

LITERATURE REVIEW: MOLECULAR MECHANISMS OF ACUPUNCTURE IN MALE INFERTILITY TREATMENT

*Literatur Review: Mekanisme Molekuler Akupunktur Dalam Pengobatan
Infertilitas Pria*

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ABSTRAK

Infertilitas adalah suatu kondisi ketidakmampuan pasangan untuk hamil setelah melakukan hubungan seksual selama satu tahun atau lebih tanpa menggunakan kontrasepsi. Pada infertilitas, faktor pria berperan sekitar 30-50%. Banyak faktor yang mempengaruhi infertilitas pada pria, salah satunya adalah parameter pria yang tidak normal. Terapi untuk mengatasi infertilitas pria dapat berupa farmakologi dan non farmakologi, salah satu terapi non farmakologi adalah akupunktur. Tujuan dari tinjauan pustaka ini adalah untuk mengetahui mekanisme molekuler akupunktur dalam pengobatan infertilitas pria. Jenis penelitian ini adalah tinjauan literatur dengan analisis sistematis. Sumber data penelitian ini berasal dari Google Scholar dengan menggunakan kata pencarian di internet, yaitu molekuler, infertilitas dan akupunktur. Diperoleh 7 artikel yang diterbitkan antara tahun 2005 sampai 2023 dan yang kemudian dianalisis tujuan, kesesuaian topik, dan variabel yang digunakan. Kriteria inklusi yang digunakan adalah jurnal yang bertemakan infertilitas pria dan akupunktur serta jurnal berbahasa Inggris. Sedangkan kriteria eksklusi adalah jurnal yang tidak ada pembahasan mengenai mekanisme molekuler dan jurnal yang tidak lengkap. Pada infertilitas pria, akupunktur dapat memperbaiki disfungsi seksual pria, analisis air mani yang abnormal, infertilitas imunologi, peradangan genital, varikokel, dan infertilitas pria idiopatik. Mekanisme akupunktur adalah meningkatkan sirkulasi darah pada testis dan epididimis, mengurangi kadar ROS air mani, mengurangi peradangan, memodulasi sistem kekebalan tubuh, dan meningkatkan motilitas sperma dan parameter air mani.

Kata kunci: akupunktur, infertilitas, infertilitas laki-laki

ABSTRACT

Infertility is a condition where the inability of a couple to conceive after one year or more of sexual intercourse without using contraception. In infertility, male factors play a role of around 30-50%. Many factors influence infertility in men, one of which is abnormal male parameters. Therapy to treat male infertility can be pharmacological and non-pharmacological, one of the non-pharmacological therapies is acupuncture. The purpose of this literature review is to determine the molecular mechanism of acupuncture in the treatment of male infertility. This type of research is a literature review with systematic analysis. The data source of this research is from through Google Scholar using keywords used in internet searches, namely infertility and acupuncture. 7 articles were obtained and then analyzed for purpose, suitability of topics, and variables used. The inclusion criteria used were journal themes with male infertility and acupuncture and English-language journals. While the exclusion criteria are journals with no discussion of

molecular mechanisms and incomplete journals. In male infertility, acupuncture can improve male sexual dysfunction, abnormal semen analysis, immunological infertility, genital inflammation, varicocele and idiopathic male infertility. Mechanism acupuncture is improve blood circulation in the testicles and epididymis, reduce semen ROS levels, reduce inflammation, modulate the immune system, and improve sperm motility and semen parameters.

Keywords: acupuncture, Infertility, male infertility

INTRODUCTION

Infertility is a condition where a couple is unable to conceive after one year or more of unprotected sexual intercourse.¹ The incidence of infertility varies depending on social, cultural, and geographic factors in different nations. According to global infertility statistics from the World Health Organization (WHO), approximately 8–12% of couples experience infertility during their reproductive years.² It is estimated that 60–80 million childless couples live worldwide, representing about 8% of the global population. Additionally, 2 million new cases of infertility are diagnosed each year.³ Infertility can stem from both female and male factors. Since male and female factors often coexist, it is crucial to evaluate infertility in both partners and consider joint treatment approaches.¹ Male factors are responsible for around 30-50% of infertility cases.⁴

