The Influences of Acupuncture and Chinese Herbal Medicine On Semen Parameters and Male Subfertility, A Research Synthesis

A Capstone Project

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By

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Abstract

This research synthesis examined the effects of acupuncture and Chinese herbal medicine on sperm parameters and male subfertility. Nineteen studies pertaining to both animal and human subjects were included in this review. Data pertaining to sperm count, concentration, motility, and morphology in response to TCM treatment modalities, were abstracted into charts and analyzed. Seven of the total nineteen studies involved acupuncture intervention. Eleven studies involved Chinese herbal medicine intervention. One study involved a combination of acupuncture Chinese herbal medicine and Moxibustion intervention. All nineteen studies showed improvement in at least one sperm parameter following intervention with either TCM treatment modality. Different modalities were used as control intervention without impacting sperm parameters in thirteen of the nineteen studies. However, one study found statistically significant improvement in semen concentration following placebo acupuncture and four of the studies found a decrease in at least one sperm parameters in the control group. No adverse effects were reported in any of the studies. In conclusion, acupuncture and Chinese herbal medicine appear to be a safe and potentially effective treatment intervention for improving semen parameters and semen quality in men suffering from subfertility. Future studies with increased number of participants, using human subjects, and Chinese herbal formulas interventions are proposed.

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Chapter One: Introduction

Reproduction and procreation are at the core of all living beings. It is an inherent, strong, and natural drive. The wish for offspring is a powerful survival quest that exists on many different levels including physical, emotional, cultural and psychological. Understandably when one experiences difficulty reproducing one will go to great lengths to overcome this challenge.

Infertility and subfertility have mystified healers since ancient times. Advances in biotech technologies as well as investigation and communication methods over the past few decades have brought about many changes. Besides advances in treatment methods we now have more precise tools and techniques to assess our traditional treatment modalities. More than ever before we can now examine how treatment modalities including acupuncture and herbal medicine as well as our diet and life style influence our cellular makeup and in this case our fertility.

Prevalence of Infertility

Infertility is a growing concern among couples trying to achieve pregnancies. In France and the United Kingdom one in seven couples, that is 14%, (Wilkins, 2009) will experience difficulties achieving pregnancies and in similar societies this rate is between 8-20% (Alison, 2003; Wilkes, 2009; Thonneau, 1991). Male factor problems are involved in up to 57% of all cases and approximately 20% of all infertility problems are due to male factor alone with poor sperm parameters being

one of the chief causes of male factor infertility (Wilkes, 2009; Thonneau, 1991). Moreover, studies suggest a steady decline in overall sperm quality over the past 50 years (Adamopoulos, 1996; Auger, 1995; Irvine, 1996). Auger (1995) and colleagues evaluated sperm from 1351 healthy, fertile men over the span of 20 years and found a steady decline in sperm concentration, motility, and morphology.

Even though male factor infertility is so prevalent, biomedical treatment options are very limited (Deadman, 2008; Speroff, 2005; Rittenberg, 2010). Currently men with low and abnormal semen parameters have minimal options for improving these values. According to Speroff (2005) "with few specific exceptions, male infertility is not amenable to medical treatment." Available biomedical treatments offer limited options for actually improving sperm quality (Rittenberg, 2010).

Currently, one of the main biomedical solutions for male infertility is intracytoplasmic sperm injection (ICSI). However, this solution has its drawbacks, including short and long-term complications and some problems that we may not be aware of yet due to lack of long-term evidence. The introduction of ICSI in 1992 has revolutionized the treatment of male factor infertility and improved success rates of in-vitro fertilization (IVF) (Agarwal, 2008). ICSI does not cure male infertility but rather bypasses the need to improve or increase semen densities and quality in order to achieve conception (Rittenberg, 2010).

Semen Parameters and Analysis

Over the past few decades, semen analysis has been the main predictor of male fertility. Many studies show that better sperm parameters including count, concentration, motility and morphology improve fertility rates (Cooper, 2009; WHO, 1987,1992; Kruger, 1988). In rare occasions, spontaneous pregnancies may result from intercourse with men with compromised sperm parameters. However, if male factor infertility is present, it can almost always be detected by semen analysis.

The World Health Organization (WHO) normal semen reference recommendations were compiled following studies that compared fertile and infertile men excluding female infertility factors. These studies found a direct correlation between low sperm parameters, specifically low count or concentration, motility, or morphology, and fertility outcomes (Cooper, 2009; WHO, 1987,1992; Kruger, 1988). These findings stress the benefits of improving semen parameters. Since these studies show that healthier semen parameters significantly increase the chances of achieving a healthy pregnancy, one may conclude that finding treatments for improving sperm parameters will benefit male fertility outcomes.

As stated previously, semen analysis is one of the most important predictors of male fertility potential. Semen testing assesses the health of the spermatozoa by testing a variety of parameters through a variety of techniques. Semen analyses techniques are constantly evolving in search for an optimal test that can help improve fertility outcomes as well as minimize birth defects and morbidity. Sperm

parameters most commonly assessed are sperm count, sperm concentration, sperm motility, and sperm morphology. Therefore, these are the semen parameters that are compared in this study.

Sperm count refers to the number of sperm per ejaculate. Sperm concentration refers to the number of sperm per milliliter. The accepted normal sperm concentration levels are 20 million sperm/ml. Oligospermia is a condition of less than 20 million sperm/ml, azoospermia is absence of sperm while polyspermia is a condition of abnormally elevated sperm concentration associated with poor sperm quality.

According to the WHO guidelines (1999), Sperm motility is graded as A) rapid forward progress motility, B) slow or sluggish progressive motility C) non progressive motility and D) immotility. Normal motility value is defined as greater than 50% forward moving sperm.

Sperm morphology analysis is a subjective, and difficult-to-standardize test. Morphology measures each part of a single sperm, namely the head, the neck the midpiece, and the tail for a variety of abnormalities such as size, shape, extra parts (e.g. extra head or tail) or missing parts. Sperm morphology is then defined by the percentage of abnormal forms present in the semen (Wein, 2011). The most common guideline recommendations used for sperm morphology are the Kruger strict criteria (Kruger, 1988), which were also adopted as the WHO 4th edition

guidelines (1999). The Kruger strict guidelines (1988) suggest that teratozoospermia or less than 14% healthy sperm is associated with infertility or difficulty in achieving pregnancy. Some laboratories still use the older guideline recommendations of the WHO 3rd edition (1992). The WHO 3rd edition guidelines propose that abnormal fertility is over 30% healthy sperm, but the morphology examination guidelines are not as extensive as with the Kruger 1988 guidelines (Wein, 2011).

Intracytoplasmic Sperm Injection (ICSI)

Improving semen quality may also potentially benefit ICSI outcomes. According to the 2007 ART report at the Center for Disease Control and prevention (CDC), ICSI use has increased by more than 2.5 times between 1998 (24,612) and 2007 (64,629) (ART, 2007). ICSI was designed to improve fertility rates when severe male factor subfertility and low sperm quality were present. It revolutionized male infertility and dramatically improved fertilization, pregnancy, and birth rates. It enabled men that were not able to father their own offspring achieve that dream. ICSI, a technique that is performed with in-vitro fertilization (IVF), was introduced in 1992 (Palermo, 1992). It involves injecting a single sperm, chosen by the lab technician, into an oocyte that was extracted from the female's ovary. Even though the sperm ejaculate is first washed and processed to eliminate most of the deformed and dead sperm cells prior to choosing the one cell that will insert into the oocyte, ICSI still bypasses the natural selection process. The sperm cell, selected to be injected into the oocyte, may look good, but may still possess

defective genes. Thus, even though ICSI with IVF benefits couples seeking infertility treatments by improving embryo fertilization and pregnancy rates, it also raises a variety of cost and safety issues (Wein, 2011).

A growing body of evidence is showing an increased risk of major and minor birth defects as well as possible imprinting disorders (e.g. Beckwith-Wiedemann syndrome, Angelman syndrome) in babies conceived with ICSI and IVF when compared to babies conceived naturally (Hansen, 2002, 2005; Maher, 2005; Rimm, 2004). In a meta-analysis published in 2004 investigators found an approximately 29% increased rate of major malformation in infants born with assisted reproductive therapies (ART) when compared to infants conceived naturally (Rimm 2004). In light of these findings, improving semen parameters can potentially decrease malformation and birth defect rates in babies conceived with ART including IVF and ICSI.

Studies also show a negative correlation between the percentage of sperm motility, and morphology in an ejaculate and percentage of sperm DNA fragmentation. When the sperm parameters are low in motility and or morphology, chances of abnormal DNA fragmentation increase by 27% (Sun, 1997; Irvine, 2000; Kasimanickam, 2006). A growing body of evidence is now pointing to a negative correlation between percent of DNA fragmentation in sperm and conception failure, abortions, malformations and genetic diseases (Sun 1997; Fernandez-Gonzales, 2008).

Additionally, researchers found increased rates of negative long-term effects resulting from ICSI with DNA fragmented sperm. Fernandez-Gonzales et al. (2008) found that use of DNA fragmented sperm in ICSI, generated higher rates of negative characteristics that only emerged later in the life of rats. They found statistically significant increase of problems such as abnormal growth, premature aging, abnormal behavior, and mesenchymal tumors (Fernandez-Gonzales, 2008). Other researchers found increased apoptosis rate and marked damage to the spermatogenic epithelia of adult mice conceived with ICSI and IVF when compared with mice conceived with IVF but without ICSI (Yu, 2011).

Since ICSI is mostly used when men present with poor semen parameters, the chances of choosing one sperm with defective DNA are increased. Therefore, improving sperm parameters and semen quality when using ICSI may potentially benefit ICSI outcomes. It may increase the chance of choosing a healthy sperm when injecting it into the oocyte and that in turn will improve embryo cleavage rates, implantation rates, and potentially, birth rates and healthy offspring.

In summary, studies show that when male factor is involved as an etiology in a couple's infertility, healthy semen parameters are the most accurate predictor of the male ability to conceive. Currently, very few biomedical options are available for men who wish to improve their sperm quality and semen parameters.

Spermatozoa Structure

The word sperm is derived from the Greek word for seed. The spermatozoon is a remarkable, complex, metabolic and genetic structure. A spermatozoon is composed of three morphological sections: the head, neck and tail or flagellum. The sperm head contains the nucleus, which houses the DNA and the genetic material. The nucleus sits among highly concentrated chromatin and is surrounded by the acrosome, an organelle that contains enzymes used to penetrate the ovum. The sperm neck includes the connecting piece and the proximal centriole. The tail includes the midpiece, principle piece and the end piece. The midpiece contains the axoneme. The axonemal complex contains ring shaped mitochondrial sheath, microtubules and is surrounded by outer dense fibers. This complex structure extends from the sperm neck to the end piece of the tail. The axoneme is responsible for the movement and motility of the sperm. The mitochondria and the enzymes that surround the axoneme are responsible for adenosine triphosphate (ATP) production (all from Wein, 2011, chap. 20).

Male Infertility

Current recommendations by the American Society for Reproductive Medicine (ASRM) and the Practice Committee of the American Urological Association suggest an infertility evaluation if twelve months of unprotected intercourse did not result in a pregnancy (The Male Infertility Best practice, 2006). These recommendations follow studies that show 60% to 75% of couples practicing

unprotected intercourse will conceive within six months, and 90% will conceive within one year. Thus, the above mentioned recommendations are widely accepted even though the latest WHO (4th edition, 1999) guidelines recommendations are that infertility is defined as twenty-four months of unprotected intercourse with no pregnancy.

