the Blood : UB17, SP10 Resolve the Liver Qi stagnation : LV3, LV14
Kidney Yin Deficiency with excess Heat,	Short cycles, profuse menstruation, afternoon tidal fever, dry mouth, sore throat, constipation, red eyes, dizziness, tinnitus, low back pain, lower leg weakness, heart irritation, and easy anger Tongue : thin, red, dry Pulse : find, rapid	Enrich Yin and clear heat to bring the fire down	Supplement the Kidney Yin and clear heat with KD3, REN3, SP10, and LI11
Damp Heat	Profuse, yellow vaginal discharge, possibly with a	Clear Heat, drain	LV2, SP6, SP9, SP10

	foul odor, late of menstruation, may be early menstruation, profuse or diminished blood flow, slimy clots, vaginal or rectal itching (usually premenstrual), chronic lower abdominal pain with the menstrual period, lower back pain Tongue : red with moist yellow coating Pulse : fine, slippery, rapid	dampness, supplement and move the Qi	
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### **Moxibustion for Autoimmune Thyroid Dysfunction and Fertility**

In the research by Han *et al.* (2014), it was found that Moxibustion (Moxa) treatment improves disease activity, repairs damaged colonic mucosa, suppresses secretion of serum IL-8 while activating that of IL-10, inhibits activation of NF- $\kappa$ B p65, and decreases expression of TLR-9 in Ulcerative Colitis (UC) rats. The result shows that the effect of moxibustion therapy in UC rats is possibly related to the inhibition of inflammatory cells by suppressing secretion of pro-inflammatory cytokine IL-8 and activating secretion of anti-inflammatory cytokine IL-10, and blocking of the inflammatory signaling transduction pathway by inhibiting activation of transcription factor NF- $\kappa$ B p65 and repressing the pattern recognition receptor TLR9 (Han *et al.*, 2014).

Bao *et al.* (2016) proposed in the research that Moxibustion regulates the default-mode network (DMN) in the brain and suppressed abnormal prefrontal cortex (PFC) activation in patients with chronic visceral pain (Bao *et al.*, 2016). This shows the effect of Moxibustion on Crohn's Disease enhancing the bodily attention on the abdomen region to promote healing (Bao *et al.*, 2016). In another study, indirect Moxibustion on the

acupuncture points of ST36 and SP6 for 1 week could elevate CD3+ and CD4+ T lymphocytes in normal subjects, whereas decrease relative proportions of CD8+ T lymphocytes in patients with Systemic Lupus Erythematosus (Kung *et al.*, 2006). This means indirect Moxibustion has different immunomodulation in normal conditions and in autoimmune conditions (Kung *et al.*, 2006). According to the study, Moxibustion possibly promote CD3+ and CD4+ but suppress CD8+ in Autoimmune conditions. Another research shows that Moxibustion with levothyroxine as a treatment for Hashimoto's thyroiditis can improve clinical symptoms and thyroid function as compared with levothyroxine alone (Xia, 2012). The study showed that Moxibustion treatment significantly increased FT4 and FT3 ( $P < 0.01$ ) and lowered S-TSH (Xia, 2012).

For infertility due to Kidney Yang deficiency, Moxibustion can be used on REN8 (Maciocia, 1998). Moxibustion also can be used for Coldness in the Uterus and Blood deficiency (Maciocia, 1998). Moxibustion should not be used for infertility related to Yin deficiency, Dampness in the lower burner, Qi stagnation, and Blood heat (Maciocia, 1998). According to De La Vallee (2007), Moxibustion can be applied on Ren Mai to warm up the whole lower abdomen including uterus (De La Vallee, 2007).

**Table 9. Studies/Results after Moxibustion treatments**

Studies	Diagnosis and protocol	Results
Han <i>et al.</i> , 2014	Ulcerative Colitis	Improves disease activity, repairs damaged colonic mucosa, suppresses secretion of serum pro-inflammatory cytokine IL-8 while activating anti-inflammatory cytokine IL-10, inhibits activation of NF- $\kappa$ B p65, and decreases expression of TLR-9

