Treatment of Anovulation of Polycystic Ovary Syndrome Patients with Chinese Herbal Medicine: A Literature Review Synthesis

A Capstone Project
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By

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Abstract

This literature review synthesis focuses on Polycystic Ovary Syndrome (PCOS), a commonly encountered complex endocrinal, reproductive, and metabolic disorder affecting 5-10% of women of reproductive age (NIH, 2012). PCOS women's lives revolve around their illness dealing with chronic anovulation, irregular menstruation, hyperandrogenism, acne, obesity, anxiety, depression, and infertility. $4 billion annually is spent within the U.S. healthcare system to identify and manage PCOS. This estimate does not include treatment of the serious conditions associated with PCOS such as Type 2 Diabetes, cardiovascular disorder, and endometrial cancer (NIH, 2012). The objective of this study is to analyze current research in the effectiveness of Chinese medicine alone or in combination with western medicine in the treatment of anovulatory for management of PCOS. Through this qualitative, retrospective research study, a thematic style of analysis was conducted on twenty-two articles. The study entailed the collection and analysis of data from the emerging themes. The implications are discussed regarding the integration of Traditional Chinese Medicine (TCM) with western medicine and its clinical application. Finally, limitations of the scope of treatment and further recommendations as regards future treatments are provided.

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CHAPTER 1: INTRODUCTION

Polycystic Ovarian Syndrome (PCOS), also known as Stein-Leventhal Syndrome, is a complex endocrinal and metabolic disorder that affects a woman's menstrual cycle, hormones, fertility, insulin production, circulatory system, and appearance (Speroff & Fritz, 2011). Women affected with this condition experience a host of symptoms, which include irregular or absent menstrual cycles, an increased number of small follicles in each ovary, abnormal hair growth, and acne. Additionally, they can experience a metabolic syndrome in the form of glucose intolerance, insulin resistance, an increased risk of Type 2 diabetes, obesity, dyslipidemia, hypertension, cardiovascular disorder, and endometrial cancer (Sheehan, 2003). This disorder, affecting 5% to 10% of women of reproductive age based on U.S. National Institutes of Health (NIH) criteria and as high as 15% when the broader Rotterdam criteria are applied (Lentz, 2012), can and has caused physical and emotional strain on women and families when left undiagnosed. The use of Chinese herbal medicine alone and in conjunction with western medicine, in regards to PCOS, has been a subject of much research.

Traditional Chinese medicine (TCM), ancient medicine practiced for thousands of years in China, has become an integral part of western medicine, especially concerning female disorders (Macioca, 1998). The purpose of this study is to identify successful treatment modalities combining Eastern and Western medicine for anovulatory PCOS females. As a result, this study seeks to respond to the following questions:

- What types of TCM principles, formulas, and herbal combinations are used in research studies to treat anovulation in PCOS patients to stimulate ovulation?

- What type of effects does Chinese medicine alone, and also in combination of Chinese herbal medicine and western medicine modalities produce in treatment of anovulatory PCOS female patients to stimulate ovulation?
- How effective are these various modalities in inducing ovulation in anovulatory PCOS female patients?

With these in mind, the hypothesis herein is that Chinese medicine is as effective, if not more effective, as western modalities in inducing ovulation in anovulatory PCOS patients. As a corollary, this study seeks the combined current literature available concerning use Chinese medicine and Western medicine for treatment to induce ovulation in anovulatory PCOS patients. In conjunction with this literature review synthesis, this study will attempt to identify, describe, summarize, compare and assess the current research literature available regarding the efficacy of Chinese medicine versus western medicine for successful treatment to induce ovulation in anovulatory PCOS patients.

There is a wealth of information on PCOS, and so much service will be done by uncovering the strengths and weaknesses, limitations as well as similarities and differences among available researches. All of these could reveal the potential impact of TCM on women's health, thus helping to guide health providers of both eastern and western medicine to treat anovulation in PCOS patients. The researcher's particular interest in this study is borne from numerous encounters with clinic patients struggling with PCOS and experiencing infertility, and depression. A sense of moral duty propelled the researcher to seek an integrated approach to a complex hormonal, reproductive, and endocrinal disorder. This study hopes to combine the current literature available concerning use Chinese medicine and western medicine for treatment to induce ovulation in anovulatory PCOS patients.

Definition of Terms:

- **Acanthosis Nigricans:** Patches of thickened, velvety, darkened skin that is sometimes associated with insulin resistance. (Speroff & Fritz, 2011)
- **Amenorrhea.** Absence of menstruation (Speroff & Fritz, 2011)
- **Androgen:** is a steroid hormone that stimulates the development of male characteristics, controls activity of the accessory male sex organs (Speroff & Fritz, 2011).
- **Anovulation:** lack of ovulation (Speroff & Fritz, 2011).
- **Anti-mullerian hormone (AMH):** AMH are produced by the granulosa cells of preantral follicles and small antral follicles (Speroff & Fritz, 2011).
- **Antral follicles:** Ovarian follicles during later stages of folliculogenesis (Speroff & Fritz, 2011)
- **Atresia:** Cell death (Speroff & Fritz, 2011).
- **Clomiphene Citrate (CC)** Clomiphene is a non-steroidal ovulation inducing with both estrogen agonist and antagonist properties. It removes endogenous estrogen which affects the negative feedback on hypothalamic pituitary axis, hence normalizing the pituitary release of FSH and LH. It is administered at any time in amenorrhic and anovulatory patient. (Melmed, 2011).
- **DHEA:** Dehydroepiandrostene is an endogenous steroid hormone, and which is produced by adrenal cortex from cholesterol. It is the primary precursors in the biosynthesis of the androgen and estrogen (Melmed, 2011).
- **E2:** Estradiol is a sex hormone produced by the granulosa cells of the ovaries, and small amount by adrenal cortex. Testosterone is also converted to estradiol by amortization (Speroff & Fritz, 2011).
- **FSH:** Follicle stimulating hormone is produced by anterior pituitary gland, and has a function in stimulation and maturation of follicles (Melmed, 2011).
- **LH:** Luteinizing hormone is produced and released by anterior pituitary gland, and it induces ovulation and development of corpus luteum (Melmed, 2011).
- **GnRH:** Gonadotropin releasing hormone released by hypothalamic to stimulate pituitary gland (Speroff &Fritz, 2011).
- **Granulosa cells:** cells that surround follicles, and they produce hormones (Speroff & Fritz, 2011).

- **Hirsutism:** Excessive body hair in a masculine distribution growth in women (Melmed, 2011).
- **Hyperandrogenism:** (androgen excess) a medical condition characterized by excessive production and/or secretion of androgens (Speroff & Fritz 2011).
- **Hyperinsulinemia:** insulin excess circulating in the blood than expected relative to the glucose (Speroff & Fritz 2011).
- **Insulin Resistance:** (IR) is a physiological condition in which cells fail to respond to the normal actions of the hormone insulin. Cells are not able to take in glucose, amino acids and fatty acids. Thus, glucose, fatty acids and amino acids 'leak' out of the cells (Speroff & Fritz 2011)
- **Metformin (Glucophage):** an anti-diabetic drug in the biguanide class. It is normally used in non-insulin-dependent diabetes, and the mechanisms of action include inhibition of gluconeogenesis in the liver and increasing the peripheral uptake of glucose. Metformin reduces levels of luteinizing hormone, hyperinsulinemia and also decreases ovarian production of androgens (Siebert, 2012).
- **Oligomenorrhea:** infrequent menstruation, menstrual cycles that are longer than 35 day, usually fewer than eight cycles per year. It is a sign of anovulatory cycles (Speroff & Fritz, 2011).
- **PCOS:** Polycystic Ovarian Syndrome Syndrome (PCOS) is a complex endocrinal and metabolic disorder that affects a woman's menstrual cycle, hormones, fertility, insulin production, circulatory system, and appearance .
- **TCM:** Traditional Chinese medicine.
- **Theca cells:** The cells surrounding the follicles, responsible for production of androgens (Speroff & Fritz, 2011).

This capstone project will proceed with review of the literature in Chapter Two, and a description of the research method engaged in Chapter Three. The results of the project will be presented in Chapter Four, followed by a discussion of the implications of the findings in Chapter Five.

CHAPTER 2: LITERATURE REVIEW

This literature review will first cover Polycystic Ovary Syndrome (PCOS) from a western medical perspective, and thereafter from a Traditional Chinese Medicine (TCM) point of view. Information will be provided about the condition as a whole, with treatment strategies to follow. To complete this literature review, the researcher conducted an initial search of TCM and western textbooks relating to the condition of PCOS. A more systematic search was conducted through PubMed and several other search engines initially accessed through the Yo San University Library using the following key words: "PCOS" "Polycystic ovaries" and "anovulation." Subsequent to the initial search, the researcher followed up with a search through the UCLA Medical Library. To further flesh out this literature review chapter and to assure that the search is comprehensive and up to date, the researcher also conducted a search of *Dissertation Abstracts.*

Western Medicine Perspectives on PCOS

1- The History, Definition, and Diagnosing of PCOS

The first reproductive features of Polycystic Ovary Syndrome (PCOS) were discussed by Hippocrates in the fifth century B.C. (Hanson, 1975). However, it was not until the 19th century that observable signs of androgen excess coupled with metabolic abnormalities were reported. Here, the first description of enlarged smooth polycystic ovaries has been attributed to Chereau in 1844 (Diamanti-Kandarakis & Dunaif, 2012). In 1921, the coexistence of diabetes mellitus with clinical signs of androgen excess in a postmenopausal woman – the so-called "Achard-Thiers syndrome" or "diabetes of the bearded women" (diabète des femmes à barbe) was reported by Thiers (1921).

Thereafter, in 1935, it was Stein and Leventhal who first reported the clinical features of menstrual irregularity and infertility of PCOS and recommended ovarian wedge re-sectioning for improvement. As a result, enlarged ovaries associated with hirsutism, menstrual irregularity, infertility, and obesity came to be known as Stein-Leventhal syndrome (Sheehan, 2003).

There were four expert conferences all contributing to the definitional and diagnostic criteria of Polycystic Ovary Syndrome (PCOS). The first event was in April of 1990 sponsored by National Institute of Health (NIH), where the criteria PCOS were established as: 1) Chronic oligo-ovulation/ or oligo-menorrhea, 2) clinical and/or biochemical signs of hyperandrogenism and/or hyperandrogenemia and 3) exclusion of related disorders. This definition was further expanded in another expert conference held in Rotterdam in May 2003, creating two new phenotypes in addition to exclusion of related disorders: 1) Oligo- or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism, and 3) Polycystic ovaries (Azziz, 2006). Additionally, in 2006, the Androgen Excess's and PCOS Society's criteria for PCOS stressed hyperandrogenism as a key feature, and thus revised the criteria to include: 1) clinical and/or biochemical signs of hyperandrogenism and/or hyperandrogenemia, 2) ovarian dysfunction (oligo-anovulation and/or polycystic ovaries), and 3) the exclusion of related disorders (Azziz et al., 2009).

Finally, in December of 2012, in the NIH conference, it was recommended to maintain the diagnostic criteria of Rotterdam 2003, which included the NIH 1990 and AE-PCOS 2006 criteria while specifically identifying PCOS phenotype which consists of: androgen excess and ovulatory dysfunction, androgen excess and polycystic ovarian

morphology, ovulatory dysfunction and polycystic ovarian morphology, and androgen excess with ovulatory dysfunction and polycystic ovarian morphology (NIH, 2012).

Diagnostic Criteria for PCOS		
National Institute of Health 1990	***Rotterdam 2003***	***Androgen Excess Society Criteria 2006***
Chronic Anovulation Clinical and/or biochemical signs of Hyperandrogenism Exclusion of other related disorders (Both criteria needed)	Oligomenorrhea and/or anovulation Clinical and/or biochemical signs of Hyperandrogenism Polycystic Ovaries (Two of three criteria needed)	Clinical and/or biochemical signs of Hyperandrogenism Ovarian Dysfunction (Oligo-anovulation and/or polycystic ovarian morphology) (Both criteria needed)

Table-1 Diagnostic Criteria for PCOS

2- Anovulation

According to the NIH conference in 1990, the anovulatory process was a chief manifestation of PCOS. Anovulation (the absence of ovulation) will likely cause menstrual irregularity in women with PCOS, with menstrual disturbances usually present in the form of oligo-amenorrhea that are longer than thirty-five days – a sign of anovulatory cycles – but usually fewer than six to eight cycles per year (Speroff & Fritz, 2011). In a significant percentage of studies, women who reported less than ten menstrual cycles per year were considered anovulatory. However, ovulatory dysfunction may also be present in women with PCOS who report regular menstrual cycles. The medical definition of chronic anovulation in PCOS is based on: (a) the exclusion of other causes of anovulation such as hyperprolactinemia and hypothyroidism, and (b) the measurement of progesterone values eight to twelve days prior to menstrual bleeding and/or the absence of corpus luteum determined through ultrasonography, for three consecutive cycles (Macut et al., 2013).

3- Polycystic Ovaries (PCO)

In women with PCOS, ovaries are enlarged, have a 2-3 fold increase in antral follicles as compared with normal ovaries (Webber et al,, 2007), and additionally an increase in ovarian stroma, theca cell proliferation, and ovarian cortical thickening (Dunaiff, 1997). These small antral follicles, i.e. the 2-3 fold increased follicles, are arranged peripherally around the ovarian cortex like a "string of pearls" (Balen et al., 2009). According to the 2003 Rotterdam criteria, polycystic ovaries are identified by twelve or more follicles in one ovary, with each follicle measuring 2–9 millimeters in diameter . The ovarian volume must be greater than $10cm^3$. However, other studies have suggested that lower limits of ovarian volume, as low as 7 cm^3, can also potentially be part of the PCOS diagnostic criteria (Lentz, 2012).

In a comparative study of ovarian cortical biopsy, twenty-four normal ovaries and thirty-two polycystic ovaries (sixteen with normal ovulation and sixteen with oligomenorrhea), it was found that the number of small preantral follicles in polycystic ovaries were substantially increased in anovulatory PCOS (Webber et al., 2003). In tissues from twelve anovulatory PCOS women and sixteen ovulatory women, the proportions of primordial follicles were reduced, whereas and the proportion of growing follicles reciprocally increased in comparison with normal ovaries. As well, there was a decreased atresia of follicles from PCO in culture (Webber et al., 2007). It should be noted that not all women with polycystic ovaries have PCOS, and not all women with PCOS have polycystic ovaries (Balen et al., 2009)

4- Pathogenesis of PCOS

A- Ovulation Dysfunction

Women with a history of ovulatory dysfunction consisting of amenorrhea or oligomenorrhea, or other forms of irregular uterine bleeding at the onset of puberty, have a 90% chance of being diagnosed with PCOS. Ovulation is typically irregular or absent in PCOS patients (Lentz, 2012), and this has been reported in up to 32% of their menstrual cycles (Fauser et al., 2012). Women with amenorrhea have severe hyperandrogenism, and a higher antral follicle count comparing to women with oligomenorrhea or regular cycles (Fauser et al., 2012). Still, not all PCOS patients have amenorrhea or oligomenorrhea, and additionally, PCOS may occur at different stages of their lives (Azziz et al., 2009). It has been postulated that PCOS may have a genetic link, due to the greater frequency of the disorder within the same familial networks (Yarak et al., 2005).