Male Infertility Etiologies

Etiologies for male infertility are classified into three categories: pre-testicular, testicular, and post-testicular (Wein, 2011). Pretesticular or secondary testicular failure etiologies are usually endocrine related disorders. Etiologies for this category include congenital disorders, hypothalamic and pituitary disorders including tumors and surgeries, hyperprolactinemia, thyroid problems and exogenous hormones (e.g. prednisone, testosterone, estrogen, anabolic steroids, etc.) (Wein, 2011). The testicular category or primary testicular failure, like the name implies, are pathologies within the testes. Testicular etiologies may be due to chromosomal abnormalities, varicocele-induced damage, medications, environmental related damage, Steroli cell disorders, cryptorchidism, or idiopathic reasons. Post testicular etiologies are those related to such disorders as ejaculatory dysfunction, genital tract obstruction and infections (Wein, 2011).

Varicocele is the most common etiology for male infertility at 42.2% following by idiopathic etiology 22.7%, obstruction 14.3%, normal or female factor 7.9%, cryptorchidism 3.4%, immunologic 2.6%, ejaculatory dysfunction 1.3%,

testicular failure 1.3%, drugs and radiation 1.1%, endocrinopathy 1.1% and all others 2.1% (Irvine, 1998; Wein 2011). Varicocele, the most common cause of infertility, refers to enlarged veins in the testes, usually on the left gonad, and most likely due to defective valves. Increased scrotal temperature is the leading theory behind the mechanism of varicocele induced impaired spermatogenesis. Other proposed mechanisms for this condition are hypoxia due to impaired venous drainage, increased gonadotoxins due to poor clearing, and elevated oxidative stress levels. The bulk of studies report improved semen parameters following varicocele repair, though the vast majority of patients with varicocele related azoospermia would still require ART following varicocele correction surgery (Wein, 2011). Cryptorchidism occurs in 2.7% of infants but most cases correct themselves within one year. If the testicle remains undescended the condition leads to subfertility. Endocrine related causes include hyprgonadotrophic, hypogonadism, which refers to elevated FSH and LH levels while T levels are low usually due to failure at the testis level. Hypogonadotropin hypogonadism refers to low T and low FSH and LH levels (Wein, 2011).

Environmental and Life Style Factors Affecting Male Infertility

Studies suggest a steady decline in overall sperm quality over the past 50 years (Adamopoulos, 1996; Auger, 1995; Agarwal, 2008). Many causes of male infertility are idiopathic. No one culprit is directly linked to this steady decline in sperm parameters but rather many factors are associated with it. Many environmental factors have been studied extensively and show negative influence

on male semen parameters. Increased presence of environmental pollutants is associated with increased incidence of male infertility and decrease quality of spermatozoa nuclear content (Agarwal, 2008). An increased number of studies consistently show the damaging effects of environmental factors on sperm parameters and infertility (Agarwal, 2008; Jurewicz, 2009).

Moreover, many studies now show that exposure to environmental chemicals during fetal development leads to reduced reproductive health during the male's adult life as well as DNA damage in offspring during three to four generations in the future (Agarwal, 2008; Jurewicz, 2009). The precise synchrony of the endocrine system is essential for reproductive potential. Substances that may interfere with the complex hormonal system are called endocrine disruptive chemicals (EDC). Many of the chemicals have estrogen-like structure and they interfere with the endocrine system. These substances' disruptive influences have been linked to many disorders including reduced semen parameters and sperm DNA integrity. Thus, environmental chemicals, endocrine-disrupting chemicals, occupational exposures and air pollution, all have negative effect on the sperm potential.

The influences of life style choices on sperm health have also been studied at length. Many studies report that excess alcohol consumption, cigarettes smoking, and recreational drug use, reduce sperm parameters (Agarwal, 2008; Jurewicz, 2009; La Vignera, 2011). Medications are another well-researched contributing

factor in male infertility and some biomedical drugs are well documented to have negative effects on sperm (Safarinejad, 2008).

Increased age and obesity are also found to negatively influence sperm potential. Recent studies show a link between advanced paternal age and an increased rate of DNA damage as well as a decreased lifespan of female offspring (Agarwal 2008). Studies also demonstrate a correlation between obesity in men and poor semen quality. These findings report a correlation between obesity in men and increased levels of estrogen, reduced levels of inhibin B, as well as reduced total testosterone production, resulting in disruption to the synchronicity of spermatogenesis (Agarwal 2008; Pauli, 2008).

Elevated heat is a well-known cause of male infertility (Jung, 2007). The optimal testicular temperature for sperm production is 93.2°F (34°C) (Jung, 2007). Therefore elevated or prolonged heat exposure in the testicles can impair sperm quality and production (Deadman, 2008; Jung, 2007). Heat sources such as hot baths, tight underwear, computers placed close to the genital area, prolonged sitting in one place, and prolonged bicycle riding may all potentially damage the sperm. Genial infections and other medical conditions may also lead to elevated temperature in the groin area resulting in sperm damage (Deadman, 2008; Jung, 2007).

Studies also suggest reduced semen parameters with increased mobile phone use. Over the past ten years, mobile phone use has increased tremendously and so have the concerns of high-frequency electromagnetic fields (EMF) or radiofrequency electromagnetic radiation (RF-EMR) effects. Results from studies, investigating these effects on semen, show a decrease in sperm count and motility, and increase in oxidative stress (Jurewicz, 2009; La Vignera, 2011).

The list of potential damaging agents, chemicals, and life style choices is as long as the list of these available options, finding ways to mitigate these negative effects and potentially improve semen parameters can potentially benefit reproductive health and lead to better fertility results.

Male Infertility from a TCM Perspective

Early references to male fertility date to the 'Yellow Emperor'. The 'Yellow Emperor's Inner Cannon' or the 'Nei Jing' is regarded as the foundation of Chinese medicine. This text has many references to andrology related disorders such as diseases of the penis, scrotum, and testicles as well as extensive discussion of timely sexual development, puberty, sexual practices and how they relate to health and fertility (Damone, 2008). Male infertility is mentioned in the Nei Jing but the Zhu Bing Yuan Hou Lun (On the origin and indicators of Disease), a text compiled during the Tang dynasty (610 CE), is where we can find early mention of male infertility disease patterns and mechanisms (Damone, 2008).

Similar to what biomedical medicine describes today, the early Chinese medical scholars observed that the male reproductive system is a complex one. In order to produce sperm and transport it to the egg in the female, a man should have sufficient energy and substances, should be free of blockage in the semen pathway and free of excess heat or cold. Due to the complexity of the TCM diagnostic and treatment strategy, one should always keep in mind treating the whole body. However, the main patterns that are most often involved with male infertility are Kidney Yin Vacuity, Kidney Yang vacuity, Vacuity of both Kidney and Spleen Qi leading to Heart and Liver Blood deficiency, Damp Heat pouring downward, Stagnation of phlegm turbidity, Obstruction due to Blood Stasis, Cold Stagnation in the Liver Channel, and Liver Qi stagnation leading to other pathologies e.g. blood stagnation or Qi vacuity (Damone, 2008). Any energy system can be involved with the reproductive system directly or indirectly but the three systems that are most often involved in male infertility are the Kidney, Liver, and Spleen systems.

The Kidney energy system governs growth and development including reproductive system health. It stores Essence, both Pre Heaven Essence (acquired from the parents i.e. genetics) and Post Heaven essence (acquired from nourishment). The Essence is a substance that is the source for Qi, Blood, Fluids and semen. The Kidney have a Yin and a Yang aspect both equally important in the process of fertility. Kidney Yang is associated with the 'Ming-Men fire' or 'gate of vitality', an ancient Chinese medicine concept relating to a warming function essential to many processes in the body in this case healthy reproductive function,

sexual performance, puberty, libido, and fertility (Maciocia, 1989). Due to these roles, the Kidney system is closely associated with fertility problems (Damone, 2008; Deadman, 2008).

The Liver energy system influences fertility in several ways. Liver channel pathway, including its luo-connecting, divergent and sinew channels, all travel through and around the genitals. The liver governs the free flow of Qi in the body. Failure of the Qi to flow freely can result in several pathologies including Qi Stagnation, Blood stagnation, Liver Fire, Damp-Heat, all of which are conditions that may adversely affect the male reproductive system and sperm production. The Liver function of storing the Blood is closely associated with Liver Yin and Essence production, thus is closely associated with the male reproductive health. The Liver also controls the sinews and bones, and the penis is referred to as Zong-Jin, which translates to the meeting of the ancestral/one hundred sinews in Chinese (Deadman, 2008).

The relationship between the Spleen energy system and male fertility depends on its main function of governing the transformation and transportation of food and fluids. This process transforms food into Qi and Blood, a process essential to overall health and closely associated with Kidney Yang, Yin, Essence, and Liver Blood and Qi. Weakness of the Spleen in relation to male infertility may manifest as weakness of Qi and Blood affecting energy, sleep and sperm production. Additionally, failure of this function may result in Dampness that may seep down to

the genital area leading to Damp Heat accumulation in the groin, a condition often seen in male infertility (e.g. BPH, prostatitis, epididymitis, infections, blockage).

Lifestyle According to TCM Perspective

TCM healers have always stressed the importance of a healthy life style as an equally essential part of the treatment. Their wisdom that is several thousand years old is still relevant today when we look at the long list of adverse influences on sperm parameters including environmental factors such as herbicides and other toxic substances, radiation, medications, stress, diet, exercise, body size, and so on. It is evident that making healthy life style choices is an important part of preserving and improving sperm parameters and consequently, male fertility.

Exercise is recommended in order to promote the smooth flow of Qi and Blood, but avoiding excessive exercise, prolonged bicycle riding and other routines that may result in excessive heat to the genitals are equally important. Eating a healthy diet has always been emphasized as a way to improve health and quality of life. A healthy diet includes natural foods such as vegetables, grains, nuts, fruit and a small amount of meat or fish and spices while minimizing raw, sweet, greasy, spicy, and highly processed foods, since all can injure the Spleen and lead to Damp accumulation. Prolonged excessive stress, if not managed, can lead to Liver Qi Stagnation or injury to the Heart and Kidney and those in turn may interfere with sperm production and sexual performance. TCM stresses the importance of regular

sexual activity while at the same time excess intercourse or masturbation can lead to weakening of the Essence, which may lead to fertility problems.

Finally, following results from current research, men trying to conceive are advised to follow the above recommendations as well as avoid smoking, recreational drug use, excess alcohol consumption, excess heat exposure to the groin area, and minimize environmental pollution in the diet, work place and home.

Research Question and Objective

Infertility is a growing concern among couples trying to achieve pregnancies. Among these couples male factor infertility demonstrated as low sperm parameters is a major component. Studies show that semen analysis is the most accurate predictor of male infertility. Reduced sperm parameters including sperm count, concentration, motility, and morphology, are associated with reduced pregnancy outcomes. Very few biomedical treatment options are available for improving semen parameters. The main biomedical solution for resolving male infertility is IVF with ICSI. The increased success rate of IVF with ICSI, in terms of pregnancy outcomes, bypasses the need to find solutions for directly improving sperm parameters. However, IVF with ICSI increases rates of adverse effects with short and long-term negative consequences to the offspring. Directly improving sperm parameters and sperm quality may improve pregnancy outcomes and minimize the adverse effects of IVF with ICSI. Many studies show that treatment interventions with traditional Chinese medicine (TCM), which include acupuncture and Chinese

herbal medicine, are safe, and significantly improve sperm parameters. The main objective of this literature synthesis is to systematically explore whether acupuncture and Chinese medicine improve sperm parameters, taking the level of reporting into consideration before including studies into the synthesis.

Glossary of Terms

ATP: Adenosine triphosphate is a nucleotide found in the mitochondria of all plant and animal cells. It is the main source of energy in the cell for many metabolic processes. The energy is formed and released when ATP is broken down through hydrolysis into adenosine diphosphate (ADP) (Pebay-Peyroula, 2003).