Male infertility can result from various factors, including lifestyle changes, medications, diseases, and genetic mutations. Despite advancements in understanding male infertility, approximately 30% of cases remain unexplained due to idiopathic sperm abnormalities. A variety of coexisting medical conditions—such as multiple sclerosis, hemochromatosis, kidney disease, liver failure, cystic fibrosis, and chronic obstructive pulmonary disease—have been found to impact semen parameters.⁵ These conditions may affect fertility in several ways, such as altering hormone levels, compromising ejaculatory or testicular function, or decreasing spermatogenesis. Improving a man's overall health condition can enhance

semen quality, sexual performance, and fertility.⁶

Treatment options for male infertility are determined by the underlying cause. If no specific issue is identified, evidence-based treatments that aim to improve fertility may be recommended. These include surgical interventions for anatomical issues, medical procedures to assist sperm delivery, laboratory-based fertilization, and third-party egg or sperm donation. For certain male reproductive problems, medications such as those for erectile dysfunction or hormone imbalances are also used, though their effectiveness may vary, and they often come with side effects.

Given the limitations of conventional treatments, acupuncture has gained popularity as a complementary therapy for male infertility. Acupuncture is known for its relatively high success rate and minimal side effects.⁷ The growing interest in acupuncture for treating infertility stems from its potential to improve sperm quality, regulate hormone levels, and promote overall reproductive health. Recent studies have begun to explore the molecular mechanisms underlying acupuncture's beneficial effects on male infertility. Acupuncture is believed to influence the central nervous system and endocrine system, thus improving hormonal balance and promoting reproductive function.⁸ At the molecular level, acupuncture may modulate various pathways involved in spermatogenesis and sperm maturation.⁹

One key mechanism is acupuncture's ability to regulate the hypothalamic-pituitary-gonadal (HPG) axis, which controls reproductive function. By stimulating specific acupuncture points, it is suggested that

acupuncture can enhance the secretion of gonadotropins such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are critical for sperm production.¹⁰ Acupuncture has also been shown to increase testosterone levels, which directly influences spermatogenesis.¹¹

Additionally, acupuncture may reduce oxidative stress, which plays a significant role in male infertility by damaging sperm DNA and impairing sperm motility.¹² Studies indicate that acupuncture can increase the activity of antioxidant enzymes, thus protecting sperm from oxidative damage.¹³ Furthermore, acupuncture may improve blood circulation to the testes, enhancing the delivery of oxygen and nutrients essential for sperm development.¹⁴

Inflammation is another factor contributing to male infertility, and acupuncture has demonstrated anti-inflammatory effects. By regulating inflammatory cytokines, acupuncture may help reduce testicular inflammation, which can impair sperm production.¹⁵ In conclusion, acupuncture's molecular mechanisms in treating male infertility involve a multifaceted approach, including hormonal regulation, antioxidant enhancement, improved

circulation, and reduced inflammation. These effects contribute to the improvement of sperm quality and fertility in men.¹⁶

METHODS

This type of research is a literature review with systematic analysis then assessed by the suitability of the desired themes and criteria. The data for this research was sourced from various scientific publications accessed through Google Scholar using specific search keywords, including "infertility" and "acupuncture." A total of 9 articles were selected for analysis. The selection process involved a thorough evaluation of each article based on its relevance, objectives, and the variables it addressed. The inclusion criteria for article selection were: (1) journal topics specifically focused on male infertility and acupuncture, (2) articles published in English, and (3) studies published between 2005 and 2023. Articles were excluded if they did not discuss molecular mechanisms of acupuncture or if they were incomplete or lacked relevant data. The filtering process to ensure that only the most relevant and methodological studies go into the analysis can be seen in figure 1.

