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The Role of Acupuncture for the Treatment of Idiopathic Male Infertility ©

By

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ABSTRACT
Statistics from Southern California Reproductive Center in 2016 state that 40% of global infertility cases are male fertility related, and half of those cases are diagnosed as idiopathic[1]. Recent research shows a decline in overall male fertility, an increasing trend in advanced paternal age, and a link between these factors and an increased risk of cancer. Following is a discussion of male fertility diagnostics and treatment options in addition to an examination of the available literature to determine the role of acupuncture in the treatment of idiopathic male infertility. Keywords used to define the search consisted of: oligospermia, acupuncture, male fertility, male infertility, and idiopathic male infertility. Upon review of current literature spanning from 2005 to 2018, it is predicted that acupuncture is a viable treatment option and will decrease the severity of asthenospermia, oligospermia and teratospermia in males diagnosed with idiopathic infertility.

Introduction

The World Health Organization (WHO) defines clinical infertility as the inability of a sexually active, non-contracepting couple, within reproductive age to achieve pregnancy after one year of trying [2]. In females, reproductive age is considered between 15 and 49 years old [3]. In comparison, the reproductive age for males is significantly longer. Males begin to produce sperm once they enter puberty and continue to do so throughout their lives; however, there is increasing evidence showing reduced fecundity in males over the age of 40, specifically in regard to motility and morphology [4]. According to Sharma et al, the first parameter to be affected by age is the total sperm number which occurs at or

near age 34, followed by a decline in concentration and normal morphology by age 40, a decrease in motility by age 43, and decrease in ejaculate volume by age 45 [5].

In the event of suspected infertility, a couple would likely seek out a reproductive endocrinologist who would evaluate both partners. The most common parameters tested in cases of male infertility are in reference to concentration/quantity, morphology/quality, and motility of sperm within ejaculate. The World Health Organization Laboratory Manual for the Examination and Processing of Human Semen fifth edition uses the following terminology: oligozoospermia, teratozoospermia, and asthenozoospermia respectively [6]. Table 1.0 defines WHO nomenclature related to semen quality. The term idiopathic, in regards to male infertility, refers to men who have abnormal semen analysis with no known cause. There is noted dysfunction in either concentration/quantity, morphology, or motility of sperm with no noted or identifiable cause such as a history of chronic illness, traumatic injury, genetic defect, or use of medications that affect spermatogenesis. In these patients, all physical examinations and endocrine laboratory findings are normal, and there is no history of fertility issues. It should be noted that, although both are of unknown etiology, there is a very clear distinction between a diagnosis of idiopathic male infertility (IMI) as stated above and unexplained male infertility (UMI). The latter presents with a semen analysis that is normal, all female infertility factors have been ruled out, and conception remains unsuccessful. UMI comprises up to 27% of unknown male infertility cases, while IMI comprises up to 31% of infertile males [7].

The diagnostic protocols for IMI are comprehensive and often extensive. A thorough patient history should be taken by the reproductive endocrinologist or fertility specialist, inquiring about recent illnesses, previous surgeries/procedures, or traumas. This is followed by an investigation into the patient's family history looking for patterns of infertility, but also specific conditions such as cryptorchidism[1], midline defects[2], or hypogonadism[3]. A developmental history of hypospadias[4], congenital anomalies, and Diethylstilbestrol (DES)[5] exposure should also be ruled out. The use of or exposure to certain medications should be considered as they may also impact fertility [8]. Finally, the patient's lifestyle and environmental factors will be examined. Use of recreational drugs, alcohol, anabolic steroids, nutritional deficiencies, sexual history (history of sexually transmitted infections, use of spermicidal foams, etcetera), exposure to radiation, chronic heat, pesticides, herbicides, heavy metals, and many other factors may play a role in male infertility and should be ruled out [9].

In addition to a detailed patient history, a semen analysis is an integral part of male fertility assessment. As shown in Figure 1.0, there can be significant variances in both sperm quantity and concentration over the course of one year. For this reason, two to three separate samples are taken over a period of approximately three months. As

[1] Cryptorchidism: a condition in which the testes fail to descend from the abdomen into the scrotum.
[2] Midline defect: a congenital problem that occur along the vertical axis of the body.
[3] Hypogonadism: reduction or absence of hormone secretion or other physiological activity of the gonads.
[4] Hypospadias: relatively rare congenital condition where the opening of the penis is on the underside of the organ
[5] Diethylstilbestrol: a synthetic form of estrogen formerly prescribed to pregnant women that has since been shown to cause a variety of significant adverse medical complications.

stated by the WHO “it is impossible to characterize a man’s semen quality from examination of a single semen sample” [6]. The process of spermatogenesis takes approximately 74 days [10], and the optimal environment is 34 degrees Celsius [11]. The testes are a temperature sensitive environment; therefore, consideration should be taken regarding the patient’s health and lifestyle during the previous three months of the sample being examined. Febrile events [12], exposure to environmental toxins, and/or consumption of chemicals that affect spermatogenesis will have a greater effect at earlier points of spermatogenesis [13]. Multiple samples over a three month period may offer a more comprehensive overview of the assessed values.

The method of sample collection must also be considered during a semen analysis. Typical options are sample retrieval from masturbation either in clinic or at home, or post coital with a non-latex condom. Any samples collected outside of a clinical setting must be collected and stored in a sterile container, kept at body temperature, and transported to the clinic for examination within one hour [14]. Studies show the results of semen analysis is affected by the method and timing of collection, and this should be considered when collecting semen samples [15], [16]. The WHO assesses several criteria within a semen sample when examining fertility parameters, some of which are the volume of ejaculate, concentration, and quantity, quality, and motility of spermatozoa within a semen sample, pH of semen, agglutination, and vitality of spermatozoa [6]. In an optimal sample, the volume of ejaculate should be greater than or equal to 1.5 milliliters. Ideally, there is at least 15 million sperm per milliliter, which reflects the concentration of

sperm, and the total sperm number will be calculated by determining the product of the ejaculate volume and the concentration. A minimum of 32 percent show progressive forward motility (PR), while total motility [PR + non-progressive moving(NP)] is at least 40 percent. The lower reference limit for sperm morphology if analyzed with the specific techniques described in the fifth edition of the WHO Laboratory Manual for the Examination and Processing of Human Semen is 4% [6]. All WHO sperm values mentioned above are summarized in Table 2.0. Patients with IMI may present with one or more of these values below desired levels in one or more samples over a three month period.