Acrosin activity: Acrosin is a digestive enzyme released from the acrosome at the head of the spermatozoa. It aids in the penetration of the Zona Pellucida.

ACTH: Adrenocoricotropic hormone

Asthenozoospermia: Too small a proportion of sperm cells with normal motility in the ejaculate.

Azoospermia: Absence of sperm cells in the semen. Primary = always, secondary = after previously known sperm production.

cAMP: Cyclic adenosine monophosphate

CC: Clomiphene Citrate.

CM: Cordyceps Militaris or Dong Chong Cao in Chinese

CP: Cyclophosphamide, A carcinogenic, mutagenic and fertility impairing drug

CREM: Stands for cAMP response element modulator, an essential factor in spermatogenesis (Yang, 2008)

FRAP: ferric reducing antioxidant potential; a method for measuring antioxidant activity.

FSH: Follicle Stimulating Hormone, a gonadotropin hormone secreted from the anterior pituitary.

GH: Growth hormone

GnRH: Gonadotropin Releasing Hormone

HPG axis: Hypothalamic-pituitary-gonadal

ICSI: Intracytoplasmic sperm injection is a form of artificial insemination in which one sperm cell is injected into each egg cell in a Petri dish.

IVF: In vitro fertilization form of artificial insemination in which the egg is placed in a Petri dish and approximately 100,000 sperm cells with good motility is added.

IUI: Intrauterine insemination sperm cells (in most cases after special preparation) are injected using a catheter directly into the uterine cavity.

LH: Luteinizing Hormone; a gonadotropin hormone secreted from the anterior pituitary.

MO: Radix Morindae officinalis or Ba Ji Tian in Chinese

OAT: Oligoasthenoteratozoospermia Summary of the results from a sperm evaluation (oligo = too little, meaning too low a concentration per ml; astheno = too slow; terato = too small a proportion of normally formed sperm cells)

ORAC: Oxygen radical absorbance capacity; an assay for measuring oxidation levels.

RNA: Ribonucleic acid

sFAS: Soluble Fas Ligand, when binds with its receptors it induces apoptosis.

TCDD: Tetrachlorodibenzo-p-dioxin, A pollutant generated from leaded gasoline exhaust, pulp and paper industries and herbicides,

TCM: Traditional Chinese medicine

T: Testosterone

TSH: Thyroid-stimulating hormone

Zona pellucida: A membrane surrounding the oocyte.

Chapter Two: Literature Review

In recent decades an increasing number of studies have been published in English, evaluating the effect of acupuncture and Chinese herbal medicine on different conditions, including male infertility. The following studies examine the effects of Acupuncture and Chinese Herbal Medicine on several specific aspects of the semen. Understanding the spermatozoon structure may help to better understand the relevance and significance of the semen analysis and testing results in the following studies.

Effects of Acupuncture on ICSI Outcomes

Zhang et al. (Zhang, 2002) investigated 22 cases of male idiopathic infertility before and after ICSI following acupuncture treatments. Treatments were administered twice a week for two months. The investigators observed sperm concentration, motility, morphology, fertilization rates and embryo quality before and after treatments. The authors reported statistically significant improvement in quick-sperm motility ($P < 0.05$) and normal sperm ratio ($P < 0.05$) following acupuncture treatments. Moreover, the investigators found significantly improved embryo fertilization rates ($P < 0.01$) following acupuncture treatments. Improvement was also found in embryo quality after the acupuncture treatments but not a statistically significant level.

Effects of Combined Chinese Herbal Medicine and Acupuncture on Sperm Parameters

Bo et al. (2011) conducted a study with a combined intervention of acupuncture, Chinese herbal medicine and moxibustion. This combination of treatment modalities closely resembles common practice in the clinical setting. Also unique to this study is the control group treatment intervention of acupuncture with clomefene citrate (CC). CC medication is a selective estrogen receptor modulator (SERM) that acts to inhibit the negative feedback on the hypothalamus leading to an increase in gonadotropin production. Integrated TCM and biomedical interventions are commonly encountered in the TCM fertility clinic. In this study thirty-seven men with semen abnormalities were randomly divided into two groups. The experimental group consisting of 25 men received acupuncture and an herbal formula while the control group comprising of 12 men received acupuncture with CC capsules. The experimental group showed statistically significant improvement ($P < 0.05$) in sperm density, sperm one-hour survival rate, motility, and normal morphology following acupuncture and herbal treatment. The control group showed a statistically significant reduction in sperm volume and statistically significant elevation in LH and T levels. CC administration leads to increase in LH levels that in turn influences the production of T leading to elevated T levels.

Effects of Acupuncture Treatments Intervention on Sperm Parameters

A prospective, randomized, placebo controlled study was published in 2009 showing how acupuncture treatments can significantly improve sperm motility

(Dieterle, 2009). Sperm from 52 patients with severe oligoasthenozoospermia was analyzed after acupuncture in 24 patients or placebo acupuncture in 28 patients. Results showed a significant improvement in sperm motility in the acupuncture group. Improved motility after acupuncture treatments concur with results from other acupuncture studies (Pei, 2005; Siterman, 1997; Zhang, 2002). However, results also showed a decrease in semen volume after the acupuncture treatments and increase in sperm concentration after treatments in the placebo acupuncture group. The improvement in a semen parameter within the control group prompted investigation due to the inconsistency with results reported in other studies. It may point to flaws in using sham acupuncture as control due to possible positive influence that shallow stimulation, such as the ones used with sham acupuncture, to an acupuncture point, may exert on study outcomes (Lund, 2006).

Siterman, in cooperation with other investigators published several studies investigating the influence of acupuncture on sperm parameters. In 1997 at a time when very few studies, investigating the influence of acupuncture on sperm parameters, were published in English, Siterman and colleagues published a prospective controlled study (Siterman, 1997). The study investigated the effect of acupuncture on sperm quality of males that suffer from subfertility associated with sperm abnormalities. Semen samples of 16 men with subfertility were analyzed before and after acupuncture treatments and compared to semen samples of sixteen untreated men with similar condition. Results following acupuncture treatments showed an increase in the fertility index ($P \leq .05$) derived from calculation of

improvement in total functional sperm fraction, percentage of viability, total motile spermatozoa per ejaculate and integrity of the axonema ($P \leq .05$).

In 2000 Siterman et al. published a pilot study aiming at finding potential effects of acupuncture on semen parameters. Sperm samples from twenty men with a history of azoospermia where examined. The participants where divided into three groups according to the etiology of their conditions. One group included six men with spermatogenic failure due to elevated levels of FSH (follicle stimulating hormone) and or LH (luteinizing hormone) without signs of genital tract infection. A second group was comprised of nine men with normal basal blood FSH and LH levels and with symptoms of genital tract infection. These patients had a history of prostatitis or vesiculitis. The third group consisted of the remaining five men with elevated FSH and or LH levels as well as genital tract infection. The control group was comprised of 20 men with similar andrological profiles to the study group. The control group did not receive any treatments. Each patient in the experimental group received two acupuncture treatments a week with a total of ten acupuncture treatments. A total of twelve acupuncture points were selected according to TCM diagnosis, from 30 predetermined points. Results showed distinct increase in sperm count following acupuncture treatments in 65% of the men from the experimental group while no semen parameter changes where detected in the control group.

In 2009, following results from their previous studies that showed an increase in sperm density after acupuncture treatments, Siterman et al. conducted

another study. In this study they state that poor spermatogenesis in patients with genital tract infection is associated with scrotal hyperthermia. The study was aimed at investigating the mechanism behind the increase in sperm output following acupuncture. They found that the influence of acupuncture treatments on sperm output in patients with low sperm density is associated with a decrease in scrotal temperature (Siterman, 2009).

Pei et al. (2005) evaluated the spermatozoa ultra structure after acupuncture treatments. Forty men with idiopathic oligospermia, asthenospermia, or teratozoospermia participated in the study. Twenty-eight of the participants received acupuncture twice a week for five weeks while the remaining twelve received no treatments. Results showed a statistically significant decrease in the ultrastructure defects of the sperm and a statistically significant increase in the percentage and number of healthy sperm after five weeks of acupuncture therapy. Additionally, statistically significant improvement was observed in several components of the sperm ultrastructure including the acrosome position and shape, nuclear shape, axonemal pattern and shape, and accessory fibers of the sperm organelles. Increase in sperm motility was also observed but median number and volume of the ejaculate did not significantly change or improve.

In another study, Gurfinkel et al. (2003) examined the effect of treatments with acupuncture and moxa, on semen abnormalities. 19 infertile men with idiopathic semen abnormalities of concentration, morphology and or progressive

motility participated in this prospective, controlled, and blinded study. The nineteen participants where randomized into two groups. Men in the study group received acupuncture and moxa at therapeutic points, while men in the control group received acupuncture and moxa at non-therapeutic points. Results showed significant increase in percentage of normally formed sperm when compared to the control group. No difference was found in the other parameters, namely: volume, concentration, progressive motility and number of round cells, between the two groups.

Effects of Chinese Herbal Medicine Intervention on Sperm Parameters

Chinese Herbal Medicine Combined with Carcinogenic Substances

Hwang et al. (2004) and Yang et al. (2008) investigated the effect of combined carcinogenic substances and Chinese herbal substances. Hwang et al. (2004) investigated the survival rate and sperm quality of guinea pigs exposed to Tetrachlorodibenzo-p-dioxin (TCDD) (A pollutant generated from leaded gasoline exhaust, pulp and paper industries and herbicides), combined with various dosages of Panax Ginseng (PG). Investigators found that animals died within 18 days after exposure to TCDD alone while 40-70 % of the animals exposed to TCDD but treated with PG survived until 40 weeks. Sperm motility of the PG treated animals following exposure to TCDD was higher ($P< 0.01$) when compared to animals not exposed to TCDD and not treated with PG. Improved sperm motility was detected even after discontinuing the administration of PG. Yang, and Chang, et al. investigated the effect of Psoralea Corylifolia (PC) or Bu-Gu-Zhi, an herbal substance on

spermatogenesis. The investigators divided rats into three groups. One group was not treated, the control group received Cyclophosphamide (CP) (a carcinogenic, mutagenic and fertility impairing drug), and the experimental group was treated with CP and PC. Investigators found that sperm count following CP with PC was statistically significantly higher ($p<0.05$) but sperm motility was statistically significantly lower ($p<0.01$) when compared to the control CP only group. This experiment is especially significant in light of all the negative influences of environmental factors on sperm. This experiment shows that herbal substances can promote spermatogenesis even when exposing the semen to a carcinogenic mutagenic drug.

Chinese Herbal Medicine Impact on Disomy

In 2007 Tempest et al. published an intriguing study. Investigators examined the disomy levels of six men with severe semen abnormalities. They observed that disomy levels fell significantly following treatments with TCM. Fluorescence in situ hybridization (FISH) was performed on sperm heads taken from these six patients before and after treatments with a Chinese herbal medicine formula. Results showed significant reduction in sperm disomy in all six men. The samples from the six men were also compared to samples from donors with normal fertility and samples from men with oligoasthenoteratozoospermia (OAT) that did not receive TCM treatments. Control group one was comprised of nine sperm samples from men with proven fertility. Control group two consisted of sperm samples from men with severe OAT. Control group three included the original samples taken from the

six men with disomy before treatment started. Results showed a significant reduction in sperm disomy levels in the experimental group, to levels not significantly different from those of the control group with proven fertility. The reduction in disomy levels coincided with the Chinese herbal formula treatment, leading investigators to hypothesize that the Chinese herbs were the cause of the disomy reduction. The authors state that this study was too small, not a placebo-controlled clinical trial and remarked that more studies are needed.