Bao <i>et al.</i> , 2006	Crohn's Disease, Systemic Lupus Erythematosus, (ST36, SP6)	Indirect Moxibustion for 1 week could elevate CD3+ and CD4+ T lymphocytes in normal subjects, whereas decrease relative proportions of CD8+ T lymphocytes in patients with Systemic Lupus Erythematosus. Different immunomodulation in normal condition and autoimmune status
Xia, 2012	Hashimoto's Thyroiditis, DU4	Improved clinical symptoms and thyroid function compared with levothyroxine alone. Increased FT4 and FT3 significantly after Moxibustion treatment ( $P < 0.01$ ); lower S-TSH in the Moxibustion group

### Summary

The presence of TPO Ab in autoimmune thyroid dysfunctions is known to be associated with a higher risk of miscarriage. Conventional Western treatment consists primarily of thyroid hormone replacement when hypothyroidism develops, but no known medical therapy that arrests the progressive thyroid gland destruction in Hashimoto's Thyroiditis currently exists (Gaby, 2011). This gives Traditional Chinese Medicine as an alternative way having potential to treat autoimmune thyroid dysfunction. The essential concept of Acupuncture and/or Moxibustion treatment for autoimmune disease is clearing heat, reinforcing Yin, supporting Qi and resolving Blood stasis.

The personalized and individual approach of Traditional Chinese Medicine would make an attempt to discover as many sources to diagnose the origin instead of merely narrowing down the cause. It seems unnecessary and impossible to pinpoint a single acupuncture point or multiple acupuncture points as one diagnosis for everyone. However, successive Electro-acupuncture treatment on ST36 may restore the balance to the T-cell responses by stimulation the hypothalamus to increase ACTH production and/or  $\beta$ -

endorphins according to Liu *et al.*(2013). And also indirect moxibustion on the acupuncture points of ST36 and SP6 for 1 week could elevate CD3+ and CD4+ T lymphocytes in normal subjects, whereas decrease relative proportions of CD8+ T lymphocytes in patients with Systemic Lupus Erythematosus (Kung *et al.*, 2006). This means indirect moxibustion has different immunomodulations for normal conditions and an autoimmune status (Kung *et al.*, 2006). And also Moxibustion with levothyroxine as a treatment for Hashimoto's thyroiditis was demonstrated the improvement of clinical symptoms and thyroid function as compared with levothyroxine alone (Xia, 2012). This results shows that Acupuncture and/or Moxibustion may have possible effectiveness to reduce inflammation causing miscarriage and difficulties of conception.

## Chapter 5: Discussion

Autoimmune disease is chronic disorder that have been difficult to cure or recover from it. The characteristic of autoimmune disease is immune system attacking the body components, so that the body components and the function is damaged temporarily or progressed destruction rapidly leading to permanent damage. Hashimoto's Thyroiditis is an autoimmune disease which the immune system destroys the thyroid gland. Thyroid dysfunction interferes with human reproductive physiology and it possibly reduces the fertility or pregnancy which adversely affects pregnancy outcomes. Pregnant women affected by Hypothyroidism or Hashimoto's Thyroiditis may have issues like an increased risk of preeclampsia, perinatal mortality, and miscarriage.

After a thorough review of the studies, it showed that Acupuncture and Moxibustion improve overall health of patients with autoimmune thyroid dysfunction and increase the anti-inflammatory cytokine. The researches show that Acupuncture has been used as an anti-inflammatory which has shown the Acupuncture may balance modulation of Th1/Th2 when the patients have Thyroid dysfunction with inflammation. The books from Chinese Medicine practitioners suggest that Acupuncture/Moxibustion for infertility is commonly used to tonify Kidney or Spleen and move stagnated Qi or any blockage like phlegm or dampness. Because the Kidney in Chinese medicine controls the reproductive system and Spleen produces the blood which many women are lacking of. When dealing with autoimmune disorder, Liver Qi stagnation and Yin deficiency with heat in the Heart and Liver should be addressed primarily (Lewis, 2004). Because the pituitary and ovarian function imbalance and the Heart symptoms like

palpitation, restlessness, and insomnia may be accompanied together in women (Lewis, 2004).