Current biomedical options for IMI patients include sperm aspiration from either the vas deferens (PVSA, MVSA)[6], the epididymis (MESA, PESA)[7], or the testicle (TESA, TESE, or Micro-TESE)[8]. Typically the above listed procedures are completed as outpatient procedures with minimal recovery time [17]. The retrieved sperm will then be assessed for viability in one of the following Assisted Reproductive Techniques (ART): Intrauterine Insemination (IUI)[9], Intracytoplasmic Sperm Injection (ICSI)[10], or In Vitro Fertilization (IVF). The cost of sperm aspiration techniques depends on the complexity of the technique required and varies widely throughout the United States in addition to the chosen ART cost.

[6] Percutaneous Vasal Sperm Aspiration (PVSA), Microscopic Vasal Sperm Aspiration (MVSA)
[7] Percutaneous Epididymal Sperm Aspiration (PESA), Microscopic Epididymal Sperm Aspiration (MESA)
[8] Testicular Sperm Aspiration (TESA), Testicular Sperm Extraction (TESE)
[9] IUI: sperm extracted from a semen sample are separated then injected directly into the uterus using a catheter
[10] Intracytoplasmic sperm injection (ICSI): a single sperm cell is injected into the cytoplasm of a mature ovum.

Traditional Chinese Medicine (TCM) has had excellent anecdotal success treating male infertility and many couples trying to conceive include TCM as a complement to their allopathic medical care. Early acupuncture is documented as far back as 90 B.C. [18]. Since that time, the process has been greatly refined and over the last several decades, a great deal of scientific research has been done to prove its efficacy. In more recent history, acupuncture is gaining popularity for a variety of concerns including fertility. Research is showing promising results on the efficacy of acupuncture for a multitude of fertility issues, including IMI. Jane Lyttleton discusses the positive effect of acupuncture on met-enkephalin levels, which are responsible for the motility of sperm within semen[18,19]. Riegler et al noted a significant increase in all parameters with the exception of volume after acupuncture treatment [20]. Siterman et al noted a positive effect of acupuncture on three parameters; percentage of sperm viability, total number of motile spermatozoa, and total functional sperm fraction (TFSF) [20,21]. Zhang et al concluded "acupuncture can improve sperm quality and fertilization rates in assisted reproductive technology" [22]. Acupuncture in conjunction with moxibustion was found to significantly increase normal-form sperm percentages according to Gurfinkel et al [22,23]. Siterman et al found that men with decreased sperm density related to genital tract inflammation could benefit from acupuncture [22–24]. Wang et al concluded electroacupuncture combined with a chinese herbal formula can improve semen quality in patients with oligospermia and asthenospermia [22–25].

As mentioned above, certain values within a semen analysis below normal range are part of the diagnostic criteria for IMI. The aim of acupuncture treatment in these cases is to optimize sperm numbers. The diagnostic focus in TCM is on determining a possible root cause of the asthenospermia, teratospermia and/or oligospermia by assessing the patient's constitution and current presentation of symptoms. Similar to the above mentioned intake process, a TCM intake covers many, if not all, of the same criteria. The information gathered in the intake, in addition to any objective data collected from lab evaluations (CBC with differential, semen analysis, nutritional and/or food sensitivity panels, etcetera), acts as evidence to support a TCM diagnosis. Once a diagnosis has been made, treatment modalities such as acupuncture and adjunctive techniques[11], herbal medicine, supplements, and/or lifestyle modifications will be chosen that best address the diagnosis.

Some experts state an initial treatment course should be six months in duration to account for the spermatogenesis cycle taking approximately three months [19]; however, several studies show positive results treating IMI with a treatment course as short as 10 weeks with biweekly treatment [21,26–28]. Outcomes are directly dependant on patient compliance; therefore, the patient must be committed to completing the entire treatment course to achieve optimal results. Needle retention times vary between practitioners but tend to be in the range of 25-45 minutes per session [21,26–28] and points chosen vary based on the patient diagnosis.

[11] Electro-stimulation, moxibustion, gua sha, cupping

The most common TCM diagnoses seen in IMI can be divided into two categories; Excess or Deficiency. Excess implies that there is a pathogenic factor impeding spermatogenesis and/or the delivery of sperm through the genital tract. Any detectable obstruction, for example, vasectomy reversal, varicocele/hydrocele repair, trauma, tumors, or other duct abnormalities, would exclude the patient from the category of IMI; however, it is possible for a patient to experience idiopathic obstructive azoospermia [29] or have another type of undetectable blockage. The TCM diagnosis for any obstruction within the genital tract is considered stagnation of qi, and/or stasis of blood. Another Excess factor that could impede proper spermatogenesis in IMI patients is inflammation. The presence of Reactive Oxygen Species (ROS)[12] is "a major contributing factor identified as a leading cause for the progression of IMI" [31]. According to Tremellen, ROS can decrease sperm motility and hinder its ability to penetrate the oocyte, and can directly damage sperm DNA [32]. The TCM diagnosis associated with inflammation in the genito-urinary system is either heat or damp heat. Any of these Excess conditions can present individually or concurrently.

Cases of Deficiency include those in which the primary organ systems involved in reproduction are not performing optimally. In reference to male fertility, the primary TCM organ system most frequently involved in Deficiency cases is the Kidney system. The TCM Kidney system, which is differentiated from the anatomical kidney organ, strongly influences fertility. Some would argue the Kidney system includes the ovaries in women

[12] ROS: key signaling molecules that play an important role in the progression of inflammatory disorders [30]

and the testes in men, in addition to some pituitary function related to reproduction, for example the release of FSH[13], and LH[14] [19]. The Kidneys are said to store *jing*, which encompasses not only the reproductive system itself, but also the virility of that system. Therefore, even if all of the physical organs are functioning within normal range, if there is a lack of energy within the system, infertility may result. The Kidney system is also associated with the seminal fluid which is considered a *yin fluid*, and the sperm, which are considered *yang*. The fluid is referred to as *yin* because it contains and nourishes the sperm, while the sperm are referred to as *yang* because they are filled with vitality and movement. If there is a lack of fluids or the fluid is lacking certain nutrients, the TCM pathology would be called a *yin* Deficiency. If there is a problem with sperm numbers and/or motility, it would be considered a *yang* Deficiency. If the genetic makeup of the sperm is defective, it could be considered *jing* Deficiency.