Effects of Single Chinese Herbal Substance on Sperm Parameters

In 2007, Park and colleagues examined the mechanism behind Korean ginseng ability to promote spermatogenesis. Sixteen rats where divided into two groups of eight rats each to form the experimental and control groups. The experimental group received Korean ginseng and the control group received a placebo. Following treatment the semen from the experimental group showed a significant increase in sperm count ($P < 0.05$) and motility ($P < 0.05$) as well as enhanced levels of camp-responsive element modulator (CREM) messenger RNA and protein. Investigators concluded that ginseng appears to induce spermatogenesis via CREM activation in the rats' testes (Park 2007).

Cordyceps Militaris (Dong Chong Cao) (CM), a Chinese herbal substance, was also investigated for its spermatogenic effect (Lin 2007). The experimental group included seventeen boars while the control group was comprised of twelve boars. The control group was fed with regular diet and the diet of the experimental group was supplemented with CM. Semen was collected every week, then tested and

compared for sperm motility, morphology, volume and total number. Significant improvement was found in volume ($P < 0.01$), motility ($P < 0.05$), and morphology ($P < 0.01$), following the supplementation with CM. Enhanced sperm production was found at the end of the first month, peaked at the end of the second month and was maintained for two weeks after the treatment discontinued. These results show that the length or treatment time as well as treatment dose are a factor that needs to be taken into consideration.

In 2005 researchers investigated another traditional Chinese herbal substance. Choi et al. examined the effect of Radix Morindae officinalis (MO) (Ba Ji Tian in Chinese) on the sperm of rats (Choi 2005). Ten rats participated in the study and where divided into two groups of five rats each. The rats in the experimental group where given (MO) and the control group received normal saline solution. Results showed significant improvement in semen concentration ($P < 0.01$) morphology ($P < 0.01$), and motility ($P < 0.01$), following MO supplementation when compared with the control group.

Effects of Formulated Chinese Herbal Substances on Sperm Parameters

Bu Zhong Yi Qi Tang (Tonify the Middle and Augment the Qi Decoction) is a commonly used Chinese herbal formula with many applications. The author of the formula was Li Gao, and it dates back to 1249 AD, to the Pi Wei Lun (Discussion of the Spleen and Stomach) (Chen, 2009). Furuya et al. (2004) investigated the effect of this formula on semen taken from men with idiopathic infertility. Twenty-two men with idiopathic infertility, oligozoospermia and /or asthenozoospermia,

received 7.5g of Bu-Zhong-Yi-Qi-Tang daily for three months. Semen samples were analyzed before and after the three months of treatments. Results showed a statistically significant increase in sperm concentration and motility following the treatment. Investigators also found a significant increase in seminal plasma sFas levels and no significant change in seminal plasma levels of IL-6 and IL-8 following treatment. The investigators hypothesize that the increase in sFas semen plasma levels may play an important roll in the increase in semen parameters. sFas plays a role in inhibiting apoptosis and therefore may be important in the fertilization process.

Shao-Fu-Zhu-Yu-Tang (Drive Out the Blood Stasis in the Lower Abdomen Decoction) is another very famous Chinese herbal formula. It originated in 1830 AD, by Wang Qing-Ren, in a text called Yi Lin Gai Cuo (Corrections of Errors Among Physicians) (Chen, 2009). Yang and Chen et al. (2003) studied the effects of this formula on sperm parameters. The researchers observed an increase in sperm motility as well as morphology prompting further examination of the reason for the improvement. Semen from 36 patients with chronic prostatitis was evaluated before and after 60 days of treatment. The formula was administered in a capsule form and patients received 3g, three times a day for 60 days. When researchers compared semen samples before and after treatment, they found a statistically significant improvement in sperm motility ($P < 0.01$), and morphology ($P < 0.01$), following the treatment with the herbal medicine. Semen count also increased but not at a statistically significant level. Other statistically significant differences observed in the post-treatment semen samples were; an increase in the number of

lecithin crystals, a decrease in oxidation levels to normal levels ($P < 0.01$), bacteria levels vanished, and a statistically significant ($P < 0.01$) increase in acrosin activity levels. The researchers explored the correlation between acrosin activity and sperm motility. They hypothesize that reduced semen acrosin activity not only reduces the ability to penetrate the zona pellucida but also influences the motility. They also explored the connection between improved motility and reduced levels of oxidative stress as well as reduced bacteria levels in the post treatment samples. They concluded that the formula was effective in improving sperm motility levels due to its acrosone activity as well as its oxidative and antibacterial effects.

Influence of Chinese Herbal Substances on Sperm Parameters In- Vitro

Several studies (Liu, 2004; Chen, 2000; Hsu, 2003; Huang, 2004; Amano, 1996) show direct, in-vitro, effects of Chinese herbal substances on sperm parameters. Hsu et al. (2003) reported that Cordyceps Sinensis exerts in-vivo and in-vitro effect on the leydig cells. Leydig cells are the cells responsible for testosterone production in the testes. The study showed significantly increased in-vitro levels of testosterone as well as increased serum testosterone levels when tested in-vivo following administration of Cordyceps sinensis.

Liu at al. (2004) examined the in-vitro effect of several Chinese herbal extracts on semen motility. They found that soaking sperm in an herbal solution of Astragalus Membranaceus, and Acanthopanacis Senticosi, significantly improved several aspects of the sperm motility. However, they found that soaking the sperm in a solution of Panax genseng combined with Ophiopogon japonicus, P. ginseng

combined with Aconitum carmichaeli, Salviae miltiorrhiae, or Polyporus umbellatus, did not show any effect on sperm motility in vitro.

Amano et al. (1996) examined the in-vitro effect of Hochu-ekki-to, (aka Bu Zhong Yi Qi Tang or Tonify the Middle and Augment the Qi Decoction) on semen motility. Semen obtained from fourteen men was infused in several concentrations of the herbal formula solution and compared with control. Results indicated that motility of semen in the herbal solution was significantly higher when compared with the control group. Chen et al. (2001) also showed that a Ginseng solution can improve human sperm motility and forward progression in-vitro.

Influence of Chinese Herbal Substances on ATP Production

As was mentioned earlier, a major component of semen function depends on adenosine triphosphate (ATP). Several researchers (Ko, 2006; 2007) investigated the effect of Chinese herbal substances, from the Yin and Yang enhancing categories, on mitochondrial ATP production. They examined each of these substances individually and in an herbal formulation form on cells from myocardial tissue of mice. Investigators found that herbs from the Yang tonifying category stimulate mitochondrial ATP generation, while the Yin tonifying herbs possess an immunomodulatory effect. The Yin tonifying herbs boosted weak immune functions and suppressed over-reactive immune responses. The investigators also found that herbs from both the Yin and Yang categories possess antioxidant properties. Even though this study did not examine the effect of Chinese herbal substances on semen or male infertility, the herbs' functions of increasing mitochondrial ATP production,

antioxidant effect and modulating immune function, are all important contributing factors in sperm function and healthy male fertility.

Effect of Chinese Herbal substances on Oxidative Stress

A growing body of evidence is now linking increased oxidative stress in the spermatozoa to poor sperm quality, DNA damage and lipid paroxidation (Showell, 2011; Gharagozloo, 2011; Tempest, 2008). Following this rational, listed are a couple of studies that investigated the influence of Chinese herbal substances on oxidative stress levels. Even though these studies do not directly measure sperm parameters and therefore are not included in the study, they are included in the literature review section due to the growing importance now given to the influence of oxidative stress levels on sperm quality.

A group of investigators (Tempest, 2008) measured the antioxidant and estrogenic effect of Chinese herbal substances commonly used for the treatment of male infertility. They investigated 37 individual herbs and seven herbal decoctions using recombinant yeast based assay to measure their endocrine activity and ferric reducing antioxidant potential (FRAP) to measure their antioxidant activity. Fifteen individual herbs and three herbal formulas registered strong antioxidant activity, seven individual herbs and three herbal formulas showed intermediate antioxidant activity, and 15 individual herbs and one herbal formula showed weak to no antioxidant activity (0.912-1.26; 0.6-0.88; and 0–0.468 μg ascorbate equivalent/mg dried herb, respectively). Twenty of the individual herbs and five herbal formulas

displayed strong anti-estrogenic activity, while ten individual herbs and two herbal formulas showed weak anti-estrogenic response (per g of dried herb tamoxifen equivalents ranged from 1.14–1280.66 mg and 0.06–0.98 mg, respectively). Two of the individual herbs exhibited estrogenic responses and 10 herbs showed anti-androgenic activity (seven strong response and three a weak response).

Liao et al. (2007) published a study analyzing the antioxidant activity of 45 Chinese herbal substances from the blood-circulating category. These herbal substances are not directly related to male subfertility but some of them are often used for this condition. They used the oxygen radical absorbance capacity assay (ORAC) to assess the antioxidant levels of the herbs. The study also looked for a correlation between the herbal substance's antioxidant activity level and it's traditional Chinese medicine herbal classification system such as Yin, Yang, nature or flavor. Investigators found a wide range of antioxidant activity between the herbal substances with the highest antioxidant activity seen in substances that are bitter and/or sour in flavor.

Effect of Acupuncture on Erectile Dysfunction and Premature Ejaculation

Erectile dysfunction is an important component in male infertility disorders. In a placebo-controlled, randomized study, Engelhardt et al. (2003) researched the question of acupuncture effects on psychogenic erectile dysfunction. Results revealed that acupuncture was effective and improved this condition in two thirds of the patients.

An additional study (Kho, 1999) found that acupuncture treatments are effective for erectile disorder though concluded that in order to arrive at conclusive evidence the study needed to include more participants and have a placebo control arm. Investigators examined the effects of acupuncture on premature ejaculation. They compared acupuncture with a drug used to treat depressive, anxiety and panic disorders (paroxetine) and placebo. Acupuncture significantly strengthened and delayed ejaculation in comparison to placebo. However, the effect of acupuncture was not as strong as the impact of the drug paroxetine (Sunay, 2011).

Literature Review Integration

This review of literature showed that there is published evidence that TCM intervention improves crucial aspects of male infertility. This includes semen parameters, erectile dysfunction and premature ejaculation. This study will first assess the studies found to affect semen parameters following TCM intervention for levels of reporting. Data from the studies that had adequate level of reporting will then be abstracted into tables, analyzed and compared. Following the literature review for this study, the researcher found that no synthesis of data of sperm parameters following TCM intervention, with extensive evaluation of levels of reporting, exists. The goal of this research synthesis is to fill this gap and to systematically analyze and compare data from studies, with adequate levels of reporting, describing sperm parameters in response to TCM.

Chapter Three: Methods

This research synthesis is a capstone project at the Doctorate Program for Acupuncture and Oriental Medicine (DAOM) with specialty in reproductive medicine at Yo San University, Los Angeles. The goal of the study is to investigate the influences of acupuncture and Chinese herbal substances on semen parameters and male subfertility.

Research Design

This study is a research synthesis. Published studies were systematically reviewed for studies that investigate the influence of acupuncture and Chinese herbal medicine on male subfertility through their influence on semen parameters. The objective was to discern in which direction acupuncture and Chinese herbal medicine influence semen parameters, to discern a potential pattern in the changes and to discuss theoretical and practical implications. The direct correlation between low sperm parameters and fertility outcomes has been shown by previous studies (Cooper, 2009; WHO, 1987 and 1992; Kruger, 1988).