Even though there is limited information about Moxibustion for infertility related Autoimmune Thyroid dysfunction, some studies have shown that Moxibustion is found to have an effect on immunomodulation in normal condition and autoimmune status by elevating CD3+ and CD4+ T-lymphocytes in normal patients and decreasing CD8+ T-lymphocytes. Another research shows that Moxibustion with levothyroxine as a treatment for Hashimoto's thyroiditis can improve clinical symptoms and thyroid function as compared with levothyroxine alone (Xia, 2012)

### **Practical implication**

The researcher's goal for this literature review was to demonstrate the potential value and effectiveness of Traditional Chinese Medicine for patients who have been suffering due to Autoimmune Thyroiditis and infertility. This literature review suggest that Acupuncture and/or Moxibustion treatment may improve autoimmune dysfunction in female by balancing Th1 and Th2 and provoking sustained anti-inflammatory activity. This results can lead that Acupuncture can be used as a treatment of thyroid dysfunction induced infertility as an anti-inflammatory treatment which has shown modulation of Th1 and Th2 balance. However, Acupuncturist need to evaluate every patients as a unique person to determine the customized diagnosis and acupuncture points.

Moxibustion also has an effect on immunomodulation in both normal condition and autoimmune status by elevating CD3+ and CD4+ T-lymphocytes in normal patients and

decreasing CD8+ T-lymphocytes. The populations of CD3+, CD4+, and CD8+ are higher in patients with autoimmune disease than normal patients. And also Moxibustion as a treatment for Hashimoto's thyroiditis can improve better for clinical symptoms and thyroid function than using levothyroxine alone (Xia, 2012)

This review may show the potential approach of Acupuncture and/or Moxibustion to reduce possible inflammation causing miscarriage and increase pregnancy rate. It may provide alternative view for the Chinese medical integrative and allopathic medical communities to look at immune, endocrine, and reproductive health. It will hopefully be of value to the Western medical community as it may offer integrated treatment options for the patients with Autoimmune Thyroid dysfunction to reduce the risk of infertility or miscarriage and to enhance overall health. The reviewed studies generally focused on investigating whether Acupuncture and/or Moxibustion could be effective in patients with autoimmune disease or thyroid disease or pregnancy. Therefore further statistical study with clinical trials will be recommended to confirm the effective protocols of Acupuncture and/or Moxibustion on female patients with Autoimmune Thyroiditis fertility issues. The future case study may provide the confirmation whether Acupuncture and/or Moxibustion increase the number of live births in infertile women with Autoimmune Thyroiditis to reduce the risk of miscarriage and to enhance women's overall hormone balance.

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PMID: 22253557; PubMed Central PMCID: PMC3258552.

Data 1. Autoimmune, Infertility, and Traditional Chinese Medicine

Title	Author	Result/ Outcome
Immune aspects of Female infertility	Brazdova, A., Senechal, H., Peltre, G. & Poncet, P.	Immune infertility in terms of reproductive failure, has become a serious health issue including approximately 1 out of 5 couples at reproductive age. The immune rejection of male semen in the female reproductive tract is explained as the failure of natural tolerance leading to local and/or systemic immune response. Present active immune mechanism may induce high levels of anti-seminal/sperm antibodies.
Acupuncture and Immunity	Liang, F., Cooper, E.L., Wang, H., Jing, X., Quispe-Cabanillas, J.G., & Kondo, T.	The anti-inflammation effect of acupuncture may be a very important underlying mechanism of acupuncture in treating diseases.
Traditional Chinese medicine : potential for clinical treatment of rheumatoid arthritis	Moudgil, K.D., & Berman, B.M.	Tripterygium silfordii hook F (TwHF - Thunder God vine) extract has been shown to be effective in RA, and interestingly, TwHF treatment over 24 weeks showed higher efficacy than sulfasalazine, a conventionally used drug, as assessed by attainment of ACR20 response criteria. Moreover, the treatment with TwHF resulted in a significant reduction in serum IL-6, a proinflammatory cytokine involved in RA pathogenesis. Acupuncture on OA patients was an effective adjunctive treatment in controlling symptoms(pain) and improving function
Acupuncture and immune modulation	Kim, S.K. & Bae, H.S.	Electroacupuncture treatment elicits not only enhancing innate immunity but also modulating adaptive immune system.
Different brain responses to electro-acupuncture and moxibustion treatment in patients with Crohn's disease	Bao, C., Liu, P., Liu, H., Jin, X., Calhoun, V.D., Wu, L., Shi, Y., Zhang, J., Zeng, X., Ma, L., Qin, W., Zhang, J., Liu, X., Tian, J. & Wu, H.	Electroacupuncture and moxibustion were effective in normalizing the decreased cortical-subcortical coupling of the brain. The data suggest that regulation of the homeostatic afferent processing network, including the insula, ACC, Thalamus, and HIPPO, may be the primary pattern of brain response to electroacupuncture treatment. Regulation of the DMN, including nPFC and PCC, may be the primary pattern of brain response to moxibustion treatment.
Role of moxibustion in inflammatory responses during treatment of rat ulcerative colitis.	Han, Y., Ma, T.M., Ren, L., Ma, X.D., Bai, Z.H. & Lu, M.L.	Moxibustion repairs damaged colonic mucosa, suppresses serum IL-8(pro-inflammatory), activates serum IL-10(anti-inflammatory) level, and blocking of the inflammatory signaling transduction pathway by inhibiting activation of transcription factor NF-kB p65 and repressing the pattern recognition receptor TLR-9. Direct evidence of why moxibustion is effective in the treatment of Ulcerative Colitis in rats from a modern medicine perspective.
The different immunomodulation of indirect moxibustion on normal subjects and patients with Systemic Lupus Erythematosus	Kung, Y.Y., Chen, F.P., & Hwang, S.J.	Indirect moxibustion for 1 week could elevate CD3+ and CD4+ T-lymphocytes in normal subjects, whereas decrease relative proportions of CD8+ T-lymphocytes in patients with SLE. This result confirms that indirect moxibustion has different immunomodulation in normal condition and autoimmune status.
The neuroimmune basis of Anti-inflammatory Acupuncture	Kavoussi, B.& Ross, B.E.	Anti-inflammatory actions of acupuncture are mediated via the reflexive central inhibition of the innate immune system. The electrical stimulation of the vagus nerve inhibits macrophage activation and the production of TNF, IL-1 $\beta$ , IL-6, IL-18, and other proinflammatory cytokines.