It is possible for Excess and Deficiency pathologies to overlap, and often one imbalance will lead to another. For example, a patient with a TCM diagnosis of Heat may have resulting damage to DNA from ROS. This could be considered a *jing* Deficiency resulting from Excess Heat. In a similar example, the prostate gland produces less fluid as a result of smooth muscle atrophy over time [33]. The Heat diagnosis could be caused from a lack of cooling fluids from the prostate gland (part of the Kidney system) resulting in a diagnosis of Kidney *yin* Deficiency Heat. The end result may be the same, damage to DNA from ROS; however the pathogenesis of the Heat is different. In her book The

[13] Follicle Stimulating Hormone
[14] Luteinizing Hormone

Infertility Cure, R. Lewis states that any Excess condition is usually the result of an underlying Kidney Deficiency [34] and recommends addressing both the *yin* and *yang* of the Kidney system in almost all male fertility cases. Due to the holistic nature of TCM, there are several other organs systems that could be involved and/or affected by a Kidney system imbalance with an infertility patient. Figure 2.0 shows the complex relationship between those organ systems and the vital substances associated with each.

The decline in male fecundity over the last several decades has been shown in several studies. A meta-analysis done by Levine et al shows a 52.4% decline in sperm concentration as well as a 59.3% decline in total sperm count between 1973 and 2011 [35]. However, the study of fertility, specifically paternity, has greater implications than the inability to reproduce. The overall decline in male reproductive health is recently being linked to other male health concerns such as cancer. A study done in 2013 by Eisenberg found that men diagnosed with azoospermia "were 1.7 times as likely to develop cancer as men in the general population" [36]. There is also evidence to support a decline in sperm DNA quality in men of advanced paternal age increasing the likelihood of miscarriage, fetal loss, single gene disorders, and congenital anomalies in which the authors conclude "advanced paternal age is associated with increased genetic and epigenetic risk to offspring" [37]. It should also be noted that the standard semen analysis does not offer a measurement on spermatozoa fertilization potential [38], which could be a significant factor in many infertility cases, including cases of IMI. The absence of a known cause for the declining fertility numbers results in limited treatment options within a

conventional medical model based on objective data alone. Even with all of the challenges facing potential parents and researchers, acupuncture is showing promising results in the treatment of IMI.

Methodology

Research for this review consisted of publications between 2005 and 2018. The search engines used to access the publications were PubMed, and Ebscohost. Keywords used to define the search consisted of: oligospermia, acupuncture, male fertility, male infertility, and idiopathic male infertility. The inclusion criteria allowed for studies using strictly acupuncture, any gauge disposable acupuncture needle, inserted to any depth within standard TCM guidelines, and retained for any amount of time, on male patients diagnosed with idiopathic infertility. The studies could have been performed in any country so long as an english translation of the study was available for review. Only full text publications were eligible. There was no minimum number of participants required per study. Each study needed a minimum score of five on the modified JADAD scale. All semen samples must have been analyzed based on WHO standards.

Any publication using anecdotal case study or case report has been excluded. In addition, studies involving patients with known endocrine dysfunction, systemic or infectious disease, and/or immunological conditions have also been excluded. No studies that noted female infertility factors have been included. Any study using TCM adjunctive techniques including electro acupuncture, moxibustion, and/or chinese herbal

preparations were excluded. Studies using pharmacological intervention and/or hormonal therapy were also excluded. Animal studies were not included.

The initial search using the key words resulted in 138 publications. 81 duplications were removed resulting in an assessment of 57 publications for eligibility. After applying all inclusion/exclusion criteria, 55 of the 57 eligible publications were eliminated. The two publications that met the above defined criteria were a prospective controlled trial from 2005, and a prospective randomized placebo-controlled study from 2009.
An additional 597 publications were identified using the references of 17 relevant publications from the initial search. All 597 were eliminated upon review due to lack of relevance and/or duplication. Figure 3.0 summarizes the research work flow.

Literature Review

In 2005, Pei et al published a prospective controlled trial examining the effect of acupuncture on spermatozoa ultrastructure, or fine organelles involved in fertilization, in patients with IMI using transmission electron microscopy (TEM) [26]. The study was approved by the ethics committee of the University of Ulm, and the participants of the study were existing patients of the Christian Lauritzen Institute in Ulm, Germany. Recruitment was open to couples who had been trying to conceive for a minimum of two years without success. Female partners must have had at least two failed IUI cycles, and went through rigorous infertility examinations to eliminate them as a contributing factor. The male partners also went through extensive andrological, endocrine, and laboratory

examinations before being diagnosed with idiopathic infertility. They had to have a minimum of two pathological spermiograms at six week intervals according to the WHO criteria. Any patient with thyroid dysfunction, adrenal disorders, hyperprolactinemia, pathological hormone levels, azoospermia, infectious, systemic, or immunologic-associated disease, abnormal stressors, or a detectable cause of infertility were excluded from the study. All participants gave written consent before treatment.

A total of 40 participants with a mean age of 33 (range 25 years to 46 years) were selected for the trial; 28 received acupuncture twice weekly for a period of five weeks, while the control group consisted of 12 IMI patients who received no treatment but gave semen samples at the same intervals as the treatment group. An independent researcher using computer software randomized the samples taken from the untreated control group and the treatment group. Neither group received additional intervention. All participants of the treatment group received acupuncture using Viva brand 0.25 x 25mm or 0.25 x 40mm sterile single-use disposable stainless steel needles inserted to a depth of 15-25 mm. The size of needles and depth of insertion was determined based on the anatomical location of the acupoint. All acupoints were manually stimulated until the point of *deqi*[15] sensation, after which the needles were retained for 10 minutes, then re-stimulated with a total retention time of 25 minutes. The acupoints used in the study were as follows: CV-4 Guanyuan, BL-23 Shenshu (bilateral), BL-32 Ciliao (bilateral), LIV-3, Taichong (bilateral), KI-3 Taixi (bilateral). The following acupoints were listed as

[15] A sensation of warmth, numbness, tingling, soreness, and/or tension resulting from stimulation affecting muscle nerve afferents [26]

secondary points with no further explanation: ST-36 Zusanli (bilateral), SP-10 Xuehai (bilateral), SP-6 Sanyinjiao (bilateral), ST-29 Guilai (bilateral), GV-20 Bai Hui. All locations were based on the WHO standards [39].