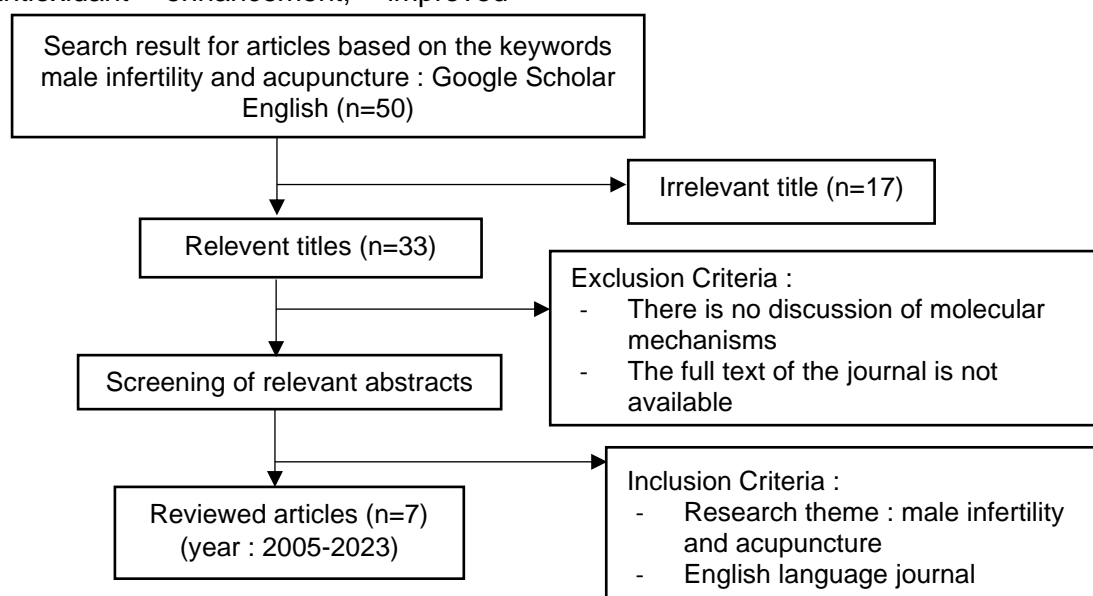


Figure 1. Article Selection Flowchart

RESULT

There are 97 articles that the author gets in this literature review. as for the articles that have been synthesized by the author are shown in table 1 below:

Table 1. Article Search Results

No	Title	Method	Intervention	Diagnosis	Effect molecular mechanisme
1	Kavoussi B, Evan ¹⁷ The neuroimmune basis of anti-inflammatory acupuncture. 2007	Experiment study Sample: 30 rats Sampling: Randomized allocation into control and acupuncture groups.	Acupuncture ST36 Duration of Research: 14 days Intervention Interval: Every day for 30 minutes	chronic inflammatory and autoimmune	<ul style="list-style-type: none"> It may eventually be possible to determine its therapeutic effectiveness in treating inflammatory and autoimmune diseases by increasing autonomic tone and ACh output while lowering inflammatory molecules (cytokines, CRP, etc.).
2	Nurwati I, et al ¹⁸ Electroacupuncture Effectiveness for Treating Idiopathic Male Infertility. 2022	case report Sample: 1 male patient. Sampling: Single-subject design	EA twice per week for up to 12 sessions, CV 4 (Guanyuan), S T 36 (Zusanli), KI 3 (Taixi), CV 6 (Qihai), SP 6 (Sanyinjiao), S T 29 (Guilai), LI 4 (Hegu). Duration of Research: 12 sessions Frequency of Intervention: 2 times a week Duration of each session: 15 minutes	Male infertility : asthenotera tozoospermia	<ul style="list-style-type: none"> Enhanced seminal plasma zinc, neutral α-glucosidase and fructose, enhanced regulation of integrin-binding protein 1, and decreased regulation of cyclin- dependent kinase 1 b.8 may all be linked to transcutaneous electroacupuncture stimulation. Acupuncture sites placed next to each other cause blood vessels, particularly those in the testicles and epididymis, to dilate. Acupuncture affects the HPA axis by lowering cortisol levels and the HPG axis by regulating the synthesis and release of central and peripheral endorphins, which in turn affects the hypothalamic release of gonadotrophin-releasing hormone and the release of hypophysis gonadotrophin.
3	Pei J, et al ¹⁹ Quantitative evaluation of spermatozoa ultrastructure after acupuncture treatment for idiopathic male infertility. 2005	prospective controlled study Sample: 28 patients (treatment group) + 12 untreated controls. Sampling: Non-randomized convenience sampling; patients recruited from infertility	Twenty eight of the patients received acupuncture twice a week over a period of 5 weeks. The samples from the treatment group were randomized with semen	idiopathic oligospermia, asthenospermia, or teratozoospermia	<ul style="list-style-type: none"> The position and shape of the acrosomes showed statistically significant improvements after five weeks. Furthermore, whereas chromatin condensation stayed constant during treatment, nuclear shape demonstrated statistically significant improvements. Improvements in two axonemal features, the