The mechanism of effective electroacupuncture on T-cell response in rats with experimental autoimmune encephalomyelitis	Liu, Y., Wang, H., Wang, X., Mu, L., Kong, Q., Wang, D., Wang, J., Zhang, Y., Yang, J., Zhou, M., Wang, G., Sun, B. & Li, H.	Stimulation through ST36 attenuated EAE severity, nevertheless rats receiving non-ST36 therapy were still suffering serious disease. Also proved that successive electroacupuncture treatment at ST36 of rats could restore the balance to the Th1/Th2/.Th17/Treg T helper cell responses by stimulating the hypothalamus to increase ACTH production. Furthermore, electroacupuncture stimulation promoted $\beta$ -endorphin production. These results suggested that opioids released following treatment with EA reduced the severity of EAE.
The effects of electroacupuncture on Th1/Th2 cytokine mRNA expression and mitogen-activated protein kinase signaling pathways in the splenic T-cells of traumatized rats	Wang, K., Wu, H., Wang, G., Li, M., Zhang, Z. & Gu, G.	EA administration increased Th1 cytokine protein and mRNA expression, suppressed Th2 cytokine protein and mRNA expression, and increased the activity of ERK1/2, p38, NF-kB, and AP-1. EA regulates a balance between Th1 and Th2 cytokines at protein and mRNA levels in splenic T cells, and, at least in part, involves the signaling pathways of ERK1/2, p38, NF-kB, and AP-1. The findings suggest that EA may improve immune suppression after surgical trauma.
Electroacupuncture and moxibustion influence the lipopolysaccharide-induced TNF- $\alpha$ production by Macrophages	Aoki, E., Kasahara, T., Hagiwara, H., Sunaga, M., Hisamitsu, N. & Hisamitsu, T.	For both EA and Mox, when treatment was administered at an acupuncture point corresponding to the Du4 in humans, macrophages were influenced in a way that the LPS reactivity was suppressed by 50%. The production of TNF- $\alpha$ is thought to be suppressed when the degree of macrophage activation is suppressed by 50%. These result suggest that activated macrophages are an important target of the immunosuppressive effects of EA and Mox and that m-opioid receptor-mediated mechanisms are responsible, to some extent, for the suppressive effect of EA, although Mox may not be dependent on these mechanisms.