Two semen samples were collected from each participant in the treatment group. The first one the day before acupuncture after a three day period of abstinence, and the second after acupuncture treatment. All samples from the control group and the treatment group were assessed based on WHO laboratory manual criteria, and randomized before examination by two experts who were blinded to the groups. Evaluation of the samples was completed using TEM, performed in Siena, Italy in the Biology Section of the University of Siena. Results of the analysis was made available to each of the participants. Following evaluation of the samples, statistical analysis of the data was performed at Augsburg University at the Institute of Mathematics.

Upon initial examination of the samples, the acupuncture group showed 0.06% healthy spermatozoa within the ejaculate, the control showed 0.16%. The expected minimum number of healthy spermatozoa per ejaculate based off the formula of Baccetti et al [40] is 2×10^6. The control group showed 0.14×10^6, and 0.04×10^6 in the acupuncture group. After the five week treatment protocol, the median percentage of healthy sperm increased to 0.26% and the median number of healthy sperm increased to 2×10^6, a statistically significant change. TEM analysis showed no significant change in median sperm number per millilitre, nor the volume of ejaculate. There was a statistically

significant difference between the two groups in regard to median percentage of total motility which increased in the control group from 32% to 37% in the control group and from 44.5% to 50% in the acupuncture group. Table 3.0 summarizes the detailed results of TEM analysis on sperm ultrastructure and organelles. Pei et al concluded that "acupuncture treatment is a simple, non-invasive method that can improve sperm quality"[26].

Following the work done by Pei et al, Dieterle et al published a prospective randomized placebo controlled study that took place between 2006 and 2008 examining the effect of acupuncture in patients with severe oligoasthenozoospermia (Dieterle et al 2009). The study took place at the University of Witten/Herdecke, Germany, and was approved by an Institutional Review Board (IRB), obtained informed consent from each patient, in addition to following the guidelines of both Consolidated Standards of Reporting Trials (CONSORT) and Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA). The study population was selected from existing patients in the Reproductive Endocrinology Infertility Division with semen samples showing <1 million sperm/mL. The selected patients were not diagnosed with hypogonadotropic hypogonadism, did not have obstructive azoospermia, and had not received chemotherapy or radiation therapy within the past year.

A total of 59 participants were divided by a computer generated random allocation sequence into an acupuncture group and a placebo acupuncture group. Both groups

received treatment twice weekly for six weeks with no additional interventions. The treatment of both groups was performed by two experienced acupuncture specialists from Tongji Hospital in Wuhan, China, with University level TCM training. 0.30 x 3.0 mm Asia-Med acupuncture needles were used on the acupuncture group, insertion depth ranged from 15-30 mm depending on the region of the body needled. Manual stimulation to the point of *deqi* sensation was performed, then manual stimulation was repeated after ten minutes. The placebo group received treatment using non-penetrating 0.30 x 3.0 mm Asia-Med placebo acupuncture needles. Both groups retained needles for a total of 45 minutes with no explanation to the patients.

The acupoint selection for both groups was based on the previous study, by Pei et al. The following acupoints were used on all patients: ST-36 Zusanli (bilateral) , SP-6 Sanyinjiao (bilateral), KI-3 Taixi (bilateral), LIV-3 Taichong (bilateral), BL-23 Shenshu (bilateral) , BL-32 Ciliao (bilateral), ST-29 Guilai (bilateral), SP-10 Xuehai (bilateral), and CV-4 Guanyuan. The acupoint GV-20 Bai Hui was used in the study by Pei et al; however, removed from this study due to fixation concerns with placebo needles. The acupuncture specialists were unaware of the laboratory data, and both patients and study personnel were blinded to group assignment. The study reported no adverse events or side effects in either group. The study outcomes consisted of motility, concentration, and volume. Morphology was not evaluated due to the possibility of subjective assessment in low sample volumes.

Participants of the study were selected to be of similar age, body mass, duration of infertility and abstinence. All semen analyses were done according to WHO standards. Four semen samples were taken for all patients . The first sample was collected five months before treatment protocols began. The second sample was taken less than three months before the treatment. The third sample was taken less than two months after the treatment and the fourth sample was taken less than or equal to three months after the treatment. Timing of samples is summarized in Table 4.0. Sperm motility before and after acupuncture was considered the primary outcome measure of this study, while sperm concentration and semen volume were considered secondary outcome measures. All outcome measures are summarized in Table 5.0.

The results of this study showed acupuncture as having a significant effect on total motility. There was a noted decrease in semen volume after acupuncture which deems further investigation. The study also found a significant increase in sperm concentration after placebo acupuncture; however it is noted that the number of patients included in the study may not have been adequate to show a statistically significant difference in concentration. Results including *P* values are summarized in Table 6.0.

Discussion

The 2005 study by Pei et al offers a detailed examination of the positive effects of acupuncture on not only total sperm numbers, but also spermatozoa ultrastructure. Improvements were shown in both the median percentage and number of healthy sperm

in the total ejaculate. The TEM analysis allowed the researchers to examine specific changes in the ultrastructure before and after acupuncture treatment. Statistically significant improvement was seen in both acrosome characteristics and nuclear shape, in addition to positive effects noted on the axoneme and accessory fibers contributing to an increase in motility from 44.5% before treatment to 50% after [26].

Although approved by the ethics committee of the University of Ulm, neither CONSORT nor STRICTA guidelines were mentioned in the Pei et al study design. The calculations used to determine sample size were not included in the publication.
Information regarding the training and/or experience of the individuals administering the acupuncture treatments was also not mentioned. The points chosen were listed in detail; however, the reasoning behind the selection was not given. There was no information given regarding the justification and/or use of the primary vs. secondary points. No information is given on the timing of the post-treatment semen samples with the exception of stating the sample was taken “after acupuncture treatment” [28]. The age of the participants was noted and the inclusion criteria of the study specifies a minimum duration of infertility. There was no mention of drop-outs, patients lost to follow up, or reported adverse events during treatment.