In a normal ovulatory menstrual cycle, in the follicular phase, there is an increase in hypothalamic releasing hormone (GnRH) which stimulates the anterior pituitary gland to produce the follicular stimulating hormone (FSH) which thereby stimulates the production of a new cohort of small antral follicles and the follicular cell lining, and thus producing the luteinizing hormone (LH). Within the ovarian follicle, the cell lining consists of theca cells and granulosa cells. The LH stimulates theca cells to produce androgens for the granulosa cells, whereas, the FSH stimulates the granulosa cells to convert androgens to estradiol (E2) by aromatase. Thereafter, ovarian follicles continue to develop and produce E2. An increased E2 levels signal the pituitary gland to reduce

the production of FSH produce LH, trigger ovulation, and release an egg from a dominant follicle, while the other follicles undergo atresia.

By contrast, in women affected with PCOS, the follicular growth is stunted by fluctuating hormones, which typically result from abnormal functioning of the hypothalamic-pituitary-ovarian (HPO) axis (Barber et al., 2010). This is verified increased levels of LH but reduced levels of FSH as compared with the levels found in women with normal ovulatory menstrual cycles, particularly in the early follicular phase (Futterweit, 2007). The increase in LH pulse frequency is characteristic of the anovulatory state (Melmed, 2011). The elevated LH levels indicate an increased sensitivity of the pituitary to GnRH stimulation, manifested by increases in LH pulse frequency and LH pulse amplitude (Speroff & Fritz, 2011), and by accelerated GnRH-LH pulsatile activity (Futterweit, 2007). An increase in amplitude and frequency of LH secretion also correlates with a raised plasma testosterone level (Barber et al., 2010). A low LH value does not rule out the diagnosis of PCOS, whereas a high LH/FSH ratio supports this diagnosis in an anovulatory woman (Melmed, 2011).

In this abnormal endocrine environment, many systems are involved. For example, in pathogenesis of PCOS, insulin resistance, insulin action, and hyperinsulinemia are common features of PCOS women (Lyttleton, 2004). There is an association between PCOS and insulin resistance and hyperinsulinemia, but this is not used as a requirement for the diagnosis thereof (Melmed, 2011). Insulin resistant is prevalent in 50-75% of obese and to lesser extent lean PCOS women. To compensate for increased insulin environment, their insulin sensitivity is decreased by an average of 30-40%. Furthermore, approximately 35% of PCOS women exhibit impaired glucose

tolerance and 7% - 10% meet the criteria for Type 2 Diabetes Mellitus (T2D), which increases the risk of developing cardiovascular disease (Speroff & Fritz, 2011). Therefore, elevated levels of insulin interacting with LH may likely be the contributing factor to anovulation in PCOS women (Baillargeon, 2005).

B- Hyperandrogenism

The primary requirement of diagnosis of PCOS is established with the clinical or biochemical presence of hyperandrogenism. Firstly, the clinical presentation is determined by idiopathic hirsutism (the presence of coarse facial and bodily hairs in females in a male-like pattern), acne, acanthosis nigricans (black brown hyper-pigmentation found in body folds), and alopecia (baldness) (Azziz, 2006). Hirsutism, i.e. excessive growth of facial or body hair in women, is most closely linked with androgen dependence, and is present in approximately 70% of women with PCOS (Fauser et al., 2012). The hormonal hyperandrogenic hair type is coarse, thickened, pigmented, and long known as terminal hair. There is a standardized scoring system for evaluating hirsutism known as modified Ferriman-Gallwey (mFG method). It is presented in nine body areas which consist of the upper lip, chin, and chest, upper and lower back, upper and lower abdomen, upper arm, and thigh. Each individual body area is visually scored on a scale of 0 to 4, where 0 indicates no terminal hair growth, and 4 indicates full male-pattern terminal hair growth (Cook, 2011).

The contributing factors to hirsutism consist of the potency of the androgen produced dihydrotestosterone (DHT), testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEA), the amount of androgen that is free, and the peripheral metabolism of androgens (primarily the intracellular production of DHT from

precursors). Several studies have reported a positive correlation between hirsutism and/or acne severity and circulating serum-free androgen levels (Liou et al., 2009). One of the etiological factors in acne is an increase in sebaceous gland activity, which is androgen dependent, and it is a common manifestation of PCOS (Timpatanapong, 1997). Polycystic ovaries have been found with ultrasonography in up to 45% of women with severe acne, elevated androgens (Melmed, 2011). Acne cases may have a higher levels of serum total testosterone (T), free T, dehydroepiandrosterone sulfate (DHEAS) and prolactin (PRL) (Timpatanapong & Rojanasakul , 1997). Another clinical presentation of hyperandrogenism is Acanthosis Nigricans.

Acanthosis Nigricans (AN) is characterized by velvety, hyperpigmentation, papillomatous, brownish-black, hyperkeratotic plaques, typically on the intertriginous surfaces and the neck (Dunaif, 1997). It is present in a majority of obese women with PCOS. However, a minority of lean women with PCOS have also exhibited the same. There is a correlation between the severity of AN with the degree of insulin resistance.

Secondly, the biochemical presentation is determined by high blood levels of androgen, testosterone is 2 ng/ml and (DHEA) up to 8 µg/ml (Melmed, 2011). Dr. Azziz demonstrated that 60% - 80% of PCOS patients have elevated levels of androgens circulating in their blood stream (Azziz, 2006). Obese women have higher serum T levels and anovulatory dysfunction than non-obese PCOS patients (Timpatanapong, 1997).

There is evidence suggesting that elevated serum insulin causes hyperandrogenism, which in turn leads to anovulation and infertility (Diamanti-

Kandarakis & Dunaif, 2012; Li et al., 2010). This is termed hyperinsulinemia - another cause of hyperandrogenism in PCOS women (Sönmez et al., 2005).

C- ***Insulin Resistant and Hyperinsulinemia***

In 1980, Burghen et al. reported that PCOS was associated with hyperinsulinemia, which indicated a relationship between insulin and gonadal function. Therefore, there is an increase in hyperinsulinemia which may directly cause premature follicle atresia and antral follicle arrest (Marthur et al, 2008). Insulin resistance is a major factor in PCOS (Dunaif, 1997), and it is more common in obese PCOS woman with 70-80% demonstrating insulin resistance and compensatory hyperinsulinemia (Hoeger, 2012). Essentially, there are two types of PCOS obesity: (1) women with the upper body obesity, a high prevalence towards androgens, which appear to encourage a male-type central obesity with an increased waist to hip ratio – known as android obesity (Hoeger, 2012), and (2) women with a lower body obesity, a high prevalence towards increased levels of estrogen – referred to as gynoid or peripheral obesity (Bohler et al., 2009).

Insulin resistance is characterized by an impaired glucose response to a specific amount of insulin (Melmed, 2011). Insulin causes biochemical changes through insulin receptors on the theca/interstitial cells distributed in the ovarian stroma, acting primarily through its own receptors and activating a signaling system. These contain α and β subunits of insulin and IGF-1 receptors, which are structurally alike, and use a similar signaling. Insulin resistance is involved in the reduction of insulin binding to its receptors, or defective receptor autophosphorylation due to insulin receptor mutation (Speroff & Fritz, 2011).

In the presence of insulin resistance, pancreatic β-cell insulin secretion increases to compensate for resistance. The increased insulin level stimulates adrenals and ovaries and the production of LH. Insulin enhances the transcription of the LH-β gene (*LHB*). In one study, it was shown that insulin production suppresses pituitary response to GnRH in normal women and in women with PCOS. These studies support the concept that insulin resistance or hyperinsulinemia may be responsible for abnormal gonadotropin release (Melmed, 2011). Insulin and LH act synergistically to stimulate androgen production in theca cells, causing theca cell hyperplasia. Unlike all the cells of the liver, muscles, and adipose tissues that are insulin resistant in PCOS women, the theca cells remain insulin sensitive (Speroff & Fritz, 2011). These androgens, when present in the blood stream, alter the feedback to the Hypothalamic-Pituitary-Ovarian axis (HPO axis), creating a chain reaction which first causes an increase of estrogen in relation to progesterone, which thereafter causes an increase in testosterone (T) and LH, and decrease in FSH. In normal ovulation, basal levels of LH and FSH hormones are equal ratio in the early part of the cycle. However, in women with PCOS, there are high basal levels of LH to FSH, a ratio of 3:1. LH and testosterone levels remain elevated throughout their menstrual cycle (Speroff & Fritz, 2011). Consequently, these increased levels block follicular development, thereby resulting in the degeneration of the follicles (Webber et al., 2007). The disruption of insulin signaling in the brain indicates that this pathway is important for ovulation and body weight regulation (Ke et al., 2003). As a result most PCOS patients have either/or a history of very long menstrual cycles coupled with heavy bleeding, amenorrhea, oligomenorrhea, and anovulation with scanty bleeding at the onset puberty.

High insulin concentration also inhibits hepatic sex-hormone binding globulin (SHBG) production. SHBG regulates the access of androgens to target tissues by binding to testosterone and estradiol, and decreasing the biological activities of these critical steroids. With high insulin concentration, the concentration of testosterone increase in PCOS patients by two mechanisms: suppressing SHBG and increasing the ovarian secretion of testosterone precursors (e.g., androstenedione) and (Nestler, 1998). The increase in free and total serum testosterone levels results in androgenic characteristics seen in hyperandrogenism (Futterweit, 2007). It has been suggested that insulin stimulates the cytochrome p450 17α hydroxylase, a steroidogenic enzyme that is necessary for biosynthesis of androgens, which in turn increases androgen production by the theca and adrenal cells (Wickenheisser et al., 2004). Insulin's effect on SHBG and cytochrome p450 17α hydroxylase may be another mechanism by which insulin causes hyperandrogenism in PCOS women (Wang & Yu, 2008).

Abnormalities in anovulatory PCOS are further demonstrated by abnormal granulosa cell hyperplasia, abnormal growth of oocytes, and the surroundings of granulosa cells. This observation suggests that the normal communication between oocytes and granulosa cells in these early growing follicles is altered. There is evidence that atypical follicle-to-follicle signaling of Anti-Müllerian Hormone (AMH) may play a part in abnormal folliculogenesis (Franks, 2008). AMH is a glycoprotein produced by granulosa cells of preantral follicles. It delays the primordial follicle growth, and diminishes the sensitivity of the ovarian follicle towards FSH (Parco et al., 2011). Therefore, it correlates with the number of preantral follicles. And, with the increase number of preantral follicles, the AMH is elevated in PCOS women, and shows the

intrinsic defect of individual granulosa cells (Homburg, 2013). Further evidence has shown that normal levels AMH ranged 3.64 +/- 1.51 ng/ml, whereas in PCOS patients they were 2-3 times the normal levels 10 +/- 2.28ng/ml, this being a good indicator for PCOS and infertility (Parco et al., 2011). Therefore, AMH likely plays an important role in the pathophysiology of anovulation (Homburg, 2013).

5-Management of PCOS

The goals of treating PCOS are to correct or prevent its immediate and long-term medical consequences which consist of regulating menstrual cycles, increasing ovulation, reducing the risk of developing endometrial hyperplasia and neoplasia, treating infertility, reducing the risk of developing type 2 diabetes, and hyperinsulinemia, and reducing the risk of developing cardiovascular disease.

The first line of treatment for PCOS involves life style changes, ie weight loss, diet, and exercise. These lifestyle modifications improve metabolic and reproductive functions, increase SHBG concentrations by reducing free androgen levels, and improving insulin sensitivity. A 2-5% weight reduction can result in significant improvement in metabolic and reproductive function (Speroff & Fritz, 2011)

Oral Contraceptives

From a western perspective, there are many treatment options for PCOS. Oral contraceptives (OCPs) have been a key component of the chronic treatment of polycystic ovary syndrome (PCOS) by regulating menstrual cycles and improving androgen excess. OCPs reduce hyperandrogenism by suppression of LH secretion as well as by stimulating SHBG production (Speroff & Fritz, 2011). For PCOS patients, OCPs may control the timing of ovarian stimulation, improve the follicular

development, and increase the duration of gonadotropin stimulation and consumption, but may cause moderate to severe OHSS (Wu et al., 2007).

An example of OCP is Diane-35 which contains ethinyl-estradiol 35µg and cyproterone acetate (2mg) in each tablet. Cyproterone acetate has anti-androgen and progestin activity which can inhibit the secretion of pituitary gonadotropin, particularly blocking androgen receptors, thereby reducing ovarian-source androgen secretion. Ethinyl-estradiol belongs to estrogens. Diane-35 can increase the serum SHBG in the liver, hence reducing free T, and improving hyperandrogenism characteristic such as acne and hirsutism. It can regulate menstruation and inhibit endometriosis (Kuek et al., 2011).

Clomiphene Citrate (Clomid)

Clomiphene Citrate (CC) is the initial method for ovulation induction in anovulatory PCOS patients. It acts by inhibiting the estrogen-negative feedback regulatory mechanism resulting in an increased secretion of FSH and LH (Speroff &Fritz, 2011). PCOS patients have a higher incidence of complications, such as ovarian hyperstimulation response with multiple follicular developments, which increases the risk of multiple pregnancies (4%–10%), particularly in obese PCOS women with clomiphene resistance, and may require a higher dosage (Kay, 2007). Clomiphene Ovarian hyperstimulation syndrome (OHSS) may occur, causing abdominal distension, enlarged ovaries, ascites, pleural and pericardial effusions, and complications of enhanced vascular permeability (Abdelhamid et al., 2012). Still more, it may cause thickening of the blood with an increased hematocrit and the risk of thromboembolic complications. There is a correlation between obesity and clomiphene

resistance, and that hyperinsulinemia may account for the poor responsiveness to clomiphene (Nestler et al., 1998). The starting dose of clomiphene citrate is 50 mg per day for five days, on the 2nd and the 5th day of menstruation. Menses may be first induced with a progestin. CC dosage can increase to 250 mg per day depending on the response of the patient (Speroff & Fritz, 2011). With CC treatment, there is discrepancy between ovulation and pregnancy rates (60%–85%) , which may be caused by the anti-estrogenic properties of clomiphene, causing poor thickening of cervical mucus and endometrial growth and development rendering the uterine environment hostile for conception (Kay, 2007).

Metformin (Glucophage)

Metformin is a biguanid anti-hyperglycemic medication, and it's used as an insulin sensitizer. It has various actions in tissues responding to insulin that include the liver, skeletal muscle, adipose tissue, the endothelium of blood vessels, and the ovaries (Weickert, 2012). Metformin has little impact on anovulation and hyperandrogenism. It is beneficial for PCOS women with insulin resistance, diabetes, impaired glucose tolerance, and other metabolic disorder such as dyslipidemia, obesity, and hypertension. It can be used as a preventative measure or slow the progression of type 2 diabetes, and long term risks of cardiovascular disorder (Speroff &Fritz, 2011). It's role in improving ovulation induction in PCOS women is through the following actions: reducing insulin levels and altering the effect of insulin on ovarian androgen biosynthesis, theca cell proliferation, and endometrial growth. Additionally, it inhibits ovarian gluconeogenesis and hence reduces ovarian androgen production (Mathur, 2008). In a study, Palomba et al., (2009) concluded that Metformin therapy was

effective in PCOS patients with insulin resistance and a low body mass index (BMI), whereas clomiphene citrate treatment was beneficial in less hyperandrogenic and insulin resistant PCOS with low BMI. Metformin is used alone or in combination with CC, especially in women who failed CC (Mathur, 2008). For the majority of PCOS women, a combination Metformin and CC will be required (Speroff & Fritz, 2011).