## Data 2. Infertility and Traditional Chinese Medicine

Title	Author	Result/ Outcome
Infertility around the globe : new thinking on gender, reproductive technologies and global movements in the 21st century	Inhorn, M.C. & Patrizio, P.	Infertility remains an ongoing reproductive problem. Suggest to address the preventable causes of infertility, to provide support and alternatives for the infertile and to encourage new LCIVF initiatives to improve availability, affordability and acceptability of ART around the globe
Traditional Chinese medicine, women's experiences in the treatment of infertility	Alfred, A. & Ried, K.	Women appreciated the noninvasive diagnostic techniques TCM practitioners used to identify 'imbalances' causing infertility, learnt how to assess fertility indicators, and valued the focused personal care provided. All noticed improved menstrual cycles. Women wished for integration of holistic therapies in infertility management.
The effect of Anti thyroid peroxidase Antibodies on pregnancy outcomes in euthyroid women.	Meena, M., Chopra, S., Jain, V. & Aggarwal, N.	The prevalence of anti-TPO positivity was 11% (n=110). Out of the positives, those with elevated Thyroid stimulating hormone (TSH) were 6.5%. The prevalence of euthyroid women who were anti-TPO positive was 4% (n=40). Anti-TPO positive euthyroid females had a higher prevalence of infertility, anemia and preterm delivery as compared to the controls (p<0.0001). No differences were observed between the two groups in terms of history of abortion recurrent abortions, intrauterine growth restriction, postpartum hemorrhage, symptomatic hypothyroidism, Hypertensive disorders of pregnancy and fetal complications.
A review of controlled trials of acupuncture for	White, A.R.	Electroacupuncture group were found to have a significantly higher chance of implantation and take -home baby rates. In a recent study involving 160 women undergoing in vitro fertilization, two sessions of acupuncture immediately before and

women's reproductive health care		after embryo transfer resulted in a significantly higher pregnancy rate 42.5% than in the control group who had no acupuncture 26.3%.
Prior to conception : The role of an Acupuncture protocol in Improving women's reproductive functioning assessed by a pilot pragmatic randomized controlled trial	Cochrane, S., Smith, C.A., Possamai-Inesedy, A. & Bensoussan, A.	The acupuncture intervention, compared to lifestyle only, resulted in significant increases in fertility awareness and quality of life measures in relation to wellbeing : it increased the ability of the recipients to engage in desired activities, such as exercise or rest, and it shortened the time to conception by half. The finding provide preliminary evidence that the acupuncture intervention is acceptable and is not inert and that acupuncture dose may have a significant influence on outcomes. The multiphasic fertility acupuncture protocol tested in this trial did positively influence the women who received it compared to the women who used lifestyle modification alone. It increased their fertility awareness and improved their wellbeing.

### Data 3. Thyroid, Infertility, and Traditional Chinese Medicine

Title	Author	Result/ Outcome
Acupuncture Treatment for Hypothyroidism	Arsovska, B., Zhu, J., & Kozovska, K.	From the first treatment made the levels of TSH. T4 and TPO hormones were gradually normalizing. The last results are from the analysis when she also made her last treatment.
Questions and answers : How to give TCM differential treatment for Hypothyroidism	Chunxiang, T.	1. Yang insufficiency of the Spleen and Kidney 2. Yang insufficiency of the heart and kidney 3. Failure of Yang Qi 4. Deficiency and loss of kidney essence
Recurrent pregnancy loss in patients with thyroid dysfunction	Sarkar, D.	Universal screening for thyroid hormone abnormalities is not routinely recommended at present, but thyroid function must be examined in female with fetal loss or menstrual disturbances.
Levothyroxine treatment in pregnancy : indications, efficacy, and therapeutic regimen	Klubo-Gwiedzinska, J., Burman, K.D., Nostrand, D.V., & Wartofsky, L.	TSH range during pregnancy: First trimester: 0.1-2.5mIU/L, Second trimester: 0.2-3.0mIU/L, third trimester: 0.3-3.0mIU/L, Levothyroxine (LT4) should be increased by 25-30% upon a missed menstrual cycle or positive home pregnancy test. Hypothyroid patients who are planning pregnancy should have their dose adjusted by provider in order to optimize serum TSH values to <2.5mIU/L preconception.