Dieterle et al noted use of an IRB in addition to abiding to the guidelines of CONSORT, and STRICTA. The points chosen were sourced from a previous study with no justification for point selection and one of the points from the protocol was removed to

accommodate placebo acupuncture, which could have affected outcomes. There was also no mention of primary or secondary points which were mentioned in the study that sourced the acupoint selection. Timing of the semen samples was noted; however, a period of abstinence before collection and method of collection was not. The study notes that the sample size calculations may have had an effect on the secondary outcome of semen volume and that further investigation is required. The WHO was cited in the text of this publication as the standard for semen sample evaluation; however, there was no reference to the WHO within the bibliography to confirm the use of the newest edition and therefore, updated parameters.

Due to the complicated and individualized process of TCM diagnostics and lack of TCM diagnosis in both studies, it can be assumed that no specific diagnosis was given to each participant. One could argue the treatment may have been significantly more effective if acupoint selection was customized to each patient's specific TCM diagnosis. In fact, Dieterle et al point out that the fixed acupoint protocols applied for the purposes of a randomized control trial may negatively affect the outcomes [28].

Conclusion

Using the latest technological advances to harvest sperm from either the vas deferens, the epididymis, or the testes may solve the short term problem of reproduction; however, it does not address the long term concerns potentially facing the resulting offspring and/or the long term health of the male partner. The investigation into the correlation

between IMI, male health, and fetal development requires further research. Acupuncture offers a safe, non-invasive approach to addressing suboptimal sperm numbers with no noted side effects. The results of the studies described above show that acupuncture does have a role in the treatment of IMI by having a positive effect on sperm parameters. More research and follow up is needed to test the long term effects on male health following acupuncture treatment for IMI in addition to higher quality studies with larger samples sizes.

Figures and Tables

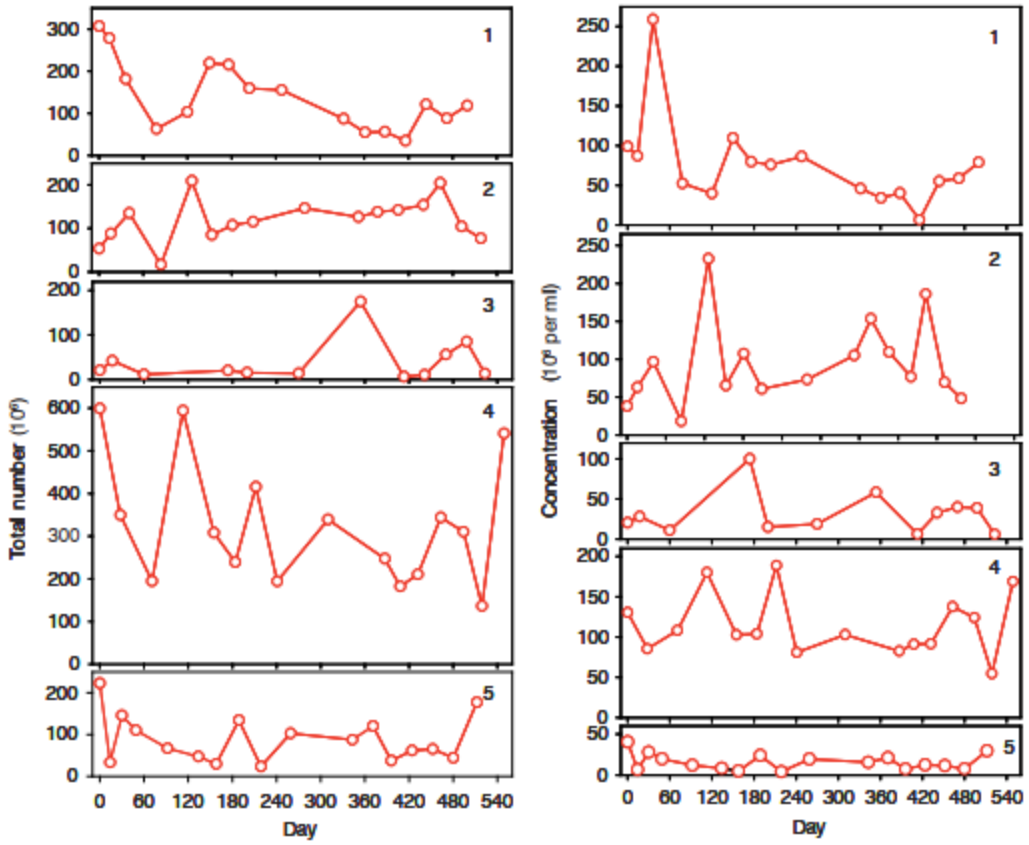
Table 1.0 WHO Semen Quality Nomenclature

aspermia	no semen (no or retrograde ejaculation)
asthenozoospermia	percentage of progressively motile (pr) spermatozoa below the lower reference limit
asthenoteratozoospermia	percentages of both progressively motile (pr) and morphologically normal spermatozoa below the lower reference limits
azoospermia	no spermatozoa in the ejaculate (given as the limit of quantification for the assessment method employed)
cryptozoospermia	spermatozoa absent from fresh preparations but observed in centrifuged pellet
haemospermia (haematospermia)	presence of erythrocytes in ejaculate
Leukospermia (leukocyto-Spermia, pyospermia)	presence of leukocytes in the ejaculate above the threshold value
necrozoospermia	low percentage of live, and high percentage of immotile, spermatozoa in the ejaculate
normozoospermia	total number (or concentration, depending on outcome reported)* of spermatozoa, and percentages of progressively motile (pr) and morphologically normal spermatozoa, equal to or above the lower reference limits
oligoasthenozoospermia	total number (or concentration, depending on outcome reported)* of spermatozoa, and percentages of progressively motile (pr) spermatozoa, below the lower reference limits
oligoasthenoteratozoo-spermia	total number (or concentration, depending on outcome reported)* of spermatozoa, and percentages of both progressively motile (pr) and morphologically normal spermatozoa, below the lower reference limits
oligoteratozoospermia	total number (or concentration, depending on outcome reported)* of spermatozoa, and percentage of morphologically normal spermatozoa, below the lower reference limits
teratozoospermia	percentage of morphologically normal spermatozoa below the lower reference limit