Side effects of Metformin consist of gastrointestinal symptoms such as of diarrhea, nausea, vomiting, abdomen discomfort, bloating, flatulence, indigestion, constipation, heartburn, and metallic taste. It can cause hypoglycemia, a condition of low blood sugar levels, and a long term use of it may cause Vitamin B12 malabsorption (Sperber, 2007).

Ovarian Drilling

Generally, surgical intervention is reserved for patients that are resistant to medical management. Laparoscopic ovarian diathermy (LOD) is a surgical procedure in which a small incision is made with electrical or laser equipment to burn holes in follicles on the surface of the ovaries to reduce circulating and intraovarian androgen levels and reduce the volume of ovarian stroma (Bates et al., 2012). Approximately 4 to 6 sites per ovaries are created (Speroff & Fritz, 2011). It has the most success in women with BMI less than 30 and an LH of greater than 10. There is a risk of adhesions or ovarian damage after ovarian diathermyin (Bates et al., 2012).

Traditional Chinese Medicine Perspective on PCOS

Definition and diagnosis of PCOS

In Traditional Chinese medicine, it is important to diagnose the patient according to her current symptoms and patterns which mark the foundation and progression of

disorder. Although there is no classification for PCOS within TCM, signs and symptoms presented can be grouped into to TCM categories such as amenorrhea and infertility (Song et al., 2009; Zhang et al., 2010). Rather, in TCM, PCOS is viewed as disorder of the kidney, liver, and spleen. For example, the kidney is responsible for reproductive functions, while at the same time the brain and emotions (Kuek et al., 2011). According to Maciocia (1998), PCOS is a disruption of the ovaries, which is attributed to kidney yang and phlegm/damp excess diagnosis.

This disruption affects the kidneys which governs the birth, growth, reproduction and development, and is responsible for all functions related to the uterus, fallopian tubes, ovaries, and hypothalamic pituitary ovarian axis (Lyttleton, 2004). When kidney yang is deficient for a long time, it leads to spleen qi deficiency. This causes spleen to fail to transform, evaporate, and transport fluids causing the body's metabolism to be severely hampered by congestion of stagnant fluids, and an accumulation in the form of phlegm and/or dampness. Therefore, according to TCM, it is the phlegm-damp which causes ovarian cysts, weight gain and even obesity, while the deficiency of kidney yang causes amenorrhea or infertility. This observation would suggest that the pathogenic factors causing polycystic ovarian disease are the same as those that cause ovarian cysts; the main difference is that PCOS is characterized by a constitutional deficiency of the kidneys (Maciocia, 1998). Tonification of kidneys can induce ovulation (Kuek et al., 2011; Zhang et al., 2010). Jane Lyttleton (2004) describes two different diagnoses for PCOS. The first type is kidney yang deficiency with phlegm damp accumulation and weight gain which conquers with Maciocia (1998). The kidney yang PCOS patient is overweight and has infrequent periods with anovulation. The second type is kidney yin

deficiency type of PCOS that is congenital, and it is due to Qi and blood deficiency or stagnation. Kidney yin deficiency easily manifests with deficiency heat symptoms such as high testosterone levels, acne and an increase in growth of body hair. The follicles are the responsibility of Kidney jing. For example, if the follicles don't mature do to estradiol – low FSH /high testosterone levels – this is interpreted as kidney yin-jing deficient.

The disruption of the menstrual cycle relates to the disturbance of the Chong (i.e. the penetrating vessels or the "sea of blood") and Ren (i.e. the conception vessel or the "sea of yin") which are governed by the Kidneys. Fibrosis of the ovarian casing represents blood stasis. The goals of the TCM treatments are to regulate the menstrual cycle from the correct cooperation of hypothalamus, pituitary, and the ovaries.

Song and colleagues (2006) , in a 2006 review, related PCOS to Shen (kidney) deficiency and blood stasis with phlegm-dampness, as well as Qi stagnation. The treatment consists of herbs to replenish Shen, activate blood circulation to remove stasis, dissolve damp phlegm, sooth the Qi, and clear heat. The herbs which replenish Shen could have an endocrine hormone like effect, showing bidirectional regulatory action on gonadal axis, and may elevate the receptivity of endometrium to the fetus. The herbal combination can increase local blood circulation in the ovary, which promotes follicular development, induces ovulation and promotes corpus luteum formation.

Certain Chinese clinicians used the LH/FSH ratio to determine the TCM diagnosis. An LH/FSH ratio less than 2.0 indicates kidney yin deficiency, and greater than 2.5 indicate kidney yang deficiency with phlegm-damp accumulation (Lyttleton, 2004). Chinese medicine treatment protocol is to regulate menstruation and induce ovulation. This initially requires clearing the excess: phlegm-damp, and tonifying the

deficiency: yin and blood all together. And as signs of ovulation develop, kidney yang will be strongly boosted to promote ovulation. Chinese medicine may be used as an effective modality in regulating menstruation and inducing ovulation in anovulatory PCOS patients alone or in combination with western medicine by affecting the endocrine and ovarian function.

Treating PCOS with Chinese Herbs:

The herbal formula Unkei-to (Wen Jing Tang) was presented in the following three researches based in Japan. Firstly, in clinical research in 2001, Ushiroyama measured the effectiveness of the Unkei-to (Wen Jing Tang) for reducing high LH levels and improving ovulation disorder. Wen Jing Tang (WJT), known as Warm the Channel Decoction, contains Wu Zhu Yu (Evodiae Fruit) 1.0g, Gui Zhi (Cinnamomi Bark) 2.0g, Dang Gui (Japanese Angelicae Root) 3.0g, Chuan Xiong (Cnidium Rhizome) 2.0g, Shao Yao (Radix Alba Paeoniae) 2.0g, Mu Dan Pi (Moutan Bark) 2.0g, E Jiao (Gelatin) 2.0g, Mai Men Dong (Ophiopogonis Tube) 4.0g, Ren Shen (Ginseng Root) 2.0g, Gan Cao (Glycyrrhizae Root) 2.0g, Ban Xia (Pinelliae Tuber) 40g, Sheng Jiang (Ginger Rhizoma) 1.0g (Ushiroyama et al., 2006). In this research, hundred patients with ovulation disorder and an LH level of at least 10 mIU/ml were recruited. Thirty-eight of the patients, with an age range of between ages 21 to 32 years, were diagnosed with PCOS. The endocrine levels of FSH, LH, estradiol basal levels, and follicular growth of fifty-two subjects were measured and compared to forty-eight subjects who were given placebo. The WJT was orally administered for eight weeks. The result indicated that treatment with WJT induced significant decrease in Plasma LH in PCOS and non-PCOS patients. The reduction of serum LH level 45.5% of PCOS and 80% non-PCOS were observed. The

mean rate of reduction of serum LH was 22.2% +/- 35.7% in PCOS patients and 49.7% +/- 15.3% in non-PCOS patients. The rate of improvement in the menstrual cycle, including ovulation was 50.0% in PCOS, and 60.0% in non-PCOS patients. The plasma estradiol increased 43.5%. There was a significant development of the dominant follicle was observed. This study demonstrated that WJT can affect and improve the endocrine function in PCOS patients by reducing plasma levels of LH and increasing estradiol, which in effect improved the menstrual cycle and induced ovulation.

In 2006, Ushiroyama and colleagues researched Wen Jing Tang's effectiveness in lowering basal plasma levels of LH and increasing ovulation with using the eight principle pattern identification and Kampo diagnosis based on Qi, blood, and fluids or the five viscera. In this study, sixty-four anovulatory PCOS patients were diagnosed with the above criteria, forty-three patients took Dang Gui Shao Yao San, and twenty-one patients were given Gui Zhi Fu Ling Wan. Dang Gui Shao Yao San consist of Dang Gui (Japanese Angelicae Root) 3.0g, Shao Yao (Peony Root) 4.0g, Fu Ling (Hoelen, Subterranean Fungus) 4.0g , Cang Zhu (Atractylodis Lancea Rhizome) 4.0g, Ze Xie (Alismatis Rhizome, Water Plantain Rhizome) 4.0g, and Chuan Xiong (Cnidium Rhizome) 3.0g. Gui Zhi Fu Ling Wan consist of Gui Zhi (Cinnamon Bark) 4.0g, Fu ling (Hoelen, Subterranean Fungus) 3.0g, Shao Yao (Peony Root) 3.0g, Mu Dan Pi (Moutan Bark) 3.0g, and Tao Ren (Peach Kernel) 3.0g. After eight weeks of administration, fifty-four patients failed to ovulate. Therefore for the next eight weeks, twenty-seven patients continued the previous prescriptions, and the other twenty-seven were administered Wen Jing Tang. Plasma levels of FSH and LH were measured before after the first eight treatments, and with the final treatment. It was reported that LH plasma levels were

reduced by 58.2% ($p<0.0001$) in patients receiving Wen Jing Tang, there was no significant change in FSH levels. The ovulation rate with the switching to Wen jing Tang was 59.3% higher than the continued use of Kampo preparation (7.4%, P=0.0036). It was concluded that Wen Jing Tang can improve the endocrine condition in the treatment regardless of 8 principle diagnosis, which is appropriate for use in treating PCOS with various constitutions (Ushiroyama et al., 2006)

Sun and colleagues (2004) investigated the in vivo effects of Wen Jing tang and its compounds on the steroidogenesis and cytokine secretion in human granulosa cells to prove its ovulation-inducing effect. The properties of WJT: Bai Shao and Gui Zhi stimulated the secretions of 17 beta-estradiol and progesterone from highly luteinized granulosa cells obtained from in vitro fertilization patients. The stimulated effect on the estradiol secretion occurred with 0.3 mcg/ml, while a significant effect was observed with the progesterone secretion which was occurred with 10 mcg/ml. These results indicate that Wen Jing tang has direct stimulatory effects on human granulosa cells to stimulate the steroidogenesis, and the ovulatory process within the ovary, as well as a stimulatory effect on the hypothalamus-pituitary axis (Sun et al., 2004).

The following research focused on the empirical formula of Dr. Chai Hao-yan, in which thirty-two PCOS patients were observed. Eighteen of these patients had previously been treated with western medicine for six months to six years. However, when they stopped their treatments, there was no improvement in their symptoms. All the women in this study were administered the empirical formula of Dr. Chai Hao-yan: Tu Si Zi (Semen Cuscutae Chinensis), Che Qian Zi (Semen Plantaginis), Yin Yang Huo (Herba Epimedii), Du Zhong (Cortex Eucommiae Ulmoidis), Dang Gui (Radix Angelicae

Sinensis), Tao Ren (Semen Pruni Persicae), Yi Yi Ren (Semen Coicis LachrymaJobi), and Chuan Xiong (Radix Ligustici Wallichii. Continuous treatment for six months equaled one course of treatment, and treatment outcomes were assessed after 1-3 (6 months to 18 months) such courses. The treatment was assessed as "cured" which is defined as: conception, normalization of menstrual cycles, and/or normal BBT curves plus a return to normal of serum hormone levels and ratios. Some effect meant that the menstrual cycle improved (more than six times a year), improvement in clinical signs and symptoms, and improvement in serum hormone levels and ratios. No effect meant that there was no obvious improvement in clinical symptoms or laboratory analyses (Ling, 2002). Based on these criteria, fourteen cases (43.75%) were judged cured, while the total effectiveness rate was 90.62% or twenty-nine out of thirty-two cases. However, total effectiveness was never defined. Eleven out of the sixteen women conceived. The conception rate was 68.75%. In addition, there was a significant mean reduction in BMI in women with BMI greater than twenty-five, while there was no statistically significant change in mean BMI in women with a BMI of less than twenty-five. There was a significant mean reduction in testosterone levels, LH levels, and improvement in insulin resistance (IR) after treatment as measured by oral glucose tolerance testing (OGTT). Tu Si Zi and Che Qian Zi functions are to warm the kidneys, and nourish the spleen, free the Qi, and transform phlegm. The combination of Dang Gui and Tao Ren nourishes the blood, disperses nodulation, and moves stagnation. Yi Yi Ren, Du Zhong, and Yin Yang Huo strengthen the spleen and the kidneys, and transform dampness. Chuan Xiong guides the blood downward to the Chong, as well as guides all the other herbs to the site of the disorder (Flaws, 2003).

A Japanese formula known as Sairei-to known as Chai Ling Tang- Bupleurum and Poria Decoction in Chinese medicine was discussed in 2 articles. These articles were based in Japan. The steroidal effect in anovulatory PCOS patients was discussed in the first article by Sakai and colleagues. Sairei-to is comprised of two formulas: Xiao Chai Hu Tang (Minor Bupleurum Decoction) and Wu Ling San (Five Ingredient Powder with Poria). Its therapeutic action consists of harmonizing the exterior and the interior, resolving dampness, and promoting the flow of yang qi. It is composed of Chai Hu (Radix Bupleuri) , Ban Xia (Rhizoma Pinelliae), Huang Qin (Radix Scutelliae) , Ren Shen (Radix et Rhizoma Ginseng) , Gan Cao (Radix et Rhizoma Glycyrrhizae) , Bai Zhu (Rhizoma Atractlodis macrocephalae), Zhu Ling (Polyporus), Fu Ling (Poria), Ze Xie (Rhizoma Alismastis), Gui Zhi (Ramulus Cinnamomi) (Chen & Chen, 2009). Sairei-to stimulated ovulation in 70.6% of anovulatory PCOS patients. There was a significant reduction of serum LH and LH/FSH ratio. However, the serum testosterone levels did not significantly change. It was concluded that steroidal medicine such Sairei-to is effective in PCOS patients, especially in ovulation (Sakai et al., 1999).

In another study, twenty-four PCOS patients, nineteen to thirty-five years old, received Saireito for three months. Serum LH, FSH, PRL, T, E2, ACTH, and Cortisol levels were measured before and after treatment and ovulation was assessed. Serum LH levels were compared ovulation group (n=21), and anovulation group (n=3) , and ovulation rates and serum LH levels between obese (n=6) and non-obese (n=18) groups. Ovulation was restored in twenty-one of twenty-four PCOS patients (87.5%). It was concluded that Sairei-to reduced serum LH levels and increased ovulatory rate (87.5%), particularly in non-obese women (94.4%). With Use of this formula, there was a single

follicular growth without any side effect. It may shift the regulatory effect of pulsation of GnRH to balance positive negative feedback response HPO axis (Okamoto et al., 2010).

Hui Shu Hua was discussed in two studies. In the first study, it was compared to Shakuyaku-Kanzo-To (Shao Yao Gan Cao, SKT). In a later study, comparison was made with clomiphene citrate. Hui Shu Hua (Maitake mushroom- SX-fraction, SX) and Shakuyaku-Kanzo-To (Shao Yao Gan Cao, SKT) were administered to determine their effects on ovulation in PCOS patients. Hui Shu Hua has been shown to have a potent immune stimulatory effect. It has been demonstrated to reduce elevated glucose levels, reduces blood pressure, and modulates serum lipids. The bioactive SX-fraction is a water soluble glycoprotein, and it improves insulin resistance and associated clinical symptoms (Chen et al., 2010; Tominaga et al., 2011). The Traditional Chinese Medicine: Shao Yao Gan Cao (Kampo formula: Shakuyaku-Kanzo-To) consist of Gan Cao (Glycyrrhiza glabra) and Bai Shao (Paeonia lactiflora). This formula has been shown to effect the hormonal regulation of androgens by lowering testosterone. It has been suggested that it acts directly on the ovary, increasing the activity of aromatase, which promotes the synthesis of estradiol from testosterone, thus lowering serum testosterone levels. Thirty patients were randomly assigned to either of the following two treatment groups for three months: the SX group consisted of fifteen patients, who prescribed 207 mg/day of Hui Shu Hua SX, and fifteen patients in the control group, which received 7.5 g/day of SKT. Ovulation was determined by the change of basal body temperature and ultrasonography. During the treatment period, 66.7% of patients in the Hui Shu Hua SX group ovulated compared with 30.8 % in the SKT group; however, the difference was not statistically significant ($p = 0.0581$). During the same period, ovulation was confirmed in twenty-two

out of forty-five menstrual cycles (48.9%) in Hui Shu Hua SX group, while for SKT group ovulation was confirmed in 15.4% (P = 0.0011). Estradiol and the estradiol/testosterone ratio also showed a statistically significant increase (P = 0.032 and 0.038, respectively) when those compared before and after treatment with SX. The SX group was 14 times more likely than the SKT group to induce ovulation (95% CI: 1.093 – 196.45). It was concluded that SX was effective in the treatment of PCOS, and SX improved the ovulation rate independent of insulin resistance, and it appears to promote aromatization of testosterone to estradiol in granulosa cells (Tominaga et al., 2011).