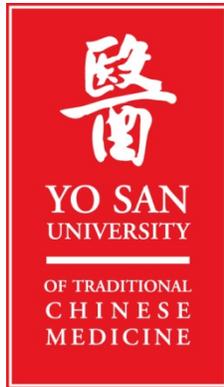
### Data 4. Autoimmune Thyroid dysfunction, Infertility, and Traditional Chinese Medicine

Title	Author	Result/ Outcome
Autoimmune thyroid disorders	Iddah, M.A. & Macharia, B.N.	The most recent studies have shown that the human autoimmune thyroid diseases (AITDs) affect up to 5% of the general population and are seen mostly in women between 30 and 50 years. Autoimmune thyroid disease is the result of a complex interaction between genetic and environmental factors. Overall, this review has expanded the understanding of the mechanism involved in pathogenesis of AITD and the relationship between autoimmune thyroid disease, neoplasm, and kidney disease.
Effect of thyroid autoimmunity per se on assisted reproduction	He, H., Jing, S., Fong, F., Tan, Y.Q., Lu, G.X., Lin, G.	In euthyroid women whose Subclinical hypothyroidism status is unknown, those with positive antithyroid antibodies had a higher miscarriage rate (pooled relative risk (RR) =1.638; 95% confidence interval (CI), 1.228-2.185) and a lower delivery rate (pooled RR =0.856; 95% CI, 0.759-0.965) than those with negative ATA. Clinical pregnancy rates

treatment outcomes		were similar between groups.
Relationship between Antithyroid Antibody and pregnancy outcome following in vitro fertilization and embryo transfer	Zhong, Y. P., Ying, Y., Wu, H.T., Zhou, C.Q., Xu, Y.W., Wang, Q., Li, J., Shen, X.T., Li, J.	Patients with antithyroid antibody showed significantly lower fertilization rate, implantation rate and pregnancy rate and higher risk for abortion following IVF-ET when compared with those without antithyroid antibody. Thus, the presence of antithyroid antibody is detrimental for the pregnancy outcome following IVF-ET.
Thyroid antibodies and risk of preterm delivery	He, X., Wang, P., Wang, Z., He, X., Xu, D., & Wang, B.	The presence of TPO-Ab in pregnant women significantly increases the risk of preterm delivery (birth occurring at or before 37 weeks of gestation).
Thyroid autoimmunity and hypothyroidism before and during pregnancy	Poppe, K. & Glinioer, D.	TAI is associated with a significant increase in the risk of miscarriages. Systemic screening of TAI and hypothyroidism during early pregnancy, monitoring of thyroid function, administration of L-thyroxine treatment in selected cases and follow up during the postpartum period have proved to be helpful and important in order to manage the patients adequately. Maternal thyroid under-function may be associated with an impairment of fetal brain development (leading to poor school performances and lower IQs) due to insufficient transfer of maternal thyroid hormones or the fetoplacental unit.
Treatment of recurrent pregnancy loss by Levothyroxine in women with high Anti-TPO antibody	Mosaddegh, M.H., Ghasemi, N., Juhaninejad, T., Mohsenifar, F., & Aflatoonian, A.	The success rate of pregnancy in women with abnormal anti-TPO with Levothyroxine therapy was 82.85%. Mean of anti-TPO in women with treatment before taking medication was 488.35 and after that it was 123.35 UI/ml. The difference was significant. (p<0.05) This study showed that Levothyroxine reduces the incidence of spontaneous abortions in women with high Anti-TPO antibody. It decreased anti-TPO antibody levels after 2-3 months treatment.
Thyroglobulin autoantibodies : Is there any added value in the detection of Thyroid Autoimmunity in Women consulting for fertility treatment?	Unuane, D., Velkeniers, B., Anckaert, E., Schiettecatte, J., Tournaye, H., Haentjens, P., & Poppe, K.	The prevalence of TAI was 16% (163/992). In 8% of cases, both types of autoantibodies were present, in 5% isolated positive TGB-Abs were found, and 4% had isolated positive TPO-Abs (p=0.025 and p=0.003 respectively). The prevalence of TAI was significantly higher in infertile women as compared to that in fertile controls (19% vs 13%; p=0.047). The median serum TSH level was significantly higher in the women with TAI and with isolated positive TGB-Abs compared to that in women without TAI(1.83[1.44] and 1.90[0.85] vs 1.47[0.94] mIU/L ; p,0.001 respectively).
What affects functional ovarian reserve, thyroid function or thyroid autoimmunity?	Weghofer, A., Barad, D.H., Darmon, S., Kushnir, V.A. & Gleicher, N.	TSH <3.0mIU/mL in euthyroid infertility patients is associated with significantly better Functional Ovarian Reserve (FOR, higher AMH) than TSH>3.0mIU/mL. A direct beneficial effect of lower TSH levels on follicular recruitment, and warrants investigations of thyroxin supplementation in infertile women with TSH levels >3.0mIU/mL in attempts to improve FOR.
High prevalence of Infertility among women with Graves' disease and Hashimoto's Thyroiditis.	Quintino-Moro, A., Zantut-Wittmann, D.E., Tambascia, M., Machado, H.D.C. &Fernandes, A.	The prevalence of infertility was 52.3% in Graves' disease and 47% in Hashimoto Thyroiditis. Mean age at diagnosis was 36.5 years and 39.2 years, in GD and HT, respectively. The mean number of pregnancies was lower in women who were 35 years old or younger at diagnosis and was always lower following diagnosis of the disease, irrespective of age. The only variable associated with infertility was a shorter time of the disease in HT.
Significance of subclinical thyroid dysfunction and thyroid autoimmunity before conception and in early	Van Den Boogaard, E., Vissenberg, R., Land, J.A., Wely, M.V., Post, J.A.M.V.D., Goddijn, M. &	Subclinical hypothyroidism in early pregnancy, compared with normal thyroid function, was associated with the occurrence of pre-eclampsia and an increased risk of perinatal mortality. In the meta analysis, the presence of thyroid antibodies was associated with an increased risk of unexplained subfertility, miscarriage, recurrent miscarriage, preterm birth, and maternal post partum thyroiditis when compared with the absence of thyroid antibodies.