**Preference should always be given to total number, as this parameter takes precedence over concentration.*

Reformatted from [6]

Figure 1.0 Variation in total number of spermatozoa and sperm concentration in five men over a one-and-a-half-year period



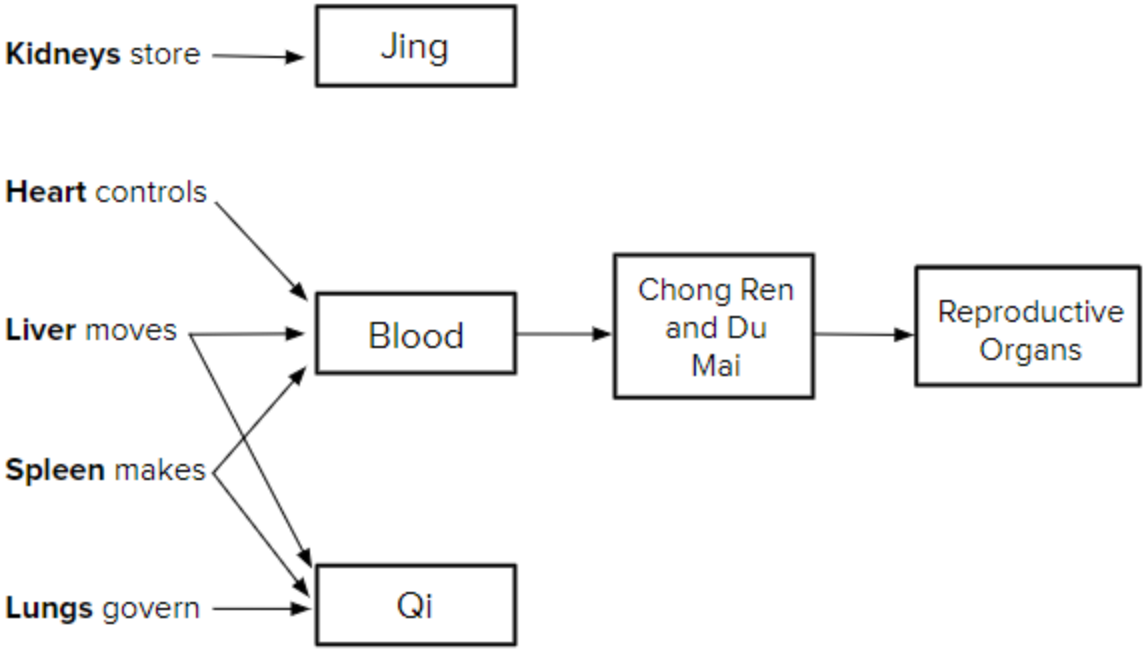
6

Table 2.0 WHO sperm values summary

Volume	≥1.5 mL
Concentration	≥15 million
Total number	Volume x Concentration
Motility	32%PR; 40% total
Morphology	≥4%

6

Figure 2.0 TCM Organ Systems and Associated Vital Substances



Modified from [19]

Table 3.0 Results of TEM analysis on Control and Acupuncture groups

	Control Group		**Acupuncture Group**		
Ultra Morphologic Features	Before	After	Before	After	*P* =
Median number of sperm/mL					0.657
Median volume of ejaculate					0.731
Median percentage of total motility in ejaculate	32%	37%	44.5%	50%	0.017
% of healthy sperm in ejaculate	0.16%		0.06%	0.26%	0.012
Median number of healthy spermatozoa	$0.14x10^6$		0.04×10^6	0.2×10^6	0.002

in ejaculate					
Acrosome in normal position	65%	71.5%	69.5%	77.5%	0.013
Acrosome of normal shape	26%		22.5%	38.5%	<.001
Normal nuclear shape	29%		30%	42.5%	<.001
Condensed chromatin	36%-39 %		36%-39%		0.506
Normal axeome pattern	52%	38.18%	46.06%	52.19%	0.005
Normal axeome shape	67.44%	55.85%	63.64%	67.71%	0.022
Normal accessory fibers	48.68%	34.06%	34.06%	48.53%	0.005
Normal fibrous sheath	44.41%		33.33%	40.59%	*
Apoptosis	8.18%	6.43%	7.80%	7.15%	0.863
Immaturity	68.23%		71.29%		0.146
Necrosis	37.28%	44.03%	36.7%	34.3%	0.072**

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*Acupuncture group showed a tendency to an increase after 5 weeks treatment

**Acupuncture group showed a trend toward a decrease after 5 weeks treatment

Table 4.0 Semen Sample Timeline

Sample 1	≤ 5 months before treatment
Sample 2	< 3 months before treatment
Sample 3	< 2 months after treatment
Sample 4	≤ 3 months after treatment

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Table 5.0 Outcomes Before and After Acupuncture

Variable	Acupuncture group	Placebo
Motility A before intervention (%)	11.5 ± 12.5	16.0 ± 13.4
Motility A after intervention (%)	12.1 ± 8.6	13.1 ± 13.3
P value	NS	NS
Motility B before intervention (%)	8.1 ± 10.2	8.0 ± 8.0
Motility B after intervention (%)	10.5 ± 11.8	8.8 ± 7.5
P value	NS	NS
Motility C before intervention (%)	4.6 ± 6.9	8.2 ± 8.4
Motility C after intervention (%)	11.2 ± 13.7	7.8 ± 7.8
P value	NS	NS
Motility A–C before intervention (%)	24.2 ± 17.0	32.2 ± 18.1
Motility A–C after intervention (%)	33.8 ± 18.2	29.7 ± 17.6
P value	.035	NS
Motility D before intervention (%)	75.8 ± 17.0	67.8 ± 18.1
Motility D after intervention (%)	66.2 ± 18.2	70.3 ± 17.6
P value	.035	NS
Concentration before intervention (million/mL)	0.039 ± 0.128	0.016 ± 0.085
Concentration after intervention (million/mL)	0.465 ± 1.206	0.468 ± 1.712
P value	NS	.0180
Volume before intervention (mL)	4.2 ± 1.8	4.0 ± 1.8
Volume after intervention (mL)	3.7 ± 1.4	3.8 ± 1.6
P value	.041	NS

Note: Data are presented as mean ± SD. A–D = World Health Organization motility categories: rapid linear progressive, slow or nonlinear progressive, nonprogressive, and immotile, respectively; NS = non significant.