Literature Search Strategy

A comprehensive literature search was performed on Pub Med, Google Scholar, and EBCO host as well as, in reproductive and Chinese medicine journals. Search terms included sperm, semen and terms that describe the condition or abnormality of the semen (e.g. azoospermia, oligospermia, asthenospermia, teratozoospermia, oligoasthenoteratozoospermia), as well as male subfertility or infertility, in

combination with acupuncture, Chinese medicine, Chinese herbal medicine and traditional Chinese medicine. Also searched were reference lists from similar published studies and articles.

Inclusion Criteria

The abstract and title of every retrieved record were read to further determine the inclusion or exclusion of the article. Studies considered for inclusion were studies published in English, which reported effects of acupuncture and or Chinese herbal medicine on any semen parameter, especially, semen count or concentration, semen motility, and or semen morphology. Included were studies conducted on humans or animals.

Prior the final data synthesis, each study that met the above mentioned inclusion criteria was then further assessed for quality of reporting of intervention and semen sampling according to criteria taken from the STRICTA guidelines (MacPherson, 2002) and CONSORT guidelines (Begg, 1996, Moher, 2001).

The quality of reporting of semen sampling methods was estimated according to the following criteria:

- Semen sampling methods described
- Number of semen sampling described
- Abstinence time prior to sampling described
- Standards of measurements mentioned (Such as WHO criteria, scrotal temperature measurement, etc.)

- Semen examination lab methods described
- Statistical method of calculations reported

In studies involving acupuncture the quality of reporting was assessed according to following criteria:

- Statement of acupuncture rational reported
- Reported rational for point selection
- Sources quoted to justify point selection
- Location description for point selected reported
- Reported unilateral or bilateral needle insertion
- Reported number of needles inserted
- Reported depth of needle insertion
- Reported response to needling (e.g. De Qi)
- Reported needle stimulation
- Reported needle retention time
- Reported needle type
- Reported number of treatments
- Reported frequency of treatments
- Reported practitioner background
- Reported procedure of control intervention

In studies involving Chinese herbs intervention the quality of reporting was estimated according to these criteria:

- Plant name reported (e.g. Latin, Chinese, Botanical, Common names)
- Reported herbs including herbal formula ingredients
- Reported parts of the plant used (Roots, leaves, etc.)
- Reported type of product used (Raw, fresh, dry, etc.)
- Reported plant form of extraction
- Reported dosage used
- Reported frequency of herbal administration
- Reported concentration used
- Reported added fillers
- Reported quality testing of substance
- Reported herbal product standardization
- Reported placebo intervention

The criteria mentioned above were used to assess the levels of reporting of TCM intervention and semen sampling. Included in this synthesis were studies that reported a minimum of eight criteria of information from at least two of the categories mentioned above. In order to be included in the synthesis, studies also needed to contain detailed information displayed in table I, such as number of participants, length of study, etc. Several of the studies described in detail the Chinese acupuncture points used or the theory behind the points. Still they were

excluded from further analysis because their method section did not disclose enough information to match the above criteria.

Data Synthesis

Relevant data from studies that fulfilled the inclusion criteria and subsequently passed the quality assessment as described above were abstracted into tables. The various study designs were summarized in table I. Reported were the type of subjects (human or animal), form of intervention, number of participants, age, length of study, and study design. TCM and Western diagnosis and TCM (acupuncture and herbs) and Western intervention information including the type of control intervention used are reported in table III.

The following outcome measurements from each study where extracted into table IV: semen volume, semen concentration (per ml) or count (per ejaculate) compared with control, semen motility compared with control, semen morphology compared with control, semen quality compared with control, parameters for control compared with experimental group, adverse effects found in the study, and author comments stated in the study. Finally, all outcomes of all included studies were summarized in table V for comparison.

Exclusion Criteria

Excluded were studies that were not published in English, or studies testing the influence of Chinese herbal medicine on semen in-vitro. These studies were mentioned in the literature review but they were excluded from further analysis due

to the suspected change in substance chemistry when applying herbs directly to cells, as opposed to when taken orally and having a systemic influence. Excluded were also studies that did not adhere to the set standard of quality of reporting (see above).

Chapter Four: Results

Nineteen studies were included in the literature synthesis, of which seven involved acupuncture intervention; eleven involved Chinese herbal substances intervention and one involved a combination of acupuncture and Chinese herbal substances. The synthesis found, that traditional Chinese medicine including acupuncture and Chinese herbal medicine, improve semen parameters of quantity, motility and morphology. A thorough literature search for studies on the influence of TCM on semen parameters was performed on search engines such as Pub Med and Google Scholar. Studies found were then assessed for levels of reporting and, if found adequate, data from the studies abstracted into tables.

Patterns of TCM Effects on Sperm Parameters

The direction of change in sperm parameters in response to TCM treatments as abstracted from the included studies are displayed in table V. Ten out of the 19 studies reported a statistically significant increase in semen count or concentration in response to either acupuncture or Chinese herbs. Two studies showed increased values of semen count and concentration though not at a statistically significant level. Six studies reported no change in semen concentration or count. One study did not measure this parameter.

Semen motility was measured in all but two of the nineteen studies of this review. Motility refers to the ability of the spermatozoa to progress forward. Fourteen studies reported a statistically significant increase in sperm motility and

one study reported increase in sperm motility but not at a statistically significant level (table V). One study reported reduced semen motility after Chinese herbal substance intervention. However decreased motility was reported in a study where the effect of combined Chinese herbal substance with Cyclophosphamide (CP) ingestion was measured. CP is a carcinogenic, mutagenic and fertility impairing drug.

Semen morphology measures the percentage of sperm with normal morphology. Improved sperm number with normal morphology equates to improvement in this parameter. Many of the studies in this review reported improvement in semen morphology (see table V). In eight out of the 19 studies that where included in this synthesis, semen morphology was not analyzed. Within the remaining eleven studies, ten studies reported statistically significant improvement of semen with normal morphology while only one study showed no change.

Semen volume refers to the volume of the ejaculate. In twelve of the studies in this synthesis semen volume was not measured. In the remainder seven studies, four reported no change in volume; one reported a statistically significant decrease in volume following intervention and one showed increase meaning improvement in volume but not a statistically significant increase (see table V).

Only six of the studies included in this synthesis reported results for semen quality. Two of the studies reported statistically significant improvement in semen

quality and four studies reported improvement in semen quality but not a statistically significant improvement (see table V).

Table V: Summary of effects of acupuncture and Chinese herbal medicine on semen parameters as reported in each of the nineteen studies analyzed in this review
Acupuncture (A), Chinese herbal substance (CH), statistically significant (SS)

	Semen volume compared with control	Semen concentration and count compared with control	Semen motility compared with control	Semen morphology compared with control	Semen quality compared with control	Parameter for controls compared with experimental group
Statistically significant improvement ↑		2 A 7 CH 1 combined A+CH	4 A 9 CH 1 combine A+CH	4 A 5 CH 1 combine A+CH	2 A	1 A: SS↑ in semen concentration
Improvement ↑ but not statistically significant	1 CH	1 A 1 CH	1 CH		4 CH	
Statistically significant reduced ↓	1 A		1 CH			1 A: SS↓ morphology 1 combine A+CH: SS ↓ Volume 2 CH: reduce quality
No change found	3 A 1 CH 1 combined A+CH	4 A 2 CH	1 A	1 CH		5 A 8 CH
Not evaluated			2 A	3 A 5 CH		2 NA
Not reported or stated	3 A 9 CH	1 CH			5 A 7 CH 1 combined A+CH	

Comparison of Control Interventions

The control interventions of the various studies were too heterogeneous to compare with one another. Nine studies used no intervention in the control group. One study administered placebo acupuncture on the same points as the experimental group while another study used acupuncture on non-therapeutic points for the control group. Two studies administered biomedical drugs and one study administered a carcinogenic substance to the control group. In four animal studies a regular diet was given with a specific volume of vehicle. The same volume of vehicle was used as the placebo. Regardless of the control intervention the results are consistent between all the studies. Thirteen of the studies found no change in any of the sperm parameters of the control group. One study found statistically significant improvement in semen concentration following placebo acupuncture. Four of the studies found a decrease in any one of the semen parameters in the control group. Specifically, one study reported a reduction in healthy semen morphology, one study described a reduction in semen volume, and two studies demonstrated a reduction in semen quality in the respective control group.

Comparison of Background Data

Background data on the synthesized studies were abstracted (see table I). Participants in the studies were either animal or human subjects. All the acupuncture intervention studies where performed on human subjects. In the studies assessing herbal substances, four studies experimented with human subjects while seven studies examined the effect on animals' sperm.

The number of participants in the studies was overall small. One of the studies only had six participants but most of the other studies had between16 to 80 participants. The animal studies, therefore involuntary, included between ten to 90 subjects. Information on the age of the participants was extracted also (see table I). In the studies that involved animal subjects the age could not be compared to the human subjects, though within the human subjects groups, all the participants were within reproductive age. In most of the studies with human subjects participants were younger then 50 and only one study reported on subjects that where as old as 58. As far as length of studies, all the studies involving human subjects lasted between five to 12 weeks and studies involving animal subjects lasted between three to 12 weeks.

Level of Reporting of Intervention and Semen Sampling Methods

The level of reporting of the methods and details of information, in the included studies was assessed (see table II). Levels of reporting have improved in recent years (see discussion). Reporting levels of semen sampling show that all the studies but one provided detailed accounts of the methods used to assess semen sampling. Levels of reporting in studies with acupuncture intervention were also detailed and clear. Thus, studies and intervention methods are repeatable. The influence of the STRICTA (MacPherson, 2002) and the CONSORT (Moher, 2001) guidelines is reflected in the improved levels of reporting in TCM studies.

Detailed intervention information was extracted from the included articles (see table III). No pattern emerged from observing the acupuncture intervention. However, several points were used more frequently than others. Ren4 (Guanyuan), and SP6 (Sanyinjiao) were used in all eight studies. BL23 (Shenshu), ST36 (Zusanli), and SP10 (Xuehai), were all used in six of the studies. K3 (Taixi) was used in five studies and LV3 (Taichong), Ren6 (Qihai), and BL32 (Ciliao) were each used in four of the studies. Siterman and colleagues designed three of the acupuncture studies. Therefore many of the same acupuncture points were used in all three studies. No pattern was found among the intervention of the herbal medicine studies, since most of those studies used single herbs.

Chapter Five: Discussion

This research synthesis found, that traditional Chinese medicine including acupuncture and Chinese herbal medicine, improve semen parameters of count, concentration, motility and morphology with no adverse effects. The study also found that levels of reporting in Chinese medicine studies, published in English are improving. Other limitations and observations found while conducting this study and will be discussed in this chapter include; inconsistency between study designs, sample size, studies involving single herb intervention rather than traditional formulas, use of animal subjects, correlation between oxidative stress and TCM intervention and the in-vitro influence of Chinese herbal substances on sperm.

Implication for Theory and Practice

Improving sperm parameters with TCM interventions has implications for theory and practice. Semen analysis test measuring sperm parameters is the main predictor for male fertility. Many studies show that better sperm parameters including count, concentration, motility and morphology improve fertility rates (Cooper, 2009; WHO, 1987; 1992; Kruger, 1988). Therefore improving these parameters and other semen characteristics will likely improve male fertility and pregnancy outcomes. The literature states that allopathic medicine offers very few treatment options for improving semen parameters and semen quality (Deadman, 2008; Speroff, 2005; Rittenberg, 2010). The main biomedical approach to low sperm parameters and male subfertility is IVF with ICSI. Although ICSI can significantly improve IVF and pregnancy outcomes, ICSI does not help improve the

quality of the sperm. Therefore, the practice of ICSI has bypassed the need for finding options for improving sperm quality. More importantly, studies show an increased risk of major and minor birth defects in babies conceived with ICSI and IVF when compared to babies conceived naturally (Hansen, 2002, 2005; Maher, 2005; Rimm, 2004). Thus, the availability of evidently successful TCM interventions improving sperm quality without side effects is of utmost value.