pregnancy	Bisschop, P.H.	
Thyroid dysfunction and pregnancy outcomes	Nazarpour, S., Tehrani, F.R., Simbar, M. & Azizi, F.	Overt hyperthyroidism and hypothyroidism have several adverse effects on pregnancy outcomes. The long term effect of overt hypothyroidism on cognitive is debate on short and long term effect of subclinical hypothyroidism. Thyroid antibody positivity is associated with adverse pregnancy outcomes, but there is no consensus on fetomaternal complication of pregnant women with TPO antibody positive and euthyroid status.
The impact of thyroid function and thyroid autoimmunity on embryo quality in women with low functional ovarian reserve : a case control study	Weghofer, A., Himaya, E., Kushnir, V.A., Barad, D.H. & Gleicher, N.	TPO antibody affect embryo quality in euthyroid women with low normal TSH under 2.5mIU/mL. In women with high normal TSH levels, increasing TSH levels, and possibly TPO antibodies, appear to impair embryo quality. These results suggest that the negative impact of thyroid autoimmunity becomes apparent, once thyroid hormone function is optimized.
Maternal subclinical hypothyroidism, thyroid autoimmunity, and the risk of miscarriage	Liu, H., Shan, Z., Li, C., Mao, J., Xie, X., Wang, W., Fan, C., Wang, H., Zhang, H., Han, C., Wang, X., Liu, X., Fan, Y., Bao, S. & Teng, W.	Compared to women with ET, the risk of miscarriage was significantly higher among women with Subclinical Hypothyroidism (SCH), isolated Thyroid autoimmunity (TAI), SCH+TAI, and SCH+TAI. The gestational ages of 110 women at miscarriage were lower among women with subclinical thyroid abnormalities compared to ET. In parallel with the higher TSH levels, there were earlier gestation ages at miscarriage between subgroups of SCH and SCH+TAI. Women with SCH and TAI are at an increased risk of miscarriage between four and eight gestational weeks. Women with a combination of SCH and TAI were found to have the highest risk and earlier gestational ages of miscarriage.
Impaired Fertility Associated with subclinical hypothyroidism and thyroid autoimmunity	Feldthusen, A.D., Pedersen, P.I., Larsen, J., Kristensen, T.T., Ellervik, C. & Kvetny, J.	Women with mild hypothyroidism TPO Ab was significantly elevated and age at first child was older compared to controls. TSH and TPO Ab were negatively linearly associated with the number of children born and the number of pregnancies in the full cohort in age-adjusted and multiadjusted models. TSH or TPO Av was not associated with spontaneous abortions. Mild hypothyroidism was associated with a risk of not having children and a risk of not getting pregnant in age -adjusted and multiadjusted models. Prevalent hypothyroidism was not associated with the number of children born, the number of pregnancies, or spontaneous abortions. Impaired fertility is associated with TSH, TPO Ab, and mild hypothyroidism in Danish population of women.
Thyroid dysfunction and thyroid autoimmunity in euthyroid women in achieving fertility	Medenica, S., Nedeljkovic, O., Radojevic, N., Stojkovic, M., Trbojevic, B. & Pajovic, B.	Thyroid dysfunction and thyroid autoimmunity can cause adverse effects on mother and fetus including pregnancy loss, gestational hypertension, or pre-eclampsia, preterm delivery, low birth weight, placental abruption and postpartum hemorrhage. There is an evidence that thyroid autoimmunity, in thyroid dysfunction adversely affects conception and pregnancy outcomes, but it is unclear what impact has isolated eumetabolic thyroid autoimmunity in achieving fertility, especially in women undergoing in vitro fertilization.
Thyroid autoimmunity is associated with decreased cytotoxicity T cells in women with repeated implantation failure	Huang, C., Liang, P., Diao, L., Liu, C., Chen, X., Li, G., Chen, C. & Zeng, Y.	The prevalence of antithyroid antibodies in women with recurrent IVF failure is about 20%-50% in several studies. The prevalence of thyroid function abnormality in RIF women with TAI was 23.8%, which was not different from that in RIF women without TAI. It indicated that thyroid function abnormality was not the only cause of RIF in women with TAI. The percentage of CD3+ CD8+ TC cells was decreased and Th/Tc ratio was increased in RIF women with TAI. These results indicated that the decreased Tc percentage and increased Th/Tc ratio may be another influential factor of adverse pregnancy outcomes in RIF women with TAI.