In a review by Song et al. (2006), He demonstrated that Chinese herbs could regulate the endocrinilogical mechanism by elevating the response of the ovary to LH, regulating the function of HPO axis, promoting the development of follicles, restoring the menstrual cycle, ameliorating pregnancy disturbances. He treated forty-six PCOS women with Chinese herbs based on the four phase menstrual cycle. The base formula consisted of Yin Yang Huo (Epimedium) 30g, Xian Mao (Curculigo Rhizoma) 10g, Tu Si Zi (Dodder Seed) 30g, Lu Jiao Shuang (Deglatinated Deerhorn) 30g, Han Lian Cao (Eclipta) 30g, Nu Zhen Zi (Glossy Privet)30g, Dang Gui (Chinese Angelica) 15g, Chuan Xiong (Rhizoma Chuan Xiong) 10g, Yi Mu Cao (Motherwort) 15g, Sha Yuan Ji Li (Milkvetch)15g, Gan Cao (Licorice) 6g. The base formula can be modified according to different phases. In follicular phase, Gou Qi Zi (Wolfberry) 30g and Huang Jing (Solomonseal) 30g was added to nourish yin and regulate the Chong. In pre-ovulatory phase, Dan Shen (Red Sage Root), Ze Lan (Bugleweed), and Xiang Fu (Cyperus Tuber) was added to regulate qi and activate blood. Post ovulation phase, Du Zhong (Eucommia), Xu Duan (Teasel Root), Sang Ji Shen (Mulberry Mistletoe), and E Jiao

(Ass-Hide Gelatin) were used to tonify yang. And in the premenstrual cycle, Chuan Niu Xi (Cyanthula Root), Tao Ren (Peach Kernel), Hong Hua (Safflower), Yu Jin (Zedoary Tumeric), and San Leng (Burreed Tuber). Complications were also addressed with herbal modifications. For example, if the size of an ovary increased, herbs to soften and resolve hard masses were added, such as Xia Ku Cao (Prunella), Kun Bu (Kelp), and Shan Ci Gu (Pleione).With prolong amenorrhea, with sign and symptoms of blood stasis, herbs that up break blood stagnation were added, such as Shui Zhi (Leech), Meng Chong (Gladfly), and Tu Bie Chong (Groundbeetle). The result of this study showed ten of the forty-six patients got pregnant (21.7%), and thirty patients restored menstrual cycles accompanied with biphasic BBT charts, reduction in BMI, WHR, T levels, and increased E2.

In another study, Wang and Yu (2008) demonstrated the effects of Bushen Huayu Qutan recipe (BHQR) to promote ovulation, and balance the local environment of ovaries. BHQR consist of Dang Gui 15g, Chi Shao Yao10g, Bai Shao Yao 10g, Wa Leng Zi 15g, Sang Shen Zi 20g, Gou Qi Zi 20g, Zhi He Shou Wu 18g, Mai Men Dong 12g. Fifteen androgen-sterilized rats (ASR) were intragastrically administered BHQR for thirty days, and these rats were compared to fifteen normal rats and fifteen ASR which were administered distill water. Levels of serum testosterone, insulin, inhibin (INH), the expression of insulin-like growth factor (IGF-1), and vascular endothelial growth factors (VEGF) were measured and compared to the untreated rats. The results consisted of all the normal rats ovulated, and 66.67% of BHQR, and none of ASR. The serum T and INS, in BHQR decreased compared to the untreated group ($P<0.05$). The ovarian INH, IGF-1,

and VEGF were higher in untreated group than the normal group (P<0.01). And, the BHQR group levels decreased compared to the untreated group.

In 2010, Li and associates explored the molecular mechanism of Chinese herbal formula Bushen Tongmai recipe (BSTMR) on PCO. BSTMR consists of Huang Qi (Astragulus membranaceus Bge), He Shou Wu (Radix Polygoni Multiflori), Rou Cong Rong (Herba Cistanches), Dan Shen (Radix Salviae Miltirrhizae), San Qi (Radix Notoginseng), Ge Gen (Radix Puerariae), Yin Yang Huo (Herba Epimedii), Chuan Xiong (Rhizoma Chuan Xiong), Shu Di Huang (Radix Rehmanniae). PCO rats were divided into two groups, normal rats as the control group (n=15), the model group with PCO (=23), and BSTMR group (n=21), which received treatment for two weeks. The histological changes in the ovaries were observed in all three groups, as well as fasting blood glucose (FBG), serum fasting insulin (FINS), and insulin sensitivity index (1/FBGxFINS). The mRNA level of protein kinase B α (PKBα) was measured by reverse transcription polymerase chain reaction (RT-PCR). The results demonstrated that in comparison to the control group, the untreated group showed multiple follicular cysts, and the levels of FBG and FINS were increased (p<0.05 or P<0.01). The mRNA and protein expression of PKBα were low However, the BSTMR group's stratum granulosa of the ovarian follicle increased, and the mRNA and protein expressions of PKBα were elevated. The authors concluded that BSTMR could improve insulin resistance (IR) and ovulation dysfunction in PCO rats with IR. Chinese medicine and diagnosis and treatment method was shown to reduce insulin levels, serum testosterone, induce ovulation, regulate menstruation, regulate biphasic BBT chart, and help patients conceive. In Jia and Wang study, forty-three PCOS patients were divided in two groups:

twenty patients with Kidney Yin deficiency diagnosis and eighteen with Sp Qi deficiency diagnosis. The herbal formula for nourish the kidney yin and cleat heat consist of: Sheng Di Huang 10g, Gui Ban 10g, Ze xie 10g, Huang Bai 6g, Zhi Mu 6g, Sheng Gan Cao 6g. And, the herbs to tonify Sp Qi were Dang Shen 10g, Cao Bai Zhu 10g, Fu Ling 10g, Gan Cao 6g, Chen pi 6g, Ban Xia 6g. The result indicated with the use of Kidney Yin nourishing herbs, serum levels of T were reduced significantly. This infers the interrelations of between elevated testosterone levels and Kidney Yin deficiency. PCOS patients diagnosed with SP Qi deficiency experienced a significant decrease in insulin levels. There is a relationship with SP Qi deficiency and PCOS and hyperinsulinemia. Twenty out of twenty-five PCOS subjects ovulated and had a biphasic BBT. Eighteen patients had regular menstruation ranging between twenty eight to forty days, and nine patients conceived. It should be mentioned three out of twenty-five patients did not have any changes (Li et al., 2010).

Treating PCOS with Chinese Herb and Western Medicine:

A meta-analysis research by Han et al., (2008), they investigated whether Chinese herbs could improve Clomiphene Citrate (CC) treatment outcome in PCOS patients. The herbs chosen were herbs which promoted blood circulation, and enforced the function of reproductive system such as Ying Yang Huo (Herba Epimedii), Shu Di Huang (Prepared Radix Rehmanniae), Ban Xia (Rhizoma Pinelliae), Dan Shen (Radix et Rhizoma Salviae Miltiorrhizae), and other herbs with similar functions. Systematic review and meta-analysis of randomized controlled trials (RCT) and controlled clinical trials (CCT) were utilized to compare the treatment outcomes of using CC alone and CC with Chinese herbs

in PCOS patients. A total of three hundred and eighty-two relevant studies and review articles were retrieved and examined to select RCT and CCT. In the selected trials, all patients were given 50-100 mg of CC daily starting from day five of menstruation for five days. Herb decoctions were given to patients in the experimental group from the day of starting CC for ten days or throughout the menstrual cycle. After receiving treatment for three cycles, patients were considered cured by achieved pregnancies, or had three continual regular cycles each with ovulation confirmed by biphasic body temperature, or by transvaginal sonography and mid-luteal phase progesterone level. It was concluded that the CC treatment outcome in PCOS patients may be significantly improved by using Chinese herbs (Han et al., 2008).

In a clinical study, Yang and Zhang (2005) treated twenty-seven PCOS patients with clomiphene citrate resistance (CC-resistant) to assess improvement CC-resistant with GanShao Capsules (GSC). GSC ingredients were not available. Twenty-seven hyperandrogenic PCOS patients were administered GSC for 8 weeks. Changes in serum reproductive hormones, BMI, adverse reaction, pelvic ultrasonographic feature (US) were observed before and after the treatment. After the use of GSC, CC was used on patients with anovulation and serum testosterone level less than 2.1nmol/L. Serum reproductive hormones were significantly changed after four weeks. After eight weeks of GSC treatments, bilateral ovarian volume, number and diameter of follicles reduce, and endometrium thinned. Within two months of cessation of GSC, 6 of 27 patients had regular ovulation, and two got pregnant. The other nineteen patients received CC during 37^{th} cycles, seventeen ovulated in 25^{th} cycles, and seven got pregnant. The ovulation rate was 89.5%, the ovulation cycle rate 67.6%, the pregnancy rate 36.8%, and the pregnant

cycle rate 28.0%. It was concluded that ovarian morphology, endometrium, BMI, and sensitivity to ovulation via CC induction were improved.

Hua and colleagues (2003) observed a hundred and seven PCOS patients to determine the effect of Yishen Jianpi Yangxue Tongli Therapy (YJYTT), translated as tonify Kidney, strengthen Spleen, nourish Blood, eliminate on PCOS, and explore its therapeutic mechanism. The formula used is the empirical formula of Dr. Chai Hao-Yan : Tu Si Zi (Semen Cuscutae Chinensis) 12g, Che Qian Zi (Semen Plantaginis) 10g, Yin Yang Huo (Herba Epimedii) 10g, Du Zhong (Cortex Eucommiae Ulmoidis)10g, Dang Gui (Radix Angelicae Sinensis) 10g, Tao Ren (Semen Pruni Persicae) 10g, Yi Yi Ren (Semen Coicis LachrymaJobi), 10g, and Chuan Xiong (Radix Ligustici Wallichii) 3g. With syndrome differentiation of TCM, patients were randomly divided into two groups, the treated group (n = 76) received Chinese herbal medicine, while the control group (n = 31) received clomiphene. The therapeutic effect in both groups and the change of body mass index (BMI), Ferriman-Gallway (F-G) score, serum sex hormones and serum glucose tolerance test (OGTT) before and after treatment were observed. The comparison of the total effective rate between two groups was insignificantly different, but pregnancy rate of the treated group (65.7%) was markedly higher than that of the control group (25.0%, $P < 0.01$). Also, the significant difference was shown in the aspect of BMI, F-G score, T, LH and OGTT, etc. between the two groups ($p < 0.05$). The YJYTT could markedly improve the clinical symptoms and the pregnancy rate, particularly showing good effect to the clomiphene resistant patients. The mechanism possibly was due to its regulation on hypothalamus-pituitary-ovarian axis and reducing the insulin resistance (IR) and inducing ovulation (Ling et al, 2002).

A study was conducted on the effects of Shen invigorating and Chong-channel Regulating Method (SCRM) on AMH and its effect on oocytes quality and follicular fluid in the PCOS patients. The subject consisted of sixty PCOS patients undergoing IVF and embryo transfer (IVF-ET) who were divided in two groups: thirty patients received ErZhi Tian Gui granule combined with Western medicine, and the other thirty patients received only Western medicine. The ingredients for ErZhi Tian Gui consist of Nu Zhen Zi (Fructus Ligustri Lucidi), Han Lian Cao (Herba Ecliptae), Gou Qi Zi (Fructus Lycii), Tu Si Zi (Semen Cuscutae), Dang Gui (Radix Angelicae Sinensis), Bai Shao (Radix Paeoniae Albae), Sheng Di Huang (uncooked Radix Rehmanniae), Chuan Xiong (Rhizoma Chuanxiong), processed Xiang Fu (Rhizoma Cyperi), Gan Cao (Radix Glycyrrhizae) . The following was observed in both groups: single oocyte estradiol (E2) level, the number of follicles, the high quality oocyte rate, the fertilization rate, the cleavage rate, the high quality embryo rate, and the difference of AMH in the serum and the follicular fluid. The correlation tests were performed between the levels of AMH in the serum and the follicular fluid and rates of high quality oocyte and high quality embryo. It was reported that the single oocyte E2 level, the high quality oocyte rate, the fertilization rate, and the high quality embryo rate was significantly higher in the treatment group than in the control group. And, the levels of AMH in the serum and the follicular fluid were lower in the treatment group than in the control group. The AMH levels in the serum and the follicle fluid were positively correlated. The level of AMH in the follicular fluid was negatively correlated with the high quality oocyte rate and the high quality embryo rate. ErZhi Tian Gui granules improved the oocyte quality of PCOS patients. Its mechanisms were correlated with regulating the AMH levels in the serum

and the follicular fluid, adjusting the androgen level, improving the pathophysiological changes of PCOS patients, and activating the ovarian microenvironment (Lian & Zhao, 2012).

A clinical trial examined the efficacy of Tian Gui Capsule in PCOS patients with kidney yin deficiency and internal heat diagnosis, and compared its effects with metformin and ethinyl estradiol plus cyproterone acetate (Diane-35). Tian Gui Capsule consists of Shu Di Huang (Radix Rehmanniae), Zhi Mu (Rhizoma Anemarrhenae Asphodeloidis), Yin Yang Huo (Herba Epimedii), Huang Jing (Rhizoma Polygonati Sibrici), Dang Gui (Radix Angelicae Sinensis), Tao Ren (Semen Persicae), Shi Chang Pu (Rhizoma Acori Graminei), Gui Jia (Carapa et Plastram Testudinis), Bu Gu Zhi (Fructus Psoraleae Corylifoliae), Hu Zhang Gen (Radix Polygoni Cuspidati), and Ma Bian Cao (Herba Verbenae).Forty-seven PCOS patients were divided into three groups. In group A, nineteen patients were given Tian Gui Capsule; in group B, seventeen patients were given metformin, and in group C eleven patients were given Diane-35. The three groups of patients were treated for three months. The following serum levels were measured before and after the treatment: serum testosterone (T), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S) levels, free androgen index (FAI), fasting blood glucose (FPG), fasting insulin (FINS), homeostasis model assessment of insulin resistance (HOMA-IR), insulin sensitive index (ISI), and left and right ovary volumes of the 3 groups. After three months of treatment, it was concluded that the effects of Tian Gui treats PCOS by regulating ovarian functions and reducing blood insulin level without inhibiting the function of the hypothalamic-pituitary-ovarian axis. It

should be noted that metformin had a significant effect on hyperinsulinemia, and Diane-35 had a significant effect on hyperandrogenism (Kuek et al., 2011).