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Table 6.0 Summary of Results Dieterle et al

Outcome	**After Acupuncture**	**Placebo**	***P* value**
Total Motility	Significant Increase		*P* = .035
Category A	No Significant Change		
Category B	No Significant Change		
Category C	No Significant Change		
Semen Volume	Decreased		*P* = .041
Sperm Concentration		Significant Increase	*P* = .018

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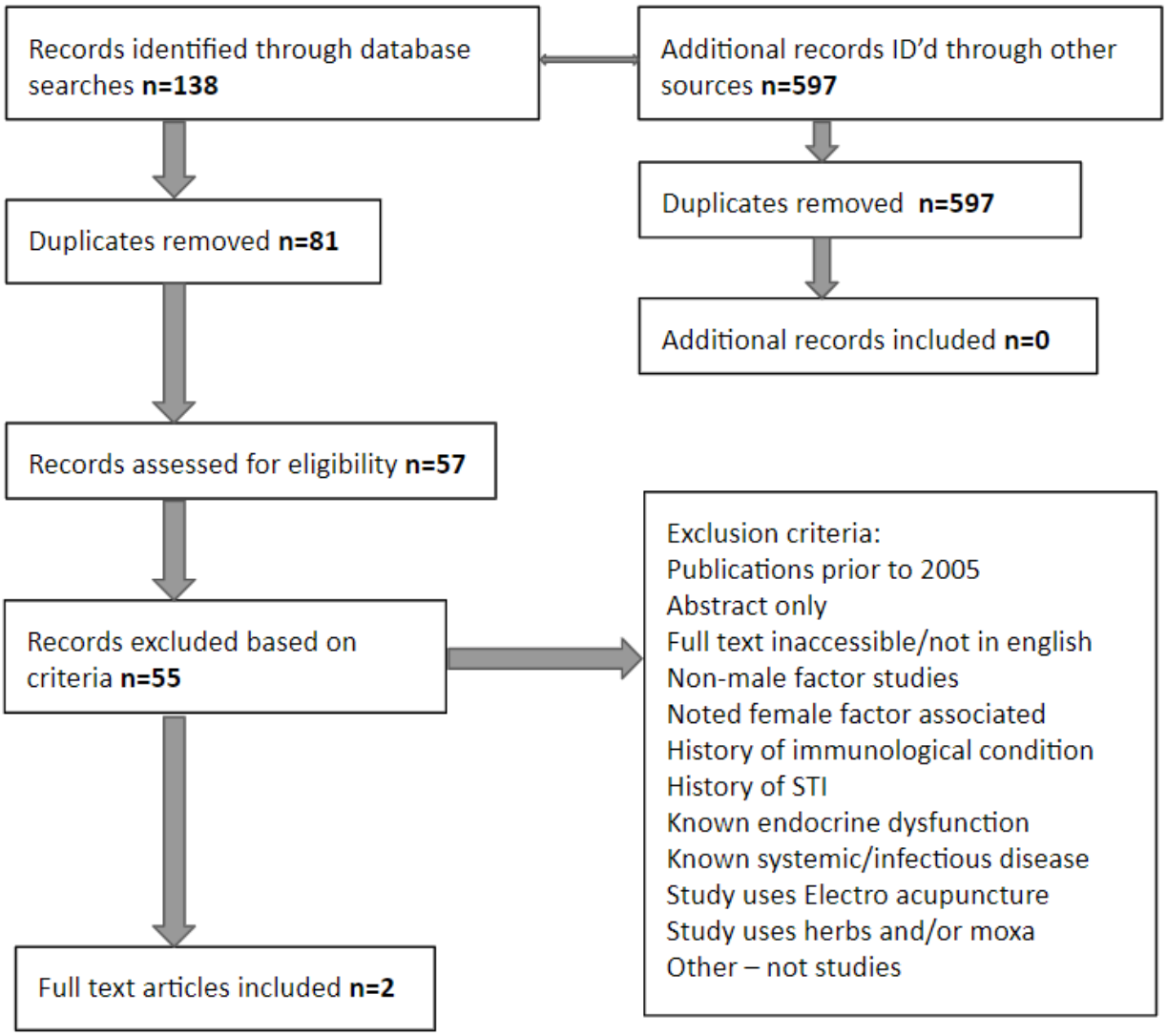
Figure 3.0 Research Flow Chart



References

1. Contributor S. The Most Common Causes of Male Infertility. https://blog.scrcivf.com/male-infertility-common-causes-and-issues. Accessed August 27, 2018.

2. WHO | Infertility definitions and terminology. October 2016. http://www.who.int/reproductivehealth/topics/infertility/definitions/en/. Accessed August 27, 2018.

3. WHO | Infertility definitions and terminology. October 2016. http://www.who.int/reproductivehealth/topics/infertility/definitions/en/. Accessed August 27, 2018.

4. Harris ID, Fronczak C, Roth L, Meacham RB. Fertility and the aging male. *Rev Urol*. 2011;13(4):e184-e190.

5. Sharma R, Agarwal A, Rohra VK, Assidi M, Abu-Elmagd M, Turki RF. Effects of increased paternal age on sperm quality, reproductive outcome and associated epigenetic risks to offspring. *Reprod Biol Endocrinol*. 2015;13:35.

6. World Health Organization. *WHO Laboratory Manual for the Examination and Processing of Human Semen*.; 2010.

7. Hamada A, Esteves SC, Agarwal A. Unexplained male infertility. *Human Andrology*. 2011;1(1):2-16.

8. Website. (https://www.theturekclinic.com/male-infertility-evaluation-including-semen-analysis-sperm-test/. Accessed April 29, 2019.

9. Website. (https://www.theturekclinic.com/male-infertility-evaluation-including-semen-analysis-sperm-test/. Accessed April 29, 2019.