No	Title	Method	Intervention	Diagnosis	Effect molecular mechanisme
		clinic, controls matched retrospectively.	<p>samples from the 12 men in the untreated control group acupoints as main points: Guan Yuan (CV 4), Shen Shu (GB 23, bilateral), Ci Liao (GB32, bilateral), Tai Cong (LR 3, bilateral), and Tai Xi (KI 3, bilateral). The secondary points were Zhu San Li (ST 36, bilateral), Xue Hai (SP 10, bilateral), San Yin Jiao (SP6, bilateral), Gui Lai (ST 29, bilateral), and Bai Hui (GV 20)</p> <p>Duration of Research: 5 weeks</p> <p>Frequency of Intervention: 2 times per week</p> <p>Total number of sessions 10: acupuncture sessions</p>		<p>traditional 9 + 2 pattern and its form, were statistically significant.</p> <ul style="list-style-type: none"> Acupuncture treatment had less of an impact on the fibrous sheath, but accessory fibers were similarly responsive to treatments. Following acupuncture treatment, the median percentage of progressive motility in the ejaculate rose from 44.5% to 50%. Axonemal pattern, axonemal shape, and accessory fiber enhancements were all associated with this statistically significant increase in motility.
4	Huang D, et al ²⁰ Acupuncture for infertility: Is it an effective therapy? 2011	<p>Randomized, single-blind, placebocontrolled trial</p> <p>Sample: 22 acupuncture group + 22 sham control</p> <p>Sampling: Computer-generated randomization with allocation concealment; participants</p>	<p>Acupuncture twice weekly for 6 weeks.</p> <p>Acupoints : Zusanli (ST 36, bilateral), Sanyinjiao (SP 6, bilateral), Taixi (KI 3, bilateral), Taichong (LIV 3, bilateral), Shenshu (BL 23, bilateral), Ciliao (BL 32, bilateral),</p>	Male infertility	<ul style="list-style-type: none"> Serum levels of FSH, LH, and testosterone were all markedly raised by acupuncture, and higher serum testosterone levels were linked to higher sperm motility.

No	Title	Method	Intervention	Diagnosis	Effect molecular mechanisme
		recruited from fertility clinic meeting inclusion criteria	Guilai (ST 29, bilateral), Xuehai (SP 10, bilateral), and Guanyuan (Ren 4). Duration of Research: 12 weeks		
5	Nareswari I, Lestari SW, Notonegoro C ²¹ Acupuncture Therapy for Severe Oligoasthenoteratozoospermia. 2020	Case report Sample: 1 male patient Sampling: Single case selected based on: - Confirmed severe OAT diagnosis - No response to conventional treatment - No anatomical abnormalities	Manual acupuncture therapy was performed at CV3, CV4, CV5, CV6, CV7, ST29, SP6, SP 3, ST 36, and KI 3, alternating with KI 7 5 days per week and at LR 8 once per week, for a total of 28 sessions. Duration & Frequency : 5 days/week for 2 therapy series (14 sessions per series), total 28 sessions	Severe OAT	<ul style="list-style-type: none"> Sperm motility and semen parameters are improved, inflammation is decreased, and the immune system is modulated by acupuncture. By stimulating somatic afferent nerves that innervate the skin and muscles, acupuncture can have a local, segmental, or systemic mechanism. This can alter the activity of the somatic and autonomic nervous systems, including metabolism and endocrine function. Numerous studies have demonstrated that acupuncture considerably lowers seminal ROS levels, particularly in males with varicocele or genital tract inflammation. It also enhances blood circulation in the testes and epididymis. It has been demonstrated that acupuncture increases the activity of two antioxidant enzymes that can lower ROS levels: glutathione peroxidase (GPx) and superoxide dismutase (SOD).
6	Gao J, et al ²² Electroacupuncture enhances spermatogenesis in rats after scrotal heat treatment. 2012	Laboratory experiments (animal studies) Samples: 3-6 Sprague-Dawley rats per group (control, heat treatment, and heat treatment + electroacupuncture). e).	Ten sessions of EA were given at Baihui (GV20), Guanyuan (CV4), Zusanli (ST36) and Sanyinjiao (SP6) from day 9 to day 36 post-treatment	a scrotal heat-treated rat model	<ul style="list-style-type: none"> By promoting the proliferation of germ cells and reestablishing normal levels of inhibin B, electroacupuncture enhances sperm production through spermatogenesis. Changes in hormone levels, testicular blood flow, and Sertoli and Leydig cell activity could all