Hou and research partners (2000) observed the efficacy of Chinese herbal formula Tian Gui Fang (TGF) in PCOS patients with hyperandrogenism and hyperinsulinemia in comparison with metformin. The ingredients were not discussed. Twenty-two CC-resistant patients were divided into two treatment groups: ten received TGF and twelve received metformin for three months. Serum level of LH, FSH, T, E2 and waist to hip ratio (WHR), body mass index (BMI), and insulin tolerance test during an oral glucose tolerance test were measured before and after treatment. After three months, the TGF patients' insulin levels, log T/E2, WHR, and BMI reduced. Six out of eight patients had restored menstruation and ovulation with confirmation of biphasic BBT. Metformin patients also had a reduction of insulin and log T/E2, but not a significant change in WHR and BMI. It was concluded that TGF was better in promoting ovulation, regulating menstruation, and improving insulin resistance; whereas, metformin was better at lowering insulin. Also, metformin was shown to improve the ovaries, help follicular maturation, and increase the ovulation rate without any risk of multiple pregnancy. It was suggested that both medicines could improve clinical efficacy.

In a Cochrane collaboration review, meta-analysis was conducted in 2010 to evaluate the efficacy and safety of Chinese herbal medicine (CHM) for subfertile women with PCOS. In addition, all reference listed of included trials were searched and experts and researchers were contacted to locate trials. The selection criteria were randomized controlled trials (RCT) including the use of CHM for the treatment of infertile women

with PCOS. Four RCTs involved three hundred and forty-four patients. There was no evidence of statistically significant difference in improving ovulation rate per PCOS patient between CHM and clomiphene (odds ratio 1.42, 95% confidence intervals 0.19 to 10.49), between CHM plus laparoscopic ovarian drilling (LOD) and LOD (odds ratio 2.43, 95% confidence interval 0.39 to 15.08). There were no statistically significant differences between CHM plus follicle aspiration, ovulation induction and follicle aspiration plus ovulation induction for adverse events including LUFS, OHSS and multiple pregnancies. There was evidence of statistically significant difference seen improving pregnancy rate per patient between CHM plus clomiphene and clomiphene (odds ratio 2.97, 95% confidence intervals 1.71 to 5.17). This systematic review concluded that there was no statistically significant difference seen in the other comparison groups for improving pregnancy rate. Live birth rate was not reported by any of the studies. There is limited evidence that the addition of CHM to clomiphene is associated with improved clinical pregnancy outcomes. There is insufficient evidence to support using CHM in treating PCOS women (Zhang et al., 2010).

In a research study, Tao and associates (2003) evaluated the effect of Chinese herbal medicine with western medicine compound Cyproterone Acetate (CPA). In this study, 86 PCOS women were divided in three groups. The TCM group, twenty-six patients received Chinese Herbal medicine for six menstrual cycles based on TCM diagnosis, Shen deficiency with blood stasis, or Shen deficiency and Phlegm dampness syndrome, and the different menstrual cycles: follicular phase, ovulation phase, luteal phase, and menstruation. In follicular phase, Shen deficiency with blood stasis patients received modified GuiShao Di Huang Decoction: Shu Di Huang (Prepared Rehmania

Root) 10g, Shan Zhu Yu (Dogwood Fruit) 9g, Shan Yao (Chinese Yam) 10g, Gou Qi Zi (Wolfberry) 10g, Bai Shao (White Peony Root) 10g, Fu Ling (Poria) 10g, Ze Xie (Water Plantain Tuber) 9g, Mu Dan Pi (Moutan Bark) 15g, Xu Duan (Teasel Root) 10g, Tu Zi Si (Dodder Seed)15g, Dang Gui (Chinese Angelicae Root) 10g, Huai Niu Xi (Twoteethed Achyranthes) 12g to nourish the yin and blood with yang herbs assisting to improve the cervical mucous. In Ovulation Phase, Cupailuan Decoction was prescribed to activate blood circulation, improve the blood supply to the uterus and ovaries, and promote ovulation. It consists of Zi Shi Ying (Amethyst) 30g, Dang Gui (Chinese Angelicae Root) 10g, Chi Shao (Red Peony Root) 10g, Bai Shao (White peony Root) 10g, Xiang Fu (Cyperus Tuber)10g, Lu Jiao Shuang (Degelatinated Deerhorn)10g, Tao Ren (Peach Kernel) 10g, Hong Hua (Safflower) 8g, Gou Qi Zi (wolfberry) 10g, Yi Mu Cao (Motherwort Fruit) 10g, Yin Yang Huo (Epimedium) 10g. In Luteal Phase, Modified Yulingzhu Decoction was used to nourish Shen, yin and yang to support corpus luteum. The ingredients consist of : Tu Si Zi (Dodder Seed) 15g, Du Zhong (Eucommia) 10g, Zi He Che (Human Placenta) 10g, Lu Jiao Shuang (Degelatinated Deerhorn) 10g, Shu Di Huang (Prepared Rehmania Root) 10g, Bai Shao (White peony Root) 10g, Dang Shen (Asiabell Root) 10g, Bai Zhu (White Atracylodes Tuber)10g, Fu Ling (Poria)10g, Gan Cao (Licorice Root) 6g, Mu Dan Pi (Moutan Bark) 15g. Jie Nei Jin (Chicken Gizzard-skin) 15g. In menstrual phase, modified Shixiosan was prescribed which consisted of Pu Hong (Typha) 10g, Wu Ling Zi (Trogopterus Dung) 6g, Xiang Fu (Cyperus Tuber) 10g, Wu Yao (Lindera Root) 10g, Ze Lan (Bugleweed) 10g, Chuan Niu Xi (Cyanthula Root) 10g, Qian Cao (Madder Root) 10g, Yi Mu Cao(Motherwort) 30g, Shan Zha (Hawthorn Fruit)15g, He Shou Wu (Prepared Fleeceflower Root)10g, Xu Duan (Teasel Root) 10g,

Tu Si Zi (Dodder Seed) 15g. However, to the patients with Shen deficiency phlegm/damp syndrome, the formulas were adjusted. In follicular phase, they received herbs to tonify shen and resolve Phlegm, modified Shenqiwan combined with CangFu Dao tan. It consists of Yin Yang Huo (epimedium) 10g, Rou Gui (Cassia Bark) 5g, Shu Di Huang (Prepared Rehmania Root) 9g, Shan Yao (Chinese Yam) 9g, Shan Zhu Yu (Dogwood Fruit) 9g, Mu Dan Pi (Moutan Bark)10g, Fu Ling (Poria) 10g, Ze Xie (Water-Pantain Tuber) 10g, Du Zhong (Eucommia Bark) 10g, Tu Si Zi (Dodder Seed) 10g, Xiang Fu (Cyperus Tuber) 9g, Ban Xia (Pinellia Tuber) 6g, Cang Zhu (Atractylodes Rhizome) 9g. During ovulation and menstrual phase, patients receive the same treatment as patients with Shen deficiency and blood stasis. And, in luteal phase, Chinese herbs are prescribed to supplement yin and yang, reinforce shen, assisting yang and dissolve phlegm with modified Yulingzhu combined with Cangfu Daotang wan. Modification consists of adding Tu Si Zi (Dodder Seed) 15g, Du Zhong (Eucommia Bark) 10g, Zi He Che (Human Placenta) 10g, Lu Jia Shuang (Degelatinuous Deerhorn) 10g, Cang Zhu (Atractylodes Rhizome) 9g, Ban Xia (Pinellia Tuber) 6g, Fu Ling (Poria) 10g, Xiang Fu (Cyperus Tuber) 12g, Mu Dan Pi (Moutan Bark) 15g, Gan Cao (Licorice Root) 6g, Ji Nei Jin (Chicken Gizzaed-skin) 10g. The WM group, thirty patients received Diane-35 for twenty-one days for three menstrual cycles, from the 5^{th} day of withdrawal bleeding. Ovulation was promoted by using CC and human chorionic gonadotropin (hCG). The TCM-WM group, thirty patients used medication from the above two groups. It was recorded that groups with TCM-WM and WM patients experienced nausea, breast tenderness, and a small amount of vaginal bleeding that stopped in a week. The TCM-WM and WM group had higher ovulation rate than TCM group, and the pregnancy rate

was higher in TCM-WM group than other groups. The authors concluded that Chinese herbal medicine increases blood flow to the uterus and ovaries, increases cervical mucus, supports corpus luteum, and promotes ovulation. Hence, integrative treatments are beneficial for non-obese PCOS patients with slight adverse reaction.

In another research study, Wu and associates (2007) investigated the effect and the mechanism of Bushen Huayu Qutan Recipe BHQR on PCOS. BHQR is formulated to nourish the Shen, resolve stasis and dispel phlegm. BHQR was used, both internally and externally, to treat forty-six patients with PCOS, in conjunction with metformin if necessary. Six successive months treatment was regarded as one course. The serum levels of hormones and insulin were measured, and obesity, polytrichia, acne and acanthosis, were observed before and after treatment. After the treatment, the results indicated that the serum level of testosterone ($p<0.05$), fasting serum insulin ($p<0.01$) and the values of insulin and insulin area under curve ($p<0.05$) 30 min and 60 min after glucose load were significantly reduced. There was also a reduction observed regarding obesity ($p<0.05$). The researchers concluded that BHQR could not only regulate the ovarian function, but it can also significantly relieve the symptoms and signs of patients with PCOS.

In another study, Song and colleagues (2006) included forty-six PCOS patients treated with Chinese herbs consisting of Yin Yang Huo (Epimedium) 15g, Rou Cong Rong (Desertliving Cistanche) 15g, Zhi Shi Ying (Dluoritum) 12g, Lu Jiao Shuang (Degelatinous Deerhorn) 12g, Bu Gu Zhi (Psoralea0 12g, Ba Ji Tian (Morinda Root) 12g, Tu Si Zi (Dodder Seed) 12g, Huang Jing (Siberian Solomon's Seal) 12g, Nu Zhen Zi (Glossy Privet) 12g, Huai Niu Xi (Two-Teethed Achyrantes) 12g, Gui Ban (Tortoise Plastron) 12g, Pei Lan (Eupatorium) 12g, Yu Jin (Zedoary) 12g, Jiang Huang (Turmeric

Root), Lu Lu Tong (Sweet gum Root) 30g, Shan Zhu Yu (dogwood Fruit) 12g, Shan Yao (Chinese Yam) 15g, Mu Dan Pi (Peony Bark) 15g (Song et al., 2006). This formula was given one dose a day on the 5th day of menstruation. And after two months, patients were given CC 50-100mg in conjunction with herbs, on the 5th day to the 18th day of menstrual cycle for six months. The control group (n= 40) was given CC 50-100mg on the 5th to the 9th day of menstrual cycle. Ultrasound was done on all patients on the 10th day of menstrual cycle. The result showed the treated group ovulated 82.8% and a pregnancy rate of 52.2% in comparison to the control group with an ovulation rate of 40.0% and 22.5% pregnancy rate.

In an open trial, eighty PCOS patients between the ages of eighteen to thirty-five were treated with Hui Shu Hua (Maitake mushroom extract- SX-fraction; MSX) and in comparison with, and in combination with CC. Thirty-six PCOS patients received Hui Shu Hua MSX, and thirty-six received CC alone for up to twelve weeks. Eighteen patients who did not respond to either treatment were subjected to combination therapy of Hui Shu Hua MSX and CC for up to sixteen weeks. Eight patients with a documented history of failure to CC received combination therapy from the beginning. Ovulation was assessed by ultrasonography. Twenty of the twenty-six patients in the Hui Shu Hua MSX group (76.9 %) and twenty-nine out of thirty-one patients in the CC group (93.5%) ovulated. In combination therapy, seven of seven patients who failed in Hui Shu Hua MSX and six of eight patients (75%) who failed in CC showed ovulation. In this study, three of twenty-six patients (11.5%) conceived, two from Hui Shu Hua MSX and one from combination of both Hui Shu Hua MSX and CC. It was concluded that Hui Shu Hua

MSX alone may induce ovulation in PCOS patients, and may be useful as an adjunct therapy for patients who failed first-line CC treatments (Chen et al., 2010).

Literature Review Integration

Anovulation has been identified as a critical factor in the diagnosis and the assessment of polycystic ovary syndrome (PCOS) (Spernoff & Fritz, 2011; Livadas & Diamanti-Kandarakis, 2013). The etiology of anovulation has been explored and studies have focused on endocrine influences that emerge in PCOS (Lentz, 2012: Melmed, 2011, Yarak et al., 2005). These influences include hyperinsulinemia and hyperandrogenism (Futterweit, 2007; Azziz, 2006). There is an established Traditional Chinese Medicine history regarding the treatment of PCOS (Maciocia, 1998; Lyttleton, 2004) with the use of Chinese herbal medicine with several formulations effecting PCOS (Ushiroyama et al., 2006; Sun et al., 2004). There have been a number of studies that document the impact of Western medicine on PCOS. Likewise there have been studies that show the impact of Traditional Chinese Medicine non-PCOS. However, there are no studies that have engaged a systematic literature synthesis regarding prior research studies specifically in relation to the impact of Chinese herbal medicines employed alone or in conjunction with Western medicine on the condition of PCOS. It was the objective of the current study to complete a systematic literature synthesis on the effects of PCOS and Chinese herbal medicine alone and in relation to the use of western treatments.

CHAPTER 3: Methodology

The objective of this study was to demonstrate through retrospective study using qualitative research analysis, the effectiveness of Chinese medicine alone or in combination with western medicine in treating anovulatory PCOS patients. This chapter will specify the research method and will detail the procedures used to accomplish this objective.

The current study employed systematic literature review as the designated research method. According to Guest and associates (2012) systematic literature review constitutes a deliberate and organized procedure for summarizing and clarifying currently available literature. It is a method that brings together a number of separately conducted studies with their careful analysis of their strengths and weaknesses. Finally, it is a method that provides a synthesis across many studies reviewed for the purpose of generative generalized interpretative conclusions regarding the body of research literature.

In systematic literature review, the nature of the data guided the decisions at every step of the synthesis process. The principle weakness of this approach may include researcher subjectivity. Additionally, discrepancies may arise based on differences in inclusion and exclusion engaged in the selection of literature to be part of the synthesis. The limitations encountered included the fact that a number of pertinent articles were available only in the Chinese language, and they were not accessible. And, many of the research articles were not clear regarding the results of their studies.

Thematic analysis is an important component of the systemic literature review method. It is a common form of analysis in qualitative research, and it is used to focus on

examining themes within data (Guest et al., 2012). The thematic analysis includes the processes engaged to discern identifiable patterns across the literature reviewed, and provides a means for synthesizing the information. The thematic analysis is an effective tool for organizing, interpreting, and highlighting important variables. Thematic analysis is a dynamic research method that can be usefully applied to improve understanding of a phenomenon of interest, inform theory development and strengthen clinical practice (Silverstein, et al, 2006). Several overarching themes were identified: Chinese medicine, western medicine, integrative medicine, an increase in menstruation, and an increase in ovulation. There are additional sub-themes that are likely to arise, which consist of improvements regarding hormones, insulin and other conditions. I will combine and catalogue related patterns into sub-themes in order to show a comprehensive view of information.