10. Spermatogenesis | physiology. Encyclopedia Britannica. https://www.britannica.com/science/spermatogenesis. Accessed April 29, 2019.

11. Website. (https://www.merckmanuals.com/professional/gynecology-and-obstetrics/infertility/sperm-disorders). Accessed April 29, 2019.

12. Carlsen E E al. History of febrile illness and variation in semen quality. - PubMed - NCBI. https://www.ncbi.nlm.nih.gov/pubmed/14507826, . Accessed April 29, 2019.

13. Website. https://onlinelibrary.wiley.com/doi/full/10.1111/andr.12198. Accessed April 29,

2019.

14. Sperm Test | Dr. Turek – Semen Analysis Specialist | The Turek Clinic. The Turek Clinic. https://www.theturekclinic.com/male-infertility-evaluation-including-semen-analysis-sperm-test/. Accessed April 29, 2019.

15. Elzanaty S, Malm J. Comparison of semen parameters in samples collected by masturbation at a clinic and at home. *Fertility and Sterility*. 2008;89(6):1718-1722. doi:10.1016/j.fertnstert.2007.05.044

16. Elzanaty S. Time-to-Ejaculation and the Quality of Semen Produced by Masturbation at a Clinic. *Urology*. 2008;71(5):883-888. doi:10.1016/j.urology.2007.12.009

17. Website. (https://www.theturekclinic.com/sperm-retrieval-ivf-success-rates/). Accessed April 29, 2019.

18. Unschuld PU. *Medicine in China: A History of Ideas*. Univ of California Press; 2010.

19. Lyttleton J. *Treatment of Infertility with Chinese Medicine*. Elsevier Health Sciences; 2013.

20. Riegler R, Fischl F, Bunzel B, Neumark J. [Correlation of psychological changes and spermiogram improvements following acupuncture]. *Urologe A*. 1984;23(6):329-333.

21. Siterman S, Eltes F, Wolfson V, Zabludovsky N, Bartoov B. Effect of acupuncture on sperm parameters of males suffering from subfertility related to low sperm quality. *Arch Androl*. 1997;39(2):155-161.

22. Zhang M, Huang G, Lu F, Paulus WE, Sterzik K. Influence of acupuncture on idiopathic male infertility in assisted reproductive technology. *J Huazhong Univ Sci Technolog Med Sci*. 2002;22(3):228-230.

23. Gurfinkel E, Cedenho AP, Yamamura Y, Srougi M. Effects of acupuncture and moxa treatment in patients with semen abnormalities. *Asian J Androl*. 2003;5(4):345-348.

24. Siterman S, Eltes F, Schechter L, Maimon Y, Lederman H, Bartoov B. Success of acupuncture treatment in patients with initially low sperm output is associated with a decrease in scrotal skin temperature. *Asian J Androl*. 2009;11(2):200-208.

25. Wang Z-Q, Huang Y-Q, Liang B. [Clinical observation on electroacupuncture and Chinese drug for treatment of oligospermia and asthenospermia of the male infertility patient]. *Zhongguo Zhen Jiu*. 2008;28(11):805-807.

26. Pei J, Strehler E, Noss U, et al. Quantitative evaluation of spermatozoa ultrastructure after acupuncture treatment for idiopathic male infertility. *Fertil Steril*.

2005;84(1):141-147.

27. Siterman S, Eltes F, Wolfson V, Lederman H, Bartoov B. Does acupuncture treatment affect sperm density in males with very low sperm count? A pilot study. *Andrologia*. 2000;32(1):31-39.

28. Dieterle S, Li C, Greb R, Bartzsch F, Hatzmann W, Huang D. A prospective randomized placebo-controlled study of the effect of acupuncture in infertile patients with severe oligoasthenozoospermia. *Fertility and Sterility*. 2009;92(4):1340-1343. doi:10.1016/j.fertnstert.2009.02.041

29. Gupta R, Singh P, Kumar R. Should men with idiopathic obstructive azoospermia be screened for genitourinary tuberculosis? *J Hum Reprod Sci*. 2015;8(1):43-47.

30. Mittal M, Siddiqui MR, Tran K, Reddy SP, Malik AB. Reactive oxygen species in inflammation and tissue injury. *Antioxid Redox Signal*. 2014;20(7):1126-1167.

31. Kothandaraman N, Agarwal A, Abu-Elmagd M, Al-Qahtani MH. Pathogenic landscape of idiopathic male infertility: new insight towards its regulatory networks. *NPJ Genom Med*. 2016;1:16023.

32. Tremellen K. Oxidative stress and male infertility—a clinical perspective. *Human Reproduction Update*. 2008;14(3):243-258. doi:10.1093/humupd/dmn004

33. Kidd SA, Eskenazi B, Wyrobek AJ. Effects of male age on semen quality and fertility: a review of the literature. *Fertil Steril*. 2001;75(2):237-248.

34. Lewis R. *The Infertility Cure: The Ancient Chinese Wellness Program for Getting Pregnant and Having Healthy Babies*. Little, Brown; 2008.

35. Levine H, Jørgensen N, Martino-Andrade A, et al. Temporal trends in sperm count: a systematic review and meta-regression analysis. *Hum Reprod Update*. 2017;23(6):646-659.

36. Website. (https://med.stanford.edu/news/all-news/2013/06/men-with-low-sperm-production-face-increased-cancer-risk-study-finds.html). Accessed April 29, 2019.

37. Website. (Yatsenko, A.N. & Turek, P.J. J Assist Reprod Genet (2018) 35: 933. https://doi.org/10.1007/s10815-018-1148-y). Accessed April 29, 2019.

38. Wang C, Swerdloff RS. Limitations of semen analysis as a test of male fertility and anticipated needs from newer tests. *Fertil Steril*. 2014;102(6):1502-1507.

39. WHO Scientific Group on International Acupuncture Nomenclature. *A Proposed Standard International Acupuncture Nomenclature: Report of a WHO Scientific*

Group.; 1991.

40. Baccetti B, Bernieri G, Burrini AG, et al. Notulae seminologicae. 5. Mathematical evaluation of interdependent submicroscopic sperm alterations. *J Androl*. 1995;16(4):356-371.