If TCM interventions and IVF with ICSI were combined in practice, the spermatozoon hand picked for the procedure can be selected among sperm with improved parameters potentially leading to improved fertility in terms of increased natural pregnancy rates as well as improved embryo quality and reduced birth defect rates. This prospect is especially desirable since TCM treatments do not lead to adverse effects.

An additional positive implication of improving sperm parameters with TCM interventions is related to female age. Advanced maternal age (AMA) is one of the female infertility etiologies in which time is of the essence. With AMA, every improvement in semen parameters may not only improve the couple's chances of achieving a pregnancy sooner rather than later but may also improve their chances of achieving pregnancy with their own gametes. The outcome of this study validates the knowledge and experience that TCM practitioners have passed down through the generations. Namely, this study shows that Chinese herbal substances and acupuncture treatments, usually prescribed for male infertility, indeed possess

properties that improve male fertility. However, no real pattern or clear protocol emerged from this literature synthesis. This leads to the conclusion that more studies are needed to discern the most effective TCM methods for treating male subfertility and low sperm parameters.

Limitations of this Study

Study Designs in Acupuncture Research

This literature synthesis found that studies show that acupuncture and Chinese herbal medicine improve sperm parameters. However, because of the lack of uniformity found between the studies, the different types of engaged study designs need to be considered when interpreting their findings. In order to discern in future research which protocols improve sperm parameters, researchers need to consider the complexity of TCM as well as male infertility and balance it with the challenge of designing studies that will adhere to scientific standards while preserving the integrity and complexity of the medicine.

Traditional Chinese medicine (TCM) is a very complex medical system that has developed over several thousand years. TCM is also an empirical medicine, in which knowledge has slowly developed and been recorded through clinical observation, practitioners experience, and intentional and unintentional outcomes. There are 361 traditional acupuncture points and numerous “extra points” as well as hundreds of substances referred to as “Chinese herbs”. A commonly used medical herbology textbook (Chen, 2004) discusses over 660 herbal substances and

the formula book by the same authors (Chen, 2009) describes over 650 herbal formulas. In addition, male infertility is also a complex condition that has several different etiologies and clinical presentations. Although acupuncture has hundreds of points, only a limited number of point locations thus far have been shown to be effective for male infertility. The same is true for Chinese herbal medicine. Certain substances have been shown to specifically influence male fertility (Tempest, 2008) and a few other Chinese medicinals are then added depending on each individual's unique presentation.

Studies included in this synthesis fall into primarily two types of study designs: efficacy or explanatory trials and pragmatic trials. Explanatory trials are randomized controlled trials (RCTs) with highly controlled settings while pragmatic trials are RCTs designed to assess the efficacy of therapy as it is used in everyday practice (MacPherson, 2004). The first type of study is one that employs a protocol of specific acupuncture points or specific herbal substances where all subjects receive the same intervention regardless of the TCM diagnosis that caused the male infertility (e.g. Dieterle, 2009; Yang, 2008, 2010). The second type of study adheres to the TCM methods of diagnosis according to pattern differentiations (e.g. Siterman, 2009, 2000, 1997; Pei, 2005).

These two types of study design highlight the complexity of conducting scientific experiments with TCM. The first type of study tries to identify one standardized protocol to fit all, in an experimental setting, aimed at evaluating

efficacy. It is usually a simple intervention protocol, with limited relevance or impact on clinical practice, but is easier to blind, minimize bias or use placebo control. This type or study may also be managed with a smaller sample size and holds high internal validity but low external validity. The second type of study more closely resembles the clinical setting but is harder to establish placebo control. It also employs a complex intervention protocol, requires a skilled practitioner, has a high external validity but low internal validity, and has a greater relevance in a clinic setting. Thus, pragmatic trials are more likely to be carried out according to TCM principals than explanatory trials, addressing each patient's condition (e.g. male infertility with digestive difficulties, constipation or with feeling cold, hot or low energy etc.).

The study by Dieterle et al. (2009) illustrates the complexity of study designs with acupuncture intervention. It is the only one of the analyzed studies that showed improved sperm parameter in the control group, specifically statistically significant improved sperm concentration. This aberrant finding may be explained by the sham acupuncture method used on the control group. In this study, the sham acupuncture technique consisted of using a spring like mechanism that stimulates the point but does not insert a needle into it. Acupuncture is a multidimensional form of intervention. The theory of acupuncture includes many types of energy pathways including regular and extra meridians, twelve divergent meridians and fifteen collaterals. The twelve divergent meridians and fifteen collaterals branch out from the twelve regular meridians, thus affect the twelve regular meridians

indirectly. The divergent meridians mainly run deeper in the body while the collaterals are mainly distributed on the body surface. Stimulating the acupuncture point on the surface of the body, such as the sham acupuncture technique, activates the collaterals and indirectly affects the internal meridians thus stimulating a similar reaction to that of deep needle insertion.

Number of Studies Included in the Synthesis

The literature search retrieved only a limited number of studies published in English, examining the influence of TCM on sperm parameters, which fit the inclusion criteria. However, it is worth mentioning, that the results from the small number of studies included in this synthesis are confirmed by many abstracts as well as partially reported studies not included in this analysis. They all reached similar conclusions, namely that TCM improves sperm parameters, and helps subfertility with minimal adverse effects and dropouts of test subjects. Most of these abstracts and partially reported studies were published in Chinese and therefore excluded from this review.

Levels of Reporting

However, levels of reporting in studies published in English in recent years have been improving. Historically, levels of reporting in TCM clinical trials have been found to be of poor quality (Begg 1996; Prady 2008). These researchers suggest that in order to improve transparency, to enable better interpretation of

results and to allow replication of studies, improved consistency in reporting of clinical trials were necessary (Begg 1996; Prady 2008).

Following these findings, a group of researchers published a statement with new guidelines aimed at improving the consistency of reporting in clinical trial, when TCM is used as the intervention (Begg 1996). It was named the Consolidated Standards of Reporting Trials (CONSORT). In 2002 the STRICTA (Standards for Reporting Interventions in Controlled Trials of Acupuncture) guidelines were published (Macpherson 2002). The STRICTA guidelines were amendments added to the CONSORT guidelines in an effort to further improve the level of reporting in TCM clinical trials. In a study published in 2008, Prady and colleagues assessed the level of influence that the STRICTA guidelines had had on acupuncture clinical trials. They evaluated studies between 1994-1995, 1999-2000, and 2004-2005. The results show significantly improved standards of reporting in clinical trials involving acupuncture since the CONSORT guidelines were introduced, although not much change was found between the time CONSORT guidelines and the more recent STRICTA guidelines were adopted. Researchers attributed the lack of meaningful change subsequent to the publication of the STRICTA guidelines to the relatively short period of time between the publication of the STRICTA guidelines and the end of the study (2002 till 2005) (Pardy, 2008). Results of this review concur with these findings, namely that levels of reporting in TCM studies, published in English have significantly improved in recent years.

Lack of Studies Involving Chinese Herbal Formulas

The majority of articles involving Chinese herbal substances, analyzed in this study, utilized single herb intervention to address sperm parameters. Only four studies utilizing clear reporting, published in English, and assessing the effects of Chinese herbal formulas were included in this review. TCM herbalists are trained to prescribe Chinese herbal formulas. Herbal formulas consist of a combination of several herbal substances. Through the evolution of TCM, medical healers recognized that combining herbal substances both overcome shortcoming and enhance strengths of single herbal substances. Rarely does the TCM herbalist prescribes a single substance and almost always combines it in an herbal formula that has withstood the test of time. However, only four studies included in this review examined the effects of an herbal formula on sperm parameters, the rest of the studies examined a single herbal substance effect on sperm parameters. Thus, even though a Chinese medicine herbalist usually prescribes an herbal formula and rarely prescribes a single herbal substance, very few studies published in English with clear reporting, reflect this practice.

Studies Using Animals as Test Subjects

Several of the Chinese herbal substances included in this study involve experiments with animal subjects. Some scientists argue that results from animal experimentation cannot be applied to humans due to biological differences and dependence on the animal type. These scientists base their argument on differences in animal pathophysiology and metabolic pathways when compared with other

species or with humans (Roberts, 2002; Regan-Shaw, 2008; Pound 2004). Furthermore, scientists observe that the differences in animal variety of metabolic pathways and drug metabolites lead to variation in efficacy and toxicity (Pound 2004). Pound et al. (2004) argues that the value of animal research into potential human treatments needs rigorous evaluation and suggests systematic reviews of existing and future research as the main solutions for improving estimates of effects from animal experiments.

Additional observations

Antioxidant Activity

This review also found that some studies state, as a given, that acupuncture and Chinese herbal medicine may improve semen parameters, and that the emphasis should now be placed on determining the mechanism behind these findings (Siterman, 2009; Akashi, 2008; Choi, 2005; Yang, 2008, 2010; Park, 2007). One possible mechanism involves antioxidant activity. Numerous studies have shown that antioxidants may improve semen parameters (Showell, 2011; Gharagozloo, 2011). Besides the included studies, the literature search for this review also yielded several studies that pointed to the effect that Chinese herbal medicine may have on oxidative stress and male infertility. (Tempest, 2008; Ko, 2007; Liao, 2008).

Oxidative stress has long been known to impair normal cellular processes linking it to many major diseases including male and female infertility (Gharagozloo,

2011). Different cell types generate different oxidants referred to as reactive oxygen species (ROS). Many studies have reported a significant rise in ROS in spermatozoa of subfertile men leading to the widely acknowledged assumption that ROS is a significant contributor to sperm DNA damage and lipid paroxidation (Gharagozloo, 2011). Poor DNA structure and damaged DNA is associated with poor fertilization rates, impaired embryonic development, pregnancy loss and birth defects, as well as several developmental problems including autism, and childhood cancer (Showell, 2011; Gharagozloo, 2011).

Several studies (Tempest, 2008; Ko, 2007; Liao, 2008), especially Tempest et al. (2008) examined the antioxidant effects of Chinese medicinal plants that are used for the treatment of male infertility, and found they do possess antioxidant effects. Although these studies were not included in this review since they did not measure the direct effect they have on semen parameters, they have been included in the literature review as they do pertain to male infertility indirectly.

Influence of Chinese Herbal Substances on Sperm In-Vitro

Several studies (Liu, 2004; Chen, 2000; Hsu, 2003; Huang, 2004; Amano, 1996) reported on the in-vitro influence of Chinese herbal substances on sperm. They reported improvement in semen motility when it was soaked in an herbal solution consisting of specific herbal substances (mentioned in the literature review). These studies were not included in the review due to the metabolic difference between substances applied directly versus those ingested orally. Orally ingested herbal

substances undergo a metabolic transformation while the same substances if applied directly do not. Even though these studies were not included in the review they are worth mentioning and are listed in the literature review.

Recommendations for Future Research

Future studies investigating protocols and Chinese herbal formulas aimed at improving sperm parameters are needed in order to establish optimal treatment protocols. More studies that investigate TCM influence on the integrity of the DNA, disomy and DNA fragmentation are needed. As the rate of ICSI use is rising, finding ways to improve sperm health as well as the DNA condition may help improve pregnancy and healthy offspring outcomes.