Sampling

In the current study most of the articles were accessed digitally from numerous western medicine and traditional Chinese medicine journals. The online data bases that were used consisted of PubMed, Google Scholar, Google Books, MD Consult, *Fertility Sterility*, Springerlink, and the UCLA database. The researcher identified 22 journal articles and four books. The following descriptive words and phrases were employed in the search: polycystic ovarian syndrome, PCOS and anovulation, oligomenorrhea, Chinese medicine and anovulation, Chinese herbal medicine, herbal medicine, PCOS and Chinese medicine, and PCOS and integrative medicine. The research took place in researchers' residence, the YoSan University library, and UCLA library.

Inclusion/Exclusion Criteria

The Inclusion criteria for the current study specified the inclusion of research studies with the following criteria:

- Female or animal subjects.
- Patients who have histories of anovulation or oligomenorrhea.
- Patients with PCOS ovaries diagnosed by vaginal ultrasound.
- Patients who received western treatment for anovulation and/or oligomenorrhea.
- Patients who were in treatment with Chinese medicine for conditions PCOS and anovulation/or oligomenorrhea.

The exclusion criteria specified research studies with patients who have severe insulin resistance, androgen secreting neoplasm, Cushing's syndrome, thyroid abnormalities, hyperprolactinemia, and tumors.

Data Collection Procedures and Instrumentation

With the Article abstraction form, the researcher organized and summarized key pieces from all the studies reviewed. Data collection tables were used to extract themes from each article and to compare and summarize this information. Summary tables were constructed with the number and title of the articles used for research synthesis. The research questions were organized into various tables to allow the researcher to analyze the data's with major themes and conclusion. These tables summarize the information retrieved based on the PCOS and Chinese medicine, PCOS and western medicine, PCOS and integrative medicine. The variables found were recorded. A table with the different types of western medicine used was constructed. A table was constructed regarding specific Chinese herbal medicines and their effect on anovulation, other physiological

changes, and the efficacy and frequency of usage. A table was constructed based on methodology, such as case study, clinical trial, meta-analysis, and the inclusion and exclusion criteria engaged in each article.

Data Analysis

This section will provide a detailed description of the process that was used to extract and analyze data from the collected articles in this research synthesis. The bulk of the data gathered is categorical and resulted in simple frequency counts or tallies of the number of cases that fell into each category on the data collection form.

Data across all of the studies reviewed were compiled on separate tables. Tables were complied to manifest the data generated regarding:

- Summary of participants
- Number of months of treatments
- Inclusion/Exclusion Criteria for PCOS
- Chinese herbal formula
- TCM diagnosis
- Western vs. TCM vs. Integrated treatment engaged
- Variables used to assess ovulation in PCOS
- Ovulation and Pregnancy
- Frequency of individual herbs utilized

A copy of the data compilation form is included in the appendix of this document.

Validity and Reliability

All data's were collected by the researcher. In order to demonstrate that the researcher has collected the data accurately, the design of this study included the plan for

the researcher to ask a colleague who is a licensed acupuncturist with doctoral level education to read a sample of three of the articles included in this study and to complete article abstractions form regarding each of the article read. The researcher was to compare the outside reader's data collection with her own and hopefully demonstrate a concurrence of not less than 70%. Unfortunately, time and workload considerations did not allow for that additional demonstration of validity and reliability to be accomplished in the current study.

With its focus on research method this chapter has specified the details of how current study was carried out. The next chapter, Chapter 4: Results will summarize the findings of the current study. The final chapter will consider the implications of the findings, the limitations of the study and will make recommendations for further research.

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Chapter 4: Results

The objective of the current study was to synthesize Chinese and Western medicinal literature currently available regarding the treatment to induce ovulation in anovulatory women who are diagnosed with PCOS. This chapter presents the data that emerged from the literature review synthesis process. The first section provides a summary of the types of studies that were used in the synthesis. Additionally, a summary is provided regarding the number of subjects and their age demographic across the studies reviewed. Following is an analysis the inclusion and exclusion criteria used used to assess the articles pertaining to PCOS. The next data reporting section constitutes the number of studies using TCM diagnosis for the treatment of PCOS. Another factor that was analyzed is the use of Chinese medicine with Western medicine. A summary is provided regarding the number of weeks herbal medicine was given. An additional factor reported is the herbs used in studies. A further section of the chapter provides a summary of the conclusion categories drawn from the result of the reviewed articles. In the final section of this chapter, the author presents assessment data regarding the research methods utilized in studies.

Findings

Twenty-two studies met the inclusion requirements for consideration in the current research project. The next sections provide information regarding the nature of those studies and data regarding some of the key variables that were targeted for examination in the current study.

Summary of Participants

The average number of participants in each of twenty-two studies was 54.4, ranging from twenty-two to hundred-seven subjects per study. Rats were used as subjects in two studies, study 9 (Wang et al., 2008), and study 10 (Li et al., 2010). The average number of rats was eighty-two subjects, with use of fifty-nine and hundred-five rats in two animal studies. There were two meta-analysis studies, study 12 (Han et al., 2008) and study 18 (Zhang et al., 2010). Across two meta-analysis studies there was observed to be an average of 1613.5 participants, with a range from three hundred and forty-four and twothousand eight hundred eighty-eight. Only in one of meta-analysis studies, study 18, was the factor of age reported. The age range of the subjects in that study was from eighteen to forty-four years.

Across the other studies reviewed, the average age of participants was 26.6 years old, with a range of thirteen to forty-four years old. In two of the studies—Study 11 (Jia & Wang 2006), and study 16 (Kuek, 2011)—the minimum age presented was from thirteen to fifteen years, which indicates adolescents subjects as opposed to reproductive patients. Eight studies did not discuss the age of the patients.

Number of months of Treatment

The average number of months of treatment was 4.1 months, with a minimum of two months and a maximum of eighteen months. In two studies, the subjects were rats. Thus, the amount of time for treatment does not relate to human subjects. Three studies did not mention amount of time allocated to treatments. Only one of the meta-analyses, study 12, provided the months of treatment given to the subject as three months.

Inclusion/ Exclusion Criteria for PCOS

The inclusion/exclusion criterions, specified in the methodology chapter of this document, were found to be addressed in seven out of nineteen studies. The Rotterdam 2003 (table 1) criteria were designated in six out of nineteen studies. However, in study 11 (Jia & Wang, 2006), although the authors discussed using the Rotterdam Criteria as PCOS diagnosis, they never mention the hyperandrogenism except for serum testosterone as a diagnostic measure. Studies 11 (Jia & Wang, 2006), 16 (Kuek et al., 2011) and 19 (Tao et al., 2003) discussed exclusion criteria which excluded other related disorders.

Four studies had an inclusion criteria based on Japanese Society of Obstetrics and Gynecology 2007. Since the incidence of clinical and biochemical hyperandrogenism may be lower in Asian patients with PCOS. Hyperandrogenism is included as a referential but not as an essential factor in the diagnostic criteria. The criteria in these studies consists of PCOS patients with menstrual abnormality, the presence of polycystic ovarian morphology with use of ultrasound, and laboratory evidence of hyperandrogenism and/or elevated basal luteinizing hormone (LH) and normal basal follicle-stimulating hormone (FSH). The serum LH and FSH levels are required to be >7 mIU/mL and LH/FSH >1, with an exception that obese women with the BMI >25 can be diagnosed with PCOS if the LH/FSH ratio is greater than 1 (Chen et al., 2011). These studies consist of study 2 (Ushiroyama et al., 2006), study 5 (Sakai et al., 1999), study 6 (Okamoto, 2010), study 7 (Tominaga et al., 2011), and study 22 (Chen et al., 2010). All these studies were performed in Japan, including study 1 (Ushiroyama et al., 2001).

The two meta-analysis studies, study 12 (Han et al., 2008) used an inclusion criteria researching reviews and articles that incorporated randomized-controlled trials (RCT) and controlled clinical trials CCT); study 18 (Zhang et al., 2010) used an inclusion criteria of RCT, and PCOS patients identified using the Rotterdam 2003 criteria. Its exclusion criteria consisted of other related disorders, Quasi RCT, and non-RCT.

Chinese Herbal Medicine in the Studies

Four studies, Chinese herbal medicine were discussed without any pattern of differentiation. Study 1 (Ushiroyama et al, 2001) used Unkei-to (Wen Jing Tang) on PCOS and non-PCOS patients. Study 3 (Sun et al., 2004) was the only in-vivo study which researched the effect of Unkei-to (Wen jing Tang) on human granulosa cells from IVF patients to show the Chinese herbal direct effect on ovulatory process within the ovary. Sarei-to (Chai Ling Tang) effects for ovulation induction were examined in two studies, study 5 (Sakai et al., 1999), and study 6 (Okamoto et al., 2010). Chinese Herbal medicine was administered to PCO study 10 (Li et al., 2010). Three PCOS groups of rats were also the subjects of study 10, where the formula BuShen Tongmai recipe was administered. It explored the effects of CHM on local ovarian factors and concluded that BHQR is effective in improving the insulin resistance and ovulation dysfunction in PCO rats.

TCM Diagnosis in the Studies

There were a total of nine research articles using TCM diagnosis and approaches in the treatment of PCOS. Study 2 (Ushiroyama et al., 2006) focused on the use of Eight-Principle as well as Qi, blood and fluids as the basis for diagnosis and treatment. The researcher compared two different formulas, Dang Gui Shao Yao San and Gui Zhi Fu

Ling Wan to Wen Jing Tang (WJT). It is the only study that concluded that WJT is appropriate with various TCM diagnosis and patterns. Unlike Study 2 (Ushiroyama et al, 2006) , study 4 (Ling et al., 2002) and study 11 (Jia & Wang, 2006) used TCM diagnosis and treatments which both concluded to be effective in inducing ovulation, regulating BBT and menstruation, reducing testosterone and insulin, and pregnancy. In study 11 (Jia & Wang, 2006) the treatment plan was to nourish yin and clear heat in one group, and strengthen spleen and augment Qi in the second group. Two studies focused on the use of spleen and kidney yang deficiency herbs to treat PCOS, study 4 (Ling et al., 2002) and Study 14 (Song et al., 2006), and the treatment plan was to boost the kidneys, strengthen the spleen, nourish and invigorate blood, and clear dampness. These studies used the same empirical formula. Study 15 (Lian et al., 2012) discussed the TCM diagnosis of Shen Invigorating and Chong regulating formula ErZhi Tian Gui Granules which had a direct effect of improving the quality of oocytes, follicular fluid, and activating the ovarian microenvironment. Cyclic treatment was discussed in study 8 (Song et al., 2006) and study 19 (Tao et al., 2003). Cyclic treatment is based on follicular phase, ovulatory phase, luteal phase, and menstrual phase. Study 8 (Song et al., 2006) prescribed a base formula that was modified based on each menstrual cycle phase, as well according to manifestation of any disorders, such as amenorrhea due to blood stasis or increased ovary size.

In three studies, TCM diagnosis approach was a basis for treatment, and herbal formulas were compared to western medicine. Study 16 (Kuek et al., 2011) researched use of Tian Gui Capsule given to Kidney Yin deficiency with internal heat and compared its effect with Diane-35. Study 19 (Tao et al., 2003) and study 21 (Wu et al., 2007)

discussed TCM pattern identification of Shen deficiency with blood stasis and/ or Phlegm–Damp stagnation Syndrome. In study 19, subjects were treated based on TCM diagnosis and cyclic phase, versus western medicine. For Shen-deficiency with blood stasis syndrome, the following formulas were dispensed: in follicular phase modified GuiShao Dihuang decoction, in the ovulatory stage modified Cupailuan decoction, in luteal phase Yulingzhu decoction, and in menstrual phase modified Shixiaosan. Patients with the diagnosis of Shen (kidney) deficiency-Phlegm Damp were treated with modified Shenqiwan combined with Cangfu Daotanwan. In the ovulatory and menstrual phase the same formulas were used as the Shen deficiency-blood stasis Syndrome. In the luteal phase, modified Yulingzhu decoction combined with Cangfu Daotanwan was used. In this study the herbal combinations were compared to Diane-35. Study 21 (Wu et al., 2007), Bushen Huayu Qutan Recipe was used for treatment of Shen deficiency with blood stasis and Phlegm-damp accumulation. The effect of BHQR was combined with Metformin. In study 16 (Kuek, 2011) Tian Gui Capsule (TGC) was used to treat kidney Yin Deficiency with Internal Heat in PCOS patients versus metformin and Diane-35.

Study 9 (Wang &Yu, 2008) used Bushen Huayu Quan Recipe on 3 groups of rats, concluding that Chinese herbal medicine has an effect on ovulation dysfunction, and the internal environment of the ovary and the kidneys, nourishes and invigorates the blood, and transforms the phlegm.

Kidney deficiency was the prominent diagnosis in studies reviewed. Only two studies discussed the kidney yang deficiency with phlegm damp accumulation discussed by Maciocia (1998) and Lyttleton (2004), study 19 and 21. Kidney yin deficiency type of PCOS was discussed in study 11 and 16. It was concluded that kidney yin deficiency

easily manifests with deficiency heat, and are symptoms associated with high testosterone levels.

TCM Diagnosis	*Number of Studies*
Eight Principle	1 (2)
SP and KD Yang deficiency	2 (4) (14)
Cyclic treatment	2 (8) (19)
KD Yin deficiency with heat	1 (16)
KD Yin	1 (11)
SP Qi deficiency	1 (11)
Shen (KD) invigorating and Chong Regulating	1 (15)
Shen (KD) deficiency with Blood Stasis	1 (19)
Shen (KD) deficiency with Phlegm/Damp	1 (19)
Shen (KD) deficiency with Blood Stasis and Phlegm/Damp	1 (21)

Table-2 TCM Diagnosis in the studies
Kidney (KD) Spleen (SP)

Chinese Herbs plus Clomiphene Citrate (CC)

Two studies were meta-analyses of Chinese Herbal Medicine versus Clomiphene Citrate (CC). Study 12 (Han et al., 2008) used three hundred eighty-two studies and reviews with a grand total of two thousand eight hundred and eighty-eight participants, and it concluded that CC treatments will improve with use of Chinese herbal medicine. Whereas, study 18 (Zhang et al., 2010) used four studies with the total of three hundred forty-four participants, and it concluded that there is limited evidence that Chinese herbal medicine in combination with CC would improve sub-fertility in PCOS women.

Three studies explored the integrated use of Chinese herbal medicine with CC to treat PCOS, study 13 (Yang &Zhang, 2005), study 14 (Hua et al, 2003), and study 20 (Song et al., 2006). In study 13, CC-resistance subjects were administered GanShao

Capsules to improve ovulation induction with improved response to CC, and several patients ovulated naturally. The Chinese empirical formula was compared to CC in study 14, whereas another Chinese herbal medicine plus CC was compared to CC only. In study 20, twenty-six PCOS patients were treated with Chinese herbal formula, and after two months, CC of 50-100mg was added to the treatment for 6 consecutive months. The results indicated TCM-WM have a better efficacy than CC alone.

In study 22 (Chen et al., 2010), Hui Shu Hua (Maitake mushroom) was compared to CC. It was concluded that Hui Shu Hua alone may induce ovulation in PCOS patients (76.9%), in combination of Hui Shu Hua and CC (75%), and may be useful as an adjunct therapy for patients who failed first-line CC treatments (Chen et al., 2010).

Chinese Herbal Medicine plus Metformin

Study 17 (Hou et al., 2000) compared the effects of Chinese herbal formula TianGui Fang (TGF) versus metformin. It was concluded that TGF can regulate menstruation and promoted ovulation. However, metformin was observed to have a significant effect in lowering insulin and reducing hyperinsulinemia and hyperandrogenism. As mentioned previously, in study 21 (Wu et al., 2007) explored the therapeutic effects of Bushen Huayu Qutan Recipe (BHQR) alone or combined with metformin if necessary.