Thyroid autoantibodies in pregnancy : their role, regulation and clinical relevance	Balucan, F.S., Morshed, S.A. & Davies, T.F.	Autoantibodies to thyroglobulin and thyroid peroxidase are common in the euthyroid population and are considered secondary responses and indicative of thyroid inflammation. By contrast, autoantibodies to the TSH receptor are unique to patients with Graves' disease and to some patients with Hashimoto's thyroiditis. Both types of thyroid antibodies are useful clinical markers of autoimmune thyroid disease and are profoundly influenced but the immune suppression of pregnancy and the resulting loss of such suppression in the postpartum period.
Pathophysiological aspects of thyroid hormone disorders/thyroid peroxidase autoantibodies and reproduction	Vissenberg, R., Manders, V.D., Mastenbroek, S., Fliers, E., Afink, G.B., Ris-Stalpers, C., Goddijn, M. & Bisschop, P.H.	Altered thyroid hormone levels are associated with disturbed folliculogenesis, spermatogenesis, lower fertilization rates and lower embryo quality. Triiodothyronine (T3) in combination with FSH enhances granulosa cell proliferation and inhibits granulosa cell apoptosis by the PI3K/Akt pathway. T3 is considered a biological amplifier of the stimulatory action of gonadotrophins on granulosa cell function. T3 increases the expression of matrix metalloproteinases (MMP), MMP-2, MMP-3, fetal fibronectin and integrin $\alpha 5\beta 1$ in early placental extravillous trophoblasts. Thyroid hormone transporters and receptors are expressed in the ovary, early embryo, endometrium, uterus and placenta.
Effects of Acupuncture on Th1, Th2 Cytokines in Rats of Implantation failure	Gui, J., Xiong, F., Li, J., & Huang, G.	Significantly higher serum levels of Th2 cytokines, IL-6 and IL-10 were detected in normal pregnancy compared with unexplained recurrent pregnancy losses and significantly higher serum levels of the Th1 cytokine, IFN- $\gamma$ were present in women with recurrent pregnancy losses. Acupuncture changes the immune microenvironment of endometrium by altering the expression of cytokines in implantation failure uterus including promoting Th2 cytokines such as IL-4 and IL-10 secretion and inhibiting Th1 cytokines including IL-1 $\beta$ and IL-2 secretion to improve blastocyst implantation.



January 8, 2016

Jung Hwa Park  
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Dear Sarah,

Your research proposal has been approved, with no additional recommendations effective through March 31, 2017.

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,

Ed Mervine  
IRB Coordinator

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