Conclusion

This synthesis found that acupuncture and Chinese herbal medicine are safe, low in adverse effects, and improve sperm parameters. These improvements in sperm parameters can potentially lead to improved fertility outcomes including better embryo cleavage, increased pregnancy rates and healthier offspring. These findings may be far reaching in the clinical implications for assisted reproductive technologies (ART). If ICSI is performed on sperm with generally low sperm parameters, it might result in increased rates of birth defect as well as short and long-term negative effects due to the association with high rates of DNA fragmented sperm (Fernandez-Gonzales, 2008, Yu, 2011). Studies in this review show that treatment with TCM improves not only sperm parameters but also ICSI fertilization

rates and embryo quality (Zhang 2002) and in turn, is likely to improve IVF, embryo health and pregnancy outcomes. However, as most of the studies retrieved in this synthesis were small in number of participants, used animal subjects, and involved single herb interventions, more studies are needed with increased number or participants, using human subjects, and Chinese herbal formulas interventions.

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Table I:
Designs of studies included in the analysis.

Author, Year	Humans or animals	Acupuncture or Chinese herbal medicine intervention	# Of participants (Treatment/ Control)	Age of participants	Length of study	Study design
Siterman et al., 2009	Humans	Acupuncture	47 (39/18)	36 ± 3.4	Not clearly defined	Prospective, Controlled
Dieterle et al., 2009	Humans	Acupuncture	57 (28/29)		6 weeks	Prospective, randomized placebo controlled
Pei et al., 2005	Humans	Acupuncture	40 (28/12)	25-46	5 weeks	Prospective, Controlled
Siterman et al., 2000	Humans	Acupuncture	40 (20/20)	26-48	5 weeks	Pilot, Controlled study
Siterman et al., 1997	Humans	Acupuncture	32 (16/16)	35.8±5.5	5 weeks	Prospective, Controlled
Gurfinkel et al., 2003	Humans	Acupuncture and Moxa	19 (9/10)	24-42	10 weeks	Prospective controlled, blind
Zhang et al, 2002	Humans	Acupuncture	22 (22/0)	26-58	Two months	Clinical Trial
Bo et al, 2011	Humans	Acupuncture, Chinese herbs and Moxa	37 (25/12)	22-47	3months or 40 treatments	Prospective, Randomized, controlled
Chang et al., 2008	Animals	Chinese Herbal substance	90 (30/30/30)	Reported	6 weeks	Prospective, randomized placebo controlled 2 way
Heidary et al., 2008	Humans	Chinese Herbal substance	52 (52/0)	21-48	3 months	Clinical Trial
Akashi et al., 2008	Humans	Chinese Herbal substance	20 (20/0)	Unknown	3 months	Clinical trial
Lin et al., 2007	Animals	Chinese Herbal substance	29 (15/14)	29-40 months	2 months	Controlled study
Tempest et al., 2005	Humans	Chinese Herbal substance	6 (6/6/6)	33-39	Not mentioned	Retrospective Controlled
Choi et al., 2005	Animals	Chinese Herbal substance	10 (5/5)	Reported	28 days	Prospective, Randomized, control
Yang, Chen, et al., 2003	Humans	Chinese Herbal substance	36	26-42	60 days	Prospective, clinical trial
Yang et al., 2008	Rats	Chinese Herbal substance	32 (8/8/8)	Reported	56 days	Prospective, randomized, placebo controlled
Park et al., 2007	Animals	Chinese Herbal substance	16 (8/8)	Reported	56 days	Prospective, randomized, placebo controlled
Yang et al, 2010	Animals	Chinese Herbal substance	16 (8/8)	Reported	56 days	Prospective, randomized, placebo controlled
Hwang et al 2004	Animals	Chinese Herbal substance	80 (8x10)	Reported	12 weeks Observed for 40 weeks	Prospective, randomized, placebo controlled
*Furuya, et al, 2004	Humans	Chinese Herbal substance	22	24-43	3 months	Clinical trial
**Claici, 2008	Humans	Acupuncture	1		Unclear	Case study
** Jiasheng, 1987	Humans	Acupuncture	248	23-58	Unclear	Case studies
**Zhiyuan, 1996	Humans	Acupuncture	54	28-42	Unclear	Case studies

Table II
Quality assessment of levels of reported intervention, and semen sampling, according to the following criteria:

Author, Year	Estimated quality of reported semen sampling according to following criteria: 1) Semen sampling methods described. 2) Number of semen sampling described. 3) Abstinence time prior to sampling described. 4) Standards of measurements mentioned (Such as WHO criteria, scrotal temperature measurement, etc.) 5) Description of semen examination lab methods. 6) Statistical method of calculations reported?	Estimated quality of reporting, in studies involving acupuncture, according to following criteria: 1) Reported statement of acupuncture rational. 2) Reported rational for point selection. 3) Sources quoted to justify point selection. 4) Location description for point selected. 5) Description of unilateral or bilateral of needle insertion. 6) Reported number of needles inserted. 7) Reported depth of needle insertion. 8) Reported response to needling (e.g. De Qi) 9) Reported needle stimulation. 10) Reported needle retention time. 11) Reported needle type. 12) Reported number of treatments. 13) Reported frequency of treatments. 14) Reported practitioner background. 15) Reported procedure of control intervention.	Chinese herbs intervention 1) Clear reporting of plant name (e.g. Latin, Chinese, Botanical, Common names) 2) Reported herbs including herbal formula ingredients. 3) Reported parts of the plant used (Roots, leaves, etc.). 4) Reported type of product used (Raw, fresh, dry, etc.). 5) Reported plant form of extraction. 6) Reported dosage used. 7) Reported frequency of herbal administration. 8) Reported concentration used. 9) Reported added fillers. 10) Reported quality testing of substance. 11) Reported herbal product standardization. 12) Reported placebo intervention.
Siterman et al., 2009	6 out of 6 criteria met	10 out of 15 criteria met	Not applicable
Dieterle et al., 2009	5 out of 6 criteria met	14 out of 15 criteria met	Not applicable
Pei et al., 2005	6 out of 6 criteria met	9 out of 15 criteria met	Not applicable
Siterman et al., 2000	6 out of 6 criteria met	12 out of 15 criteria met	Not applicable
Siterman et al., 1997	6 out of 6 criteria met	9 out of 15 criteria met	Not applicable
Gurfinkel et al., 2003	6 out of 6 criteria met	6 out of 15 criteria met	Not applicable
Zhang et al, 2002	6 out of 6 criteria met	12 out of 15 criteria met	Not applicable
Bo et al, 2011	2 out of 6 criteria met	13 out of 15 criteria met	6 out of 12 criteria met
Chang et al., 2008	6 out of 6 criteria met	Not applicable	8 out of 12 criteria met
Heidary et al., 2008	6 out of 6 criteria met	Not applicable	9 out of 12 criteria met
Akashi et al., 2008	6 out of 6 criteria met	Not applicable	2 out of 12 criteria met
Lin et al., 2007	6 out of 6 criteria met	Not applicable	9 out of 12 criteria met
Tempest et al., 2005	6 out of 6 criteria met	Not applicable	5 out of 12 criteria met
Choi et al., 2005	6 out of 6 criteria met	Not applicable	11 out of 12 criteria met
Yang, Chen, et al., 2003	6 out of 6 criteria met	Not applicable	8 out of 12 criteria met
Yang et al., 2008	6 out of 6 criteria met	Not applicable	10 out of 12 criteria met

Park et al., 2007	6 out of 6 criteria met	Not applicable	11 out of 12 criteria met
Yang et al, 2011	6 out of 6 criteria met	Not applicable	12 out of 12 criteria met
Hwang, et al 2004	6 out of 6 criteria met	Not applicable	10 out of 12 criteria met
*Furuya, et al, 2004	2 out of 6 criteria met	Not applicable	2 out of 12 criteria met
**Claici, 2008	0 out of 6 criteria met	6 out of 15 criteria met	Not applicable
** Jiasheng, 1987	0 out of 6 criteria met	7 out of 15 criteria met	Not applicable
**Zhiyuan, 1996	0 out of 6 criteria met	2 out of 15 criteria met	Not applicable

* Excluded due to lack of reporting
** Case study excluded due to lack of reporting

Table III:
Diagnosis and intervention:

Article #	Biomedical diagnosis	TCM diagnosis	Acupuncture intervention	Chinese Herbal medicine intervention	Control intervention
Siterman et al., 2009	Azoospermia, Oligoazoospermia	K Yang deficiency, Damp Heat in the Lower Jiao	General points: SP6, Ren4, LU7, K6, ST30 K Yang Xu: K3, BL23, K11, BL52. Damp Heat: SP9, LV5, LI11, ST28, GB41. Additional points: LI4, ST36, SP10, HT7, BL20, PC6, REN1, REN2, REN6, DU4, DU20, GB20, LV3, K7, BG27	Not applicable	Control for comparison only, no intervention
Dieterle et al., 2009	Sperm concentration <1 million Oligoasthenozoospermia.	Not reported	ST36, SP6, K3, LV3, BL23, BL32, ST29, SP10, REN4	Not applicable	Placebo acupuncture on same points
Pei et al., 2005	Idiopathic oligospermia, asthenospermia, or teratozoospermia	Not reported	Main points: REN4, BL23, BL32, LV3, K3. Secondary points: ST36, SP10, SP6, ST29, DU20	Not applicable	No intervention in the control group.
Siterman et al., 2000	3x oligoteratoasthenozoospermic 15x Azoospermia, 2pseudoazoospermic.	Kidney deficiency Damp heat in the genital system	Main points: SP6, REN4, LU7, K6, ST30 Kidney Yang deficiency: K3, BL32, BL52, KI11 Damp heat in genitals: SP9, LV5, LI11, ST28, GB41, Secondary points: LI4, ST36, SP10, HT7, BL20, PC6, REN 1,2,6,DU 20	Not applicable	No intervention in the control group.
Siterman et al., 1997	oligozoospermia, teratozoospermia, asthenozoospermia, OAT, bacteria contamination,	Not reported	Total of 12 points chosen from the following acupuncture points: LU7, LI4, LI11, ST30, ST36, SP6, SP9, SP10, HT7, BL20, BL23, BL33, K6, K7, P6, LV5, LV8, REN1, REN2, REN4, REN6, DU4	Not applicable	Control for comparison only, no intervention
Gurfinkel et al., 2003	Oligoasthenoteratozoospermia	Not reported	Acupuncture: ST30, ST36, SP6, LV3, K3, LI4, SP4, P6. Moxa: BL23, BL52, BL22, BL32, DU4, REN3, REN4, REN5, REN6, BL20, BL21, BL13, BL14, BL15, LU9, LV14, ZIGONG	Not applicable	Non-therapeutic indifferent points.
Zhang et al., 2002	Idiopathic male infertility with at least 2 failed ICSI up to 11 failed ICSI cycles.		Du 20, PC 6, SP10, ST44, UB23, SP6, GB39, Ren6, Ren4, ST40,	Not applicable	No control. Comparison made between samples taken before and after acupuncture intervention.
Bo et al., 2011	Primary or secondary sterility with abnormal semen parameters	Kidney Qi, Yin and Yang deficiency.	Ren 4, KI12 (bilateral) with electric stim., SP6 (bilateral) 3 Moxa cones on herbal cake over area between Ren 4 and Ki 12 Herbal cake: Rou Cong Rong, Rou Gui, Fu Zi.	Herbal formula taken internally: Er Xian Tang Shui Fan Wan. Ingredients include: Xian Mao (Riz. Curculiginis), Xian Ling Pi (H. Epimedii), Dang Gui (rdx. Angelicae Sinensis), Ba Ji Tian (Rdx. Morindae Officinalis), Huang Bai (Crtx Phellodendri Chinensis), and Zhi Mu (Rzm. Anemarrhenae)	Same Acupuncture treatment + 25 g Clomifene Citrate taken for three mo.
Chang et al., 2008	Not reported	Not applicable	Not applicable	Diet supplemented with Cordyceps Militaris (CM) mycelium.	3 groups: 1) Regular diet, 2) Diet with 1% CM, 3) Diet with 5% CM.