Chinese Herbal Medicine plus Western Medicine

Three studies discussed Chinese herbal medicine therapy in comparison/combination western medicine treatments. Study 15 (Lian et al., 2012) discussed Chinese herbal medicine Shen Invigorating and Chong regulating using formula ErZhi Tian Gui Granules in addition to western medicine (not revealed). ErZhi

Tian Gui Granules were compared to PCOS patients using western medicine as control. And, study 16 (Kuek et al., 2011) compared Tian Gui Capsule to metformin and Diane-35. In study 19 (Tao et al., 2003), Chinese herbal medicine was compared to Diane-35. In all the studies TCM-WM, integrated medicine, was observed to have better efficacy than TCM or Western Medicine alone.

Types of treatment Modalities

Types	Number of Studies
TCM Diagnosis	**9**
Clomiphene Citrate	**6**
Metformin	**2**
Diane-35	**1**

Table-3 Types of treatment modalities

Chinese Herbal Formulas

Three studies used Wen Jing Tang (Unkei-to), Study 1 (Ushiroyama et al., 2001), Study 2 (Ushiroyama et al., 2006), and study 3 (Sun et al., 2004). In all three studies, it was concluded that WJT may be effective in the treatment of pituitary-ovarian dysfunction, and the endocrine system. It improves the pulsatile secretion of FSH and LH, and induces ovulation. In study 3, it was shown that WJT has stimulatory effects on human granulosa cells and stimulatory effects on both steroidogenesis and the ovulatory process in the ovary. WJT is literally known as 'Warm the Channel Decoction'. The herbs warm the channels, dispel cold, nourish blood, and dispel blood stasis (Chen & Chen, 2009). It should be noted that the ingredients in the studies discussed are in different concentrations than seen in classic formulas, such as Ban Xia (Pinelliae Tuber) 40g (Ushiroyama et al., 2006). Ban Xia is categorized as phlegm resolving herb and its

function is dry dampness, transform phlegm, and dissipate nodules and stagnation. Chai Ling Tang (Sairei-to) was discussed in two studies, study 5 (Sakai et al., 1999) and study 6 (Okamoto et al., 2010). Sairie-to reduced serum LH levels and increased ovulatory rate. Herbal formula Bushen Huayu Qutan Recipe (BHQR) was used in two studies, study 7 (Wang &Yu, 2008), and study 19 (Wu et al., 2007). In study 7, it was used on rats to show its effect on promoting ovulation and on local microenvironment of ovaries. In study 19, it was observed that BHQR can regulate the ovarian function with an effective rate of 93.48% (Wang& Yu, 2008). This formula tonifies kidney, promotes blood circulation, transform phlegm stagnation. Hui Shu Hua was researched in Japan, and was discussed in study 7 (Tominaga et al., 2011) and study 22 (Chen et al., 2010). In study7, Hui Shu Hua is compared to another herbal formula Shao Yao Gan Cao Tang (Shakuyaku-kanzo-to). And in study 22, it is compared clomiphene citrate (CC).

Chinese Herbal Formula	***Number of Studies***
Unkei-to (Wen Jing Tang)	3 (1) (2) (3)
Sairei-to (Chai Ling Tang)	2 (5) (6)
Hui Shu Hua	2 (7) (22)
Shakuyaku-kanzo-to (Shao Yao Gan Cao Tang)	1 (7)
Dr Chai Hao-yan (Empirical formula)	2 (4) (14)
Dang gui Shao Yao San	1 (2)
Gui Zhi Fu Ling Wan	1 (2)
ErZhi Tian Gui Capsules	1 (15)
Tian Gui Capsule	1 (16)
Tian Gui Fang	1 (17)
Bushen Tongmai Recipe	1 (10)
Bushen Huayu Qu Recipe	2 (9) (21)
GuiShao Di Huang decoction(modified)	1 (19)
Cupailuan decoction	1 (19)
Yu LingZhu Decoction (modified)	1 (19)
Shixiaosan (modified)	1 (19)
GanShao Capsules	1 (13)
Herbal Formula	1 (20)

Table 4- Chinese Herbal Formula used in the studies

Measurement Used to Assess Effect of Chinese Herbal Medicine on PCOS

Each study used a set of measurements and observations to assess the effects of Chinese herbal medicine on PCOS subjects. These assessments consist of observations of induction of polycystic ovary (PCO), follicles, and ovulation with transvaginal ultrasound or Doppler ultrasound which was discussed in 10 studies. Another form of confirming ovulation was with biphasic basal body temperature charting which was observed to have been done in five studies. Other observations consisted of measuring LH/FSH ratio , serum testosterone (T), estradiol (E2), progesterone, prolactin (PRL), Cortisol, Adrenocorticotropic hormone (ACTH), sex hormone binding globulin (SHBG), Dehydroepiandrosterone Sulfate (DHEA-S), Anti-Müllerian hormone (AMH), insulin (INS), fasting insulin FINS, fasting blood glucose (FPG), homeostasis model assessment (HOMA-IR), body mass index (BMI), waist-hip ratio (WHR), hirsutism, Ferriman-Gallwey score (F-G), and acne.

Ovulation and Pregnancy in the Studies

Several studies reported ovulation and pregnancy rate based on the effects of Chinese herbal medicine and/or western medicine. In the TCM group, the rate of ovulation was 40% to 89.5%. Ovulation rates of clomiphene citrate (CC) group ranged from 25% to 93.5%. The TCM-WM average rate ranged from 60.39% to 82.8%, and the ovulation rate with the use of Diane 35 was observed at 68.3%. The pregnancy rate in TCM group was 25% to 100%. In study 11, 9 patients out of 43 PCOS were diagnoses as infertile and were subsequently able to conceive, hence for that sub-group manifesting

a 100% pregnancy rate (9/9). The CC group had a pregnancy rate of which ranged from 22.5% to 25%, and the TCM-WM group range was from 52.2% to 53.8%..

In two studies, the rates for ovulation and pregnancies were designated as "cured" and most effective, study 4 (Ling et al, 2002) and study 11 (Jia & Wang, 2006). These studies used a Chinese Medicine manual which written by China's health Department to assess the clinical efficacy in the treatment of PCOS, which was categorized as amenorrhea and infertility. The assessments were categorized as either cured or noticeable effect, which is defined as a successful ovulation induction and pregnancy, as well as regular menstruation, normal biphasic BBT, or blood tests indicating all the endocrine and metabolic markers at normal values. Some effects were defined as overall menstrual symptoms improved, patients' clinical symptoms improved, and blood test markers compared to before treatments. In study 4, cure was reported as 43.75%, and total effectiveness was 90.62%. However, this study also stated a pregnancy rate of 68.75%. In study 8 (Song et al., 2006) cure rate was 65.21%, and pregnancy rate was 21.7%.

Ovulation rate reported in the studies

Study#	TCM	CC	TCM-CC	Diane-35	Single Herb	Single Herb-CC
1	50%					
2 (WJT)	59.3%					
3						
4						
5	70.6%					
6	87.5%					
7					66.7%	
8	65.2%					
9	66.67%					
10						
11	80%					
12		34.57%	60.39%			
13	89.5%					
14						
15						
16						
17	75%	25%				
18						
19	40%		73.1%	68.3%		
20		40%	82.8%			
21						
22		93.5%			76.9%	86.7%

Table 5- ovulation rate reported in the studies.

Pregnancy rate in the studies

Study#	TCM	CC	TCM-CC	Single Herb	Single Herb-CC
1					
2					
3					
4	66%				
5	17.6%				
6					
7					
8	21.7%				
9					
10					
11	(100%)				
12					
13	36.8%				
14	65.7%	25%			
15					
16					
17					
18					
19	25%		53.8%		
20		22.5%	52.2%		
21					
22				66.7%	33.3%

Table 6- Pregnancy rate in the studies
These percentages are patients that desired to conceive, not the total number of subjects.

Frequency of Herbs

A total of eighty-five different herbs were observed to have been used across the twenty-two studies. The herb used most frequently was Dang Gui (Radix Angelicae Sinensis) which accounts for 50% (11/22) of the articles reviewed in this literature synthesis. Following closely was the herb Gan Cao (Radix Glycyrrhizae) 45.5% (10/22), as well as Bai Shao (Radix Paeconiae Alba) and Chuan Xiang (Radix Ligustici Wallichii) 36.4% (8/22). Tao Ren (Semen Persicae) and Tu Si Zi (Semen Cuscutae) account for 27.3% (6/22) of the articles reviewed. Ban Xia (Pinellia Rhizoma) and Yin Yang Huo (Herba Epimedii) are used respectively 31.8% (7/22) in these studies. There were also many herbs that were used in a lower frequency in few articles selected for this literature

review synthesis. Table 7, Frequency and Percentage of Herbs Used, lists all the herbs observed to have been employed in the selected articles.

Frequency and percentage of Herb Used

Herbs	Percentage and frequency	
Dang Gui	50%	(11/22)
Gan Cao	45.5%	(10/22)
Bai Shao, Chuang Xiong	36.4%	(8/22)
Ban Xia, Yin Yang Huo	31.8%	(7/22)
Tao Ren, Tu Si Zi	27.3%	(6/22)
Fu ling, Gou Qi Zi, Gui Zhi, Mai Men Dong, Mu Dan Pi, Ren Shen, Ze Xie	22.7%	(5/22)
Bai Zhu, Du Zhong, E Jiao, He Shou Wu	18.2%	(4/22)
Chi Shao,Gui Ban, Huang Jing, Lu Jiao Shuang, Nu Zhen Zi, Sheng Jiang Shu Di Huang, Wu Zhu Yu, Xiang Fu	13.6%	(3/22)
Bu Gu Zi, Cang Zhu, Chai Hu, Che Qian Zhi Chuan Niu Xi, Dan Shen, Dang Shen, Han Lian Cao, Hong Hua, Hui shu Hua, Huang Qin, Huai Niu Xi, Rou Cong Rong, Sang Shen Zi, Shan Yao, Shan Zhu Yu, Sheng Di Huang, Xu Duan, Yi Mu Cao, Yi Yi Ren, Yu Jing, Ze Lan, Zhi Mu, Zhi Shi Ying, Zhu Ling	9.1%	(2/22)
Ba ji Tian, Bie Jia, Chen Pi, Ge Gen, Hu Zhang, Huang Bai, Huang Qi, Kun Bu, Jiang Huang, Ji Nei Jing, Lu Lu Tong, Ma Biao Cao, Mai Men Dong, Meng Chong, Pei Lan, Pu Hong, Qian Cao, Rou Gui, San Leng, San Qi, Sang Ji Shen, Sha Yuan Ji Li, Shan Ci Gu, Shan Zha, Shi Cang Pu, Shui Zhi Tu Bie Chong, Wu Ling Zi, Wu Yao, Xia Ku Cao, Xian Mao, Zi He Che,	4.5%	(1/22)

Table-7 Frequency and percentage of Herb used

Chapter 5: Discussion

Summary of Findings

In this research synthesis, twenty-two articles were reviewed which pertained to the use of Chinese herbal medicine (CHM) alone or in conjunction with western medicine (TCM-WM) in the treatment of PCOS. Through qualitative research analysis, the following factors were examined and analyzed: the effects of CHM, CHM with a TCM diagnosis, TCM-WM on ovulation induction in PCOS subjects. A summary of Chinese herbal formulas and indications of frequency of herbs used were also provided. The hypothesis of this study was that Chinese medicine is as effective, if not more effective, than western modalities in inducing ovulation in anovulatory PCOS patients. The data collected suggests that CHM in conjunction with TCM-WM may facilitate beneficial outcomes. The combination TCM-WM could lower high serum levels of luteinizing hormone (LH) and androgen, and promote ovulation.

Implications for Theory and Practice

This study was designed to investigate the types of TCM principles, formulas, and herbal combinations used in research studies to treat anovulation in PCOS patients. PCOS is related to Kidney deficiency, blood stasis with phlegm/dampness (Song et al., 2006; Kuek et al., 2011). According to Lyttleton (2004), ovulation may be induced with Chinese herbs by clearing the excess such as blood stasis or phlegm/damp accumulation, as well as, strengthening the kidney yang, and in some instances nourishing kidney yin. The Chinese herbal medicines that activate blood circulation, and transform phlegm may improve the condition of local endocrine, and supply blood to the ovaries to promote follicular development, as well and induce ovulation (Tao et al., 2003; Song et al., 2006).

From the twenty-two studies reviewed, the herbs that were most frequently used, in terms of percentage, were in the categories of blood tonic, Qi tonic, blood movers, phlegm resolving herbs, and yang tonics (Table 7). These observed herbs are consistent with the TCM theory of PCOS. An example of blood tonic herb is Dang Gui (Angelicae Sinensis Radix), which was the most utilized, (50%) in the twenty-two studies. According to TCM theory, Dang Gui (Angelica Sinensis) strengthens and invigorates blood, regulates menses, and encourages blood circulation in the blood vessels (Chen & Chen, 2009). It activates blood circulation, especially in the capillaries, hence improving microcirculation, in addition to inhibiting platelet aggregation (Lyttleton, 2004). Ferulic acid has been found in Dang Gui which significantly improves blood fluidity, decreases serum lipids, and prevents thrombus formation (Wu et al., 2011; Hou et al. 2004). Another chemical constituent of Dang Gui is Z-ligustilide, which has exhibited both inhibitory and stimulatory effects on the smooth muscles of the uterus.

An example of a Qi tonic herb is Gan Cao (Radix Glycyrrhizae), having the second highest observed frequency of 45.5% in the current study. Gan Cao tonifies the spleen to enhance transformation and transportation. Gan Cao has the glucocorticoid effect of improving ovulatory abnormalities (Zhang et al., 2010). Glucocorticoid is categorized in steroid hormones, hence plays an important role in anti-inflammatory, anti-allergic effects and immuno-suppression (Xie et al., 2011). Next, Yin Yang Huo (Herba Epimedii), with am frequency of 31.8% in the current study, is an example of a Yang tonic which tonifies the kidney, strengthens Yang, and increases endogenous hormones. Chinese herbs that tonify the kidneys may have an endocrine like effect (Tao

et al., 2003; Song et al., 2006), showing bidirectional regulatory action on the gonadal axis of women (Song et al., 2006).

Generally, all of the articles concluded that Chinese formulas are substantively effective in improving the endocrine conditions of PCOS patients (Ushiroyama et al, 2001; Ushiroyaman et al., 2006; Song et al., 2006; Tao et al., 2003). For example, Study 3 (Sun et al., 2004) demonstrated that Wen Jing Tang has direct stimulatory effects on granulosa cells, steroidogenesis, ovulation, and stimulatory effect on hypothalamic-pituitary-ovarian axis (HPO).

Chinese medicine has a long history in the treatment of PCOS, which was categorized as amenorrhea and infertility (Zhang et al., 2010). The findings of the current study reinforces the fact that TCM and western practitioners should consider treating PCOS cases with Chinese herbal medicines in conjunction with clomiphene citrate (CC). Data from across twenty-two studies reviewed show that when applying the TCM approach as opposed to western medicine alone improvements are likely to be observed in hypothalamic–pituitary ovarian axis, the endocrine system, and thus likely improvements in treatment outcome in PCOS cases as a whole. This result concurs with the meta-analysis in Study 12 (Han et al., 2008), which demonstrated that the integration of TCM, herbal medicine and western medicine may be beneficial. According to the selected and analyzed studies, combining the complementary strengths of both TCM and western medicine improves clinical efficacy.

Moreover, TCM –WM may be used in the management of medicinal side effects. For example, TCM diagnosis and Chinese herbal medicine can be used to manage clomiphene citrate side effects (Song et al., 2006). This observation is attributed to the pharmaco-energetic effects of Clomiphene Citrate (CC), which from the perspective of

Chinese medicine, are believed to be heat producing. As a result, this heat producing effect is beneficial in cases of Kidney yang deficiency diagnosis, since it results in the warming up of the yang. Furthermore, the heat producing effect is beneficial in cases of preexisting dampness and stagnation of qi and blood, by allowing movement thereof. However, if a patient has a kidney yang deficiency accompanied by a kidney yin deficiency diagnosis, clomiphene will exacerbate the internal heat causing more disorder by further damaging the yin thereby causing hot flashes, thinning of the endometriosis, drying up of cervical mucus, and causing irritability. If the phlegm heat is present, it may lead to nodule formation and ovarian hyperstimulation (Lyttleton, 2004). By combining Chinese herbal medicine, the heat producing effect of CC may balance the negative effects of clomiphene and be more beneficial to the patient.

Limitations of Current Study

Several limitations regarding the current study were identified. First and foremost, this literature review was conducted on twenty-two articles, which included researches, abstracts, reviews, and two meta-analysis researches. The articles chosen for the current analysis is a limiting factor in terms of the number of the participants involved. The number of subjects in each research was comparatively small. The average number of participants were 54.4, ranging from 22 to 107, which may limit the accuracy of the data. A further limiting factor was that many of the articles were available only in the Chinese language. As a result, some of the data's were obtained only from the English language abstracts that were provided. Nonetheless, the results from the analysis of all the studies reveal the positive impact of an integrative approach in the treatment of PCOS.

In the studies reviewed, it is observed that TCM diagnoses are individually based, and appropriate Chinese herbal medicines are prescribed based on signs and symptoms. An obvious limitation in the current study is the issue of accuracy and consistently of the diagnosis, given the wide range of education, skill, and experience levels of the numerous practitioners involved in the diagnosis processes. This factor is inherent in the retrospective literature synthesis methodology chosen for the current study.

The factors of herb safety, quality, and adverse effects were only discussed in only 2 of the 22 articles: Study 7 (Tominaga et al., 2011) and Study 22 (Chen et al., 2010). In several of the studies, there were insufficient data regarding dosages. Hence, these studies cannot be replicated. In several articles the assessment of treatment was based on cure: most effective, and not effective. Cure was defined as conception, regular menstrual cycles, and/or normal BBT, a normal of serum hormone levels, and ratios. Some effect was defined as improvement of the menstrual cycle (more than six times a year), improvement in clinical signs and symptoms, and improvement in serum hormone levels and ratios. No effect was defined as no obvious improvement in clinical symptoms or laboratory analyses. Only Study 10 (Jia & Wang, 2006) discussed the meaning of no effect. Based on the above criteria, Study 4 (Ling, 2002) reported cure as 43.7 5% (14/32) and total effectiveness as 90.62% (29/32) in a sample size of thirty-two subjects, which indicates a possible error in the results.

Other studies reported pregnancy as part of their results. The rate of pregnancy was not based on total number of subjects in the groups, but rather on the number of subjects who wished to become pregnant. In Study 11 (Jia & Wang, 2006), 9 out of 43 PCOS suffered infertility, and all nine conceived. The authors reported 100% pregnancy

outcome rate, which indicates a potential error in the reporting of results. Even more significant is the fact that the studies that reported pregnancies did not discuss the factor of variable of live births. This observation is important since PCOS patients are subjected to complication in their pregnancies associated with early pregnancy loss, gestational diabetes, pregnancy-induced hypertensive disorders, and the birth of small for gestationalage babies (Homberg, 2006).

There are two additional limitations that deserve consideration. First, is the limitation attributed to a lack of time in securing a licensed acupuncturist with a PhD to read a sample of three articles to verify the data was collected accurately (not less than 70%) as was originally planned and articulated in the Methods chapter of this document. Secondly, there is a limitation regarding the ethnicity of the patients. Most of the studies were conducted on Asian women. It is well known that the incidences of clinical and biochemical hyperandrogenism may be lower in Asian women as opposed to PCOS women of other ethnicities.

Suggestions for Future Research

As indicated above the differences between western and eastern medical theories are substantial and therefore yield different results, especially in terms of diagnosis. Furthermore, within Chinese medicine alone, not all TCM practitioners are consistent with their diagnoses and prescriptions. In future studies, common diagnostic categories, treatment strategies, an appropriate dosage and duration of treatment should be specified to create proper practice guidelines for PCOS analysis. In addition, future studies need to be more precise regarding herbal preparations and should employ research methodologies that have the potential to identify the active component or components of each individual herbal medicine.

Future studies should include large-scale randomized control trials for Chinese herbal medicine and treatment of PCOS. Such studies with higher levels of control will have stronger validity, and will therefore be more acceptable to the western medicine community. Studies focusing on the induction of ovulation in PCOS women seeking pregnancy, with a live birth outcome with the use of integrative treatments are recommended, since live birth determines the effectiveness of the treatment.

This researcher's focus was solely on Chinese Herbal medicine and PCOS. Further research should be engaged regarding PCOS cases with the application of different aspects of Chinese herbal medicine. Research consideration should be given to exploring the factors of diets, supplements, acupuncture, moxibustion, and exercises such as Tai chi and Qi gong, all with the aim of determining the percentage-yield of benefit for each.

Conclusion

The combination of Chinese medicine and Clomiphene citrate may be beneficial to PCOS women with chronic anovulation and infertility, in terms of ovulation induction, pregnancy, and the balancing of potential side effects. However, further studies are needed and should be conducted in controlled randomized clinical trials.

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Appendix A: IRB Approval Letter

YO SAN UNIVERSITY
OF TRADITIONAL CHINESE MEDICINE

April 25, 2012

Mitra Daneshrad, L.Ac.
206 So Robertson Blvd
Beverly Hills, CA 90211

Dear Mitra,

Your Claim for Exemption from the Institutional Review Board (IRB) has been reviewed. Your research proposal has been approved, with no recommendations effective April 1, 2012 through March 31, 2013.

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.

Regards,

Debra Jean Rawdin
IRB Coordinator

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

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

1. Ushiroyama, T., Ikeda, A., Sakai, M., Hosotan, T., Suzuki, Y., Tsubokura, S.(2001). Effects of unkei-to, an herbal medicine, on endocrine function and ovulation in pcos. *J Reprod Med.*, *46*(5), 451-6.

2. Ushiroyama, T., Hosotani, T., Mori, K., Yamashita, Y., Ikeda, A., & Ueki, M. (2006). Effects of switching to wen-jing-tang (unkei-to) from preceding herbal preparations selected by eight-principle pattern identification on endocrinological status and ovulatory induction in women with polycystic ovary syndrome. *The American Journal of Chinese Medicine*, *34*(02), 177-187.

3. Sun, W., Imai, A., Tagami, K., Sugiyama, M., Furui, T., & Tamaya, T. (2004). In vitro stimulation of granulosa cells by a combination of different active ingredients of unkei-to. *Am J Chin Med*,*32*(4), 569-78.

4. Ling, H. (2002) Treatment of Polycystic Ovarian Syndrome (PCOS). *Beijing Journal of Chinese Medicine*. #6: 323-326.

5. Sakai, A., Kondo, Z., Kamel, K., Izumi, S., & Sumi, K. (1999). Induction of Ovulation by Sairei-to for Polycyctic Ovary Syndrome Patients. *Endocrine Journal*, *46*(1), 217-220.

6. Okamoto, M., Sakakibara, H., Yoshida, H., Fukazawa, Y., Takashima, K., Kondo, Y., et al. (2010). Effects of Saireito on the ovarian function of patients with polycystic ovary syndrome. *Reproductive Medicine and Biology*, *9*(4), 191-195.

7. Tominaga, K., Tsuchida, M., Hayashi, M., Asahi, A., & Inui, H.(2011). Ovulatory effects of an extract from Maitake mushroom in patients with polycystic ovary syndrome. *J. Reprod. Engineer*,14, 7-12.

8. Song, J., Yan, M., Wu, X., & Hou, L. (2006). Progress of integrative Chinese and Western medicine in treating polycystic ovarian syndrome caused infertility. *Chinese Journal of Integrative Medicine*, 12(4), 312–316 (He, 2004)

9. Wang Z., Yu C. (2008) Effects of Bushen Huayu Qutan Recipe on local ovarian factors in androgen-sterilized rats. JCIM, 6(4), 1-5.

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13. Yang, YS, Zhang YL (2005) Clinical study of ganshao capsule in treating clomiphene-resistant polycystic ovarian syndrome. *Zhongguo Zhong Xi Yi Jie He Za Zhi*, *25*(8), 704-6.

14. Song, J., Yan, M., Wu, X., & Hou, L. (2006). Progress of integrative Chinese and Western medicine in treating polycystic ovarian syndrome caused infertility. *Chinese Journal of Integrative Medicine*, 12(4), 312–316 (Hua et al., 2003).

15. Lian, F., & Zhao, S. (2012). Effects of Shen invigorating and Chong-channel regulating method on anti-Müllerian hormone and oocytes quality in polycystic ovarian syndrome patients. *Zhongguo Zhong Xi Yi Jie He Za Zhi. 32*(1), 9-12.

16. Kuek, S., Wang W.J. & Gui, S.Q. **(**2011). Efficacy of Chinese patent medicine Tian Gui Capsule in patients with polycystic ovary syndrome: a randomized controlled trial. *Zhong Xi Yi Jie He Xue Bao.* 2011 Sep;9(9):965-72.

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20. Song, J., Yan, M., Wu, X., & Hou, L. (2006). Progress of integrative Chinese and Western medicine in treating polycystic ovarian syndrome caused infertility. *Chinese Journal of Integrative Medicine*, 12(4), 312–316 (Xia et al., 2004).

21. Wu, JH., Yu CQ., Zhou QL. (2007) Clinical study on effect of Bushen Huayu Qutan Recipe in treating polycystic ovarian syndrome. *Zhonghua Nan Ke Xue*; 27(10):883-6.

22. Chen, J. T., Tominaga, K., Sato, Y., Anzai, H., & Matsuoka, R. (2010). Maitake mushroom (Grifola frondosa) extract induces ovulation in patients with polycystic ovary syndrome: a possible monotherapy and a combination therapy after failure with first-line clomiphene citrate. *The Journal of Alternative and Complementary Medicine*, *16*(12), 1295-1299.

Appendix C: Data Collection Instrument

TCM/Integrative

Study	1	2	3	4	5	6	7
Info Source							
Author							
Year							
Journal/publisher							
Type of study							
Research							
Case							
meta-analysis							
Review							
Abstract							
Number of Subjects							
Age							
Diagnostic test:							
Ultrasound							
LH							
FSH							
AMH							
E2							
Progesterone							
PRL							
Serum Testosterone							
DHEA							
SHBG							
ACTH							
IR							
Fasting Insulin/ blood glucose							
HOMA-R							
Cortisol							
WHR							
Acne							
BMI/WHR							
BBT							
PCO							
Follicles							
Hirsuitism							
Symptoms present							
Annovulation							
Oligomenorrhea							
Insulin Sensitivity							
Hyperandrogenism							
Obesity							
Infertility							
polycystic ovaries							
Clomophine citrate resistance							
Control Present							

Inclusion/Exclusion
Western treatments
Birth Control Pills
Clomiphene Citrate
Metformin
Diane 35
CC/hCG
TCM Diagnosis
Eight Principle
Sp and Kd Yang deficiency
Cyclic treatment
Kd Yin deficiency with heat
Kd Yin
Sp Qi deficiency
Herbal Formulas
Wen Jing Tang
Dang gui Shao Yao San
Gui Zhi Fu Ling Wan
ErZhi Tian Gui Capsules
Dr Chai Hao-yan
Tian Gui Capsule
Tian Gui Fang
Saireito
Bushen Tongmai Recipe
Bushen Huayu Qu Recipe
GuiShao Di Huang decoction(modified)
Cupailuan decoction
Yu LingZhu Decoction (modified)
Shixiaosan (modified)
CangfuDao tang
Shenqiwan
GanShao Capsules
Hui Shu Hua
Herbal Formulas
Duration of Treatments

Appendix D: Herbs Used in the Studies

Herbs Used in Each Study

Study #	1	$	2.00	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Ba Ji Tian																					x		
Bai Shao	x		x		x			x		x						x				x		x	
Bai zhu						x	x					x								x			
Ban Xia	x		x		x	x	x					x								x			
Bie Jia																							
Bu Ghu Zi																	x				x		
Cang Zhu			x																	x			
Chai Hu						x	x																
Chi Shao										x										x		x	
Che Qian Zhi					x										x								
Chen Pi												x											
Chuan Niu Xi									x											x			
Chuan Xiong	x		x		x				x		x				x	x							
Dan Shen									x		x												
Dang Shen												x								x			
Dang Gui	x		x		x				x	x					x	x	x			x		x	
Du zhong					x				x						x					x			
E jiao	x		x						x														
Fu Ling			x			x	x					x								x			
Gan Cao	x		x			x	x	x	x			x				x				x			
Ge Gen											x												
Gou Qi Zi									x	x						x				x		x	
Gui Zhi	x		x			x	x																
Gui jia/Gui Ban												x					x				x		
Han Lian Cao									x							x							
He Shou Wou										x	x									x		x	
Hong Hua									x											x			
Hu Zhang																	x						
Huai Niu Xi																				x	x		
Huang Bai												x											
Huang jing									x								x				x		
Huang Qi											x												
Huang Qin						x	x																
Hui Shu Hua								x															x
Kun Bu									x														
Jiang Huang																					x		
Jie Nei Jin																				x			
Lu Jiao Shuang									x											x	x		
Lu Lu Tong																					x		
Ma Biao Cao																	x						
Mai Men Dong	x		x		x					x												x	
Meng Chong									x														
Mu Dan Pi	x		x		x															x	x		
Nu zhen zi									x							x					x		
Pei Lan																					x		
Pu Hong																				x			
Qian Cao																				x			
Ren Shen	x		x		x		x	x															
Rou Cong Rong											x										x		
Rou Gui																				x			
San Leng									x														
San Qi											x												
Sang Shen Zi										x												x	
Sang Ji Shen									x														
Sha Yuan Ji Li									x														
Shan Ci Gu									x														
Shan yao																				x	x		
Shan Zha																				x			
Shan Zhu Yu																				x	x		
Sheng Di huang												x				x							
Sheng Jiang	x		x		x																		
Shi Cang Pu																	x						
Shu Di Huang											x						x			x			
Shui Zhi									x														
Tao Ren			x		x				x						x		x			x			
Tu Bie Chong									x														
Tu Su Zi					x				x						x	x				x	x		
Wan Leng Zi										x												x	
Wu Ling Zi																				x			
Wu yao																				x			
Wu Zhu Yu	x		x		x																		
Xia Ku Cao									x														
Xian Mao									x														
Xiang Fu									x							x				x			
Xu Duan									x											x			
Yi Mu Cao									x											x			
Yi Yi Ren					x										x								
Yin Yang Huo					x				x		x				x		x			x	x		
Yu Jing									x												x		
Ze Lan									x											x			
Ze Xie			x			x	x					x								x			
Zi He Che																				x			
Zhi Mu												x					x						
Zhi Shi Ying																				x	x		
Zhu Ling						x	x																
Herbs not included													x	x				x	x				