Heidary et al., 2008	Infertile men	Not reported	Not applicable	Saffron	No control. Comparison made between samples taken before and after herbal intervention.
Akashi et al., 2008	Idiopathic Oligozoospermia, Asthenospermia	Not reported	Not applicable	Hochuekkito Herbal Formula (Bu Zhong Yi Qi Tang)	No control. Comparison made between samples taken before and after herbal intervention.
Lin et al., 2007	Poor sperm quality	Not reported	Not applicable	cordyceps militaris	Regular diet
Tempest et al., 2005	Severe Oligoasthenoteratooospermic (OAT)	Differential diagnosis	Not applicable	Between 5-15 gr the following herbs where prescribed: Chi Shao, Chuan Niu Xi, Fu Ling, Gou Qi Zi, Huang Bai, Mu Dan Pi, Nu Zhen Zi, Shan Yao, Shan Zhu Yu, Tao Ren, Tu Si Zi, Ze Xie, Zhi Mu, Ba Ji Tian, Bai Zhu, Che Qian Zi, Dang Shen, Fu Pen Zi, Gan Cao, hong Hua, Wang Bu Liu Xing, Zhi Ke, Lian Zi Xin, Can Zhu, Bie Xie, Chai Hu, Sheng Ma, Huang Qi, Sheng Di Huang, Chen Pi, Jin Yin Hua, Yin Yang Huo, Yi Yi Ren.	No control intervention. Post treatment semen samples of men with severe OAT where compared with A) Their own base line pre treatment, B) Men with proven fertility
Choi et al., 2005	Not reported	Not reported	Not applicable	Radix Morindae officinalis	Water as placebo
Yang, Chen, et al., 2003	Infertility with chronic prostatitis	Patients with disease pattern of blood stasis	Not applicable	Shao Fu Zhu Yu Tang, formula. Ingredients include: Dang Gui, Chuan Xiong, Chi Shao, Wu Ling Zhi, Pu Huang, Mo Yao, Yuan Hu Suo, Gan Jiang, Guan Gui, Hui Xiang.	No control. Comparison made between samples taken before and after herbal intervention.
Yang, and Chang et al., 2008	Cyclophosphamide (CP) ingestion. (A carcinogenic, mutagenic and fertility impairing drug)	Not reported	Not applicable	Psoralea Corylifolia (PC) +Cyclophosphamide (CP)	3 groups: 1) vehicle treated, 2) CP treated, 3) CP and PC treated.
Park et al., 2007	Not reported	Not reported	Not applicable	Korean ginseng	The same volume of vehicle.
Yang et al, 2011	Not reported	Not reported	Not applicable	Panax Ginseng extract	The same volume of vehicle
Hwang et al. 2004	Tetrachlorodibenzo-p-dioxin (TCDD) injection. (A pollutant generated from leaded gasoline exhaust, pulp and paper industries and herbicides.)	Not reported	Not applicable	Panax Ginseng water extract (PG-WE). With or without Tetrachlorodibenzo-p-dioxin (TCDD).	8 groups 1) normal control (NC), 2) TCDD treated (TT), 3) PG-WE 100 mg/kg body weight, 4) PG-WE 200 mg/kg body weight. 5)#3+ TT. 6) #4+TT, 7) TT with #3 taken 1 week post TT start. 8) TT with #3 taken 1 week post TT start.

Table IV
Outcomes:
Statistically significantly improvement (SSI)

Article # / Year	Semen Volume Compared with control	Semen concentration (Per ml) or count (per ejaculate) Compared with control	Semen motility Compared with control	Semen morphology Compared with control	Semen quality Compared with control	Parameter for controls Compared with Experimental group	Author comments stated in the study	Adverse effects and dropouts
Siterman et al., 2009	Not stated	↑ Concentration	Not evaluated	Not evaluated	Not stated	No change	Acupuncture improves low sperm count in patients with genital tract inflammation by reducing scrotal hyperthermia.	None Reported
Dieterle et al., 2009	SSI↓ (P= .041) Volume	No significant change Concentration	SSI ↑ (P= .035)	Not evaluated	Not stated	SSI ↑ (P= .018) Sperm concentration	These results may be due to the small number of participants. Forty-five patients in the acupuncture group are needed for a statistically significant difference in sperm concentration.	Reported: No adverse effects or dropouts
Pei et al., 2005	No statistical significant change	No statistical significant change Concentration	SSI ↑ (P= .017)	*SSI ↑ (P=. 012), and number (P= .002) of healthy sperm *Acrosome normal position SSI ↑ (P= .013) *Acrosome normal shape SSI ↑ (P< .001) *Acrosome normal nuclear shape SSI ↑ (P< .001) *Normal axoneme pattern SSI ↑ (P= .005) *Normal axoneme shape SSI ↑ (P = .022) *Normal accessory fibers SSI ↑ (P = .005)	SSI ↑	*Acrosome normal position No change *Acrosome normal shape No change *Acrosome normal nuclear shape No change *Normal axoneme pattern ↓ *Normal axoneme shape ↓ *Normal accessory fibers ↓	Authors point to the importance of sperm motility and the correlation between motility and improvement of axonemal pattern, axonemal shape and accessory fibers.	
Siterman et al., 2000	Not stated	Count per total ejaculate.SSI ↑ (Z=-2.8, P≤0.01) Men w genital infection SI ↑	Not evaluated	Not evaluated	Not stated	No changes were found	Treatment was arbitrary according to TCM diagnosis, not a protocol, and undefined clearly. Treatment was most effective for genial tract infection.	Not reported

		(Z=-2.4, P≤0.02)						
Siterman et al., 1997	Not stated	SSI ↑ (P ≤ .04) Count	Sperm Motility SSI ↑ (P ≤ .05) Sperm viability SSI ↑ (P ≤ .05) axonema integrity SSI ↑ (P ≤ .05)	SSI ↑ (P ≤ .04)	SSI ↑ (P ≤ .05) Fertility index	No changes were found	SI ↑ (P≤ .05) Fertility index derived from improvement in sperm fraction, percentage, motility and integrity of the axonema as well as Total Functional Sperm Fraction (TFSF) which includes total sperm count, motility and morphology	Not reported
Gurfinkel et al., 2003	No significant change	No significant change	No significant change	SSI ↑	Not stated	No improvement or change		Reported: No adverse effects or dropouts
Zhang et al, 2002	No significant change	No significant change Concentration	SSI ↑ (P<0.01)	SSI ↑ (P<0.05)	Not stated		Improved fertilization rate (P<0.01) after acupuncture when compared with pre-acupuncture. And improved not SS embryo quality.	Not reported
Bo et al, 2011	No significant change	SSI ↑ (P<0.05)	SSI ↑ (P<0.05)	SSI ↑ (P<0.05)	Not stated	SSI ↓ (P<0.05) In volume + SSI ↑ (P<0.05) in Testosterone and LH blood levels.	Combined acupuncture and herbal formula are more effective at improving sperm parameters then acupuncture and Clomifene Citrtare.	Drop out if achieved pregnancy prior to end of study.
Chang et al., 2008	Not stated	SSI ↑ (P<0.05) Count Compared with control	SSI ↑ (P<0.05) Compared with control	Not evaluated	Stated improvement	No change was found	Hypothesized Due to ↑ in E2 and ↑ in T No change found in FSH, LH, PRL	Reported: No adverse effects
Heidary et al., 2008	Not reported	No significant change	SSI ↑ (P < .001)	SSI ↑ (P < .001)	Not stated	No change	Improvement may be due to antioxidant effect.	Not reported
Akashi et al., 2008	No significant change	No significant change	SSI ↑ (P<0.002)	No significant change	Not stated	No change	Seminal plasma (RANTES) significantly decreased (0.024).	Not reported
Lin et al., 2007	Not stated	SSI ↑ (P<0.01) Concentration	SSI ↑ (P<0.05)	SSI ↑ (P<0.01)	Stated improvement	No change was found	Sperm production was enhanced significantly (P<0.05) at the end of the first month, peaked (P<0.01) at the second month and maintained (P<0.01) for two weeks after stopping the treatment.	Not Reported
Tempest et al., 2005	Not reported	SSI ↑ (P<0.001 to P< 0.05)	SSI ↑ (P<0.001 to P< 0.05)	Improved Disomy SSI ↑ (P<0.01 to P< 0.05)	Not stated	NA	Disomy levels improved to levels of men with normal fertility.	Not reported
Choi et al., 2005	Not evaluated	SSI ↑ (P<0.01) Concentration	SSI ↑ (P<0.01)	SSI ↑ (P<0.01)	Not stated	No change or SS lower in the treatment group	Catalase and peroxidase activity increased in the Morindae officinalis group but no significant difference was found between groups.	Not reported
Yang, Chen, et al., 2003	↑ But not SSI	↑ But not SSI	SSI ↑ (P<0.01)	SSI ↑ (P<0.01)	↑ Sperm quality (stated)	No change	Improved acrosin activity maybe due to improved free radicals, ↑ in number of lecithin crystals and ↓ in bacteria levels. Also, "Blood and Essence share common	Not Reported

							source, Blood can transform Essence and regulation of Essence can only be achieved by promoting Blood circulation"	
Yang et al., 2008	Not reported	SSI ↑ (P<0.01) Concentration	↓ (P<0.05)	Not evaluated	Not stated	NA	↑ Sperm count as well as levels of CREM messenger RNA and protein suggesting that PC induced spermatogenesis resulted from CREM activation. Also ↑ count associated with ↑ testis weight and motility is affected by physical health reflected in ↓ body weight.	Not stated
Park et al., 2007	Not reported	SSI ↑ (P< .05) Count	SSI ↑ (P< .05)	Not evaluated	Not stated	No change	↑ Sperm count and motility as well as levels of CREM messenger RNA and protein suggesting that Ginseng induced spermatogenesis results from CREM activation.	Reported: No adverse events or effects
Yang 2011	Not reported	SSI ↑ (P<0.01) Concentration	↑ But not SSI	Not evaluated	↑ Sperm quality (stated)	No change	Improved count may result from Panax Ginseng influence on Glial cell derived neurotrophic factor (GDNF) gene expression and protein biosynthesis	Not Reported
Hwang et al, 2004	Not reported	Not reported	SSI ↑ (P<0.01)	Not evaluated	Not stated	Lower sperm quality then PG treated groups.	Panax Ginseng (PG) treated animals ↑ sperm motility despite Tetrachlorodibenzo-p-dioxin induces toxicity.	Improved with PG

Table V

Summary of outcomes:
Seven studies involve acupuncture intervention (A) eleven studies involve Chinese herbal substances intervention (CH), and one study involves both CH and A intervention.

	Semen volume Compared with control	Semen concentration or count Compared with control	Semen motility Compared with control	Semen morphology Compared with control	Semen quality Compared with control	Parameter for controls Compared with Experimental group
Statistically significant improvement ↑		2 A 7 CH 1 combined A+CH	4 A 9 CH 1 combine A+CH	4 A 5 CH 1 combine A+CH	2 A	1 A: SS↑ in semen concentration
Improvement ↑ but not statistically significant	1 CH	1 A 1 CH	1 CH		4 CH	
Statistically significant reduced ↓	1 A		1 CH			1 A: SS↓ Morphology 1 combine A+CH: SS ↓ Volume 2 CH: reduce quality
No change found	3 A 1 CH 1 combined A+CH	4 A 2 CH	1 A	1 CH		5 A 8 CH
Not evaluated			2 A	3 Acupuncture 5 CH		2 NA
Not reported or stated	3 A 9 CH	1 CH			5 Acupuncture 7 CH 1 combined A+CH	