No	Title	Method	Intervention	Diagnosis	Effect molecular mechanisme
			Duration: 10 sessions Frequency: every 3 days, starting on day 9 after heat treatment		be part of the underlying causes.
7	Ketabchi AA, Salajegheh S ²³ The effects of acupuncture treatment in infertile patients with clinical varicocele. 2018	Randomized controlled clinical trial Sample Size :158 infertile men with clinical varicocele Sampling technique: Randomization (random), division into 4 subgroups	25 minutes of acupuncture manual and each course lasted about 10 weeks (twice a week) Duration & Frequency: 2 times per week for 2 months Number of Sessions : ±16 sessions	left side clinical varicocele (grade 1 - 3)	<ul style="list-style-type: none"> In individuals with varicocele, acupuncture can enhance the quality of semen and increase the likelihood that partners will become pregnant. The A delta and/or C nerve fibers that produce action potentials at histologically distinct acupuncture locations are one potential acupuncture mechanism. At the level of the posterior column medulla, this stimulation creates a somatovisceral reflex arc that ultimately travels to superior regions such the reticular formation, thalamus, and cerebral cortex. Through vasodilation, it can also enhance circulation in the testicles and epididyma. Alterations in semen's reactive oxygen species (ROS) could be another cause. Semen ROS levels dramatically dropped, particularly in patients with varicocele and genital tract irritation. Additionally, sperm parameters improved, particularly the number of normal- shaped sperm, by permitting gamete recovery.

Note : Ach: Acetylcholine, CRP: C-Reactive Protein, EA: Electro acupuncture, HPA: Hypothalamic-pituitary-adrenal Axis, HPG: Hypothalamic-pituitary-gonadal Axis, CV : Conception Vessel, GB: Gall Bladder, LR: Liver, KI: Kidney, ST: Stomach, SP: Spleen, GV: Governor Vessel, FSH: Follicle-stimulating Hormone, LH: Luteinizing Hormone, OAT: Oligoasthenoteratozoospermia, ROS: Reactive Oxygen Species, GPx: Glutathione Peroxidase, SOD: Superoxidase Dismutase

DISCUSSION

Male Infertility

Male infertility is the inability of a man to create a viable female after engaging in unprotected sexual intercourse for a

minimum of a year. According to WHO, it is estimated that 9% of couples worldwide experience fertility problems and male factors account for 50% of subfertile couples. Based on US data, on

22,682 men and women aged 15 to 44 years, it was found that 12% of men were in sub-fertile condition.⁸

Numerous factors, both reversible and irreversible, can contribute to male fertility. There may also be an influence from each partner's age, drugs, surgical history, environmental chemical exposure, genetic problems, and systemic disorders.¹ There are several reasons for male infertility, however they can all be broadly classified according to a common underlying etiology. These comprise idiopathic (i.e., an infertile male with normal sperm and semen parameters) at 10% to 20%, primary testicular defects (i.e., defective sperm parameters without a recognized cause) at 65% to 80%, 2% to 5% of cases are thought to be endocrine problems (typically brought on by hypogonadism) and 5% are thought to be sperm transport disorders (such as vasectomy).⁹ (Table 2)

Table 2. Male infertility causes categorized by mechanism¹⁰

Male Infertility	Causes categorized by	Mechanism
Pre testicular	Testicular	Post testicular
Hypogonadotropic	Cryptorchidism	Coital
hypogonadism – Kallmann syndrome	Testicular cancer	Pharmacological
Hyperprolactinemia	Radiation	Retrograde ejaculation
Pharmacologic	Chemotherapy Pharmacological	Congenital bilateral absence of the vas deferens
	Genetic azoospermia or oligospermia	Young's syndrome
	Y-chromosome microdeletions	Ejaculatory duct obstruction Or seminal vesicle dysfunction
	Klinefelter syndrome	Vasectomy or iatrogenic injury to the

Male Infertility	Causes categorized by	Mechanism
		vas deferens
	Environmental	Nerve injury
	Infection	Spinal cord injury
	Injury or trauma	

To identify and classify the severity of male factors, semen analysis is needed as the basis for laboratory evaluation of male infertility. This is done at least twice, with a minimum distance of one week. Before taking it, 2-7 days of sexual abstinence should be observed. This is done because the level of variability in semen analysis is very high. The outcomes of the semen analysis, the fertility status of the female partner, and the classification of primary or secondary fertility all have a significant impact on the prognosis and outcomes of male infertility.¹

These tend to be well-targeted and have high success rates for known causes of male infertility, some of which include pharmaceutical choices as first-line treatment. Medical care of male infertility with idiopathic or genetic etiology is often empirical and optimization-focused.¹¹

The synthesis of testosterone (T) and spermatogenesis are two aspects of testicular function that are heavily regulated by the hypothalamic-pituitary-gonadal (HPG) axis. High intratesticular T levels and Sertoli cell activation by follicle-stimulating hormone (FSH) are essential for spermatogenesis.² Even though testosterone is necessary for spermatogenesis, its administration has contraceptive effects; it should be avoided because it shows a negative feedback loop on HPG, which prevents luteinizing hormone (LH) from stimulating intratesticular T production and follicle-stimulating hormone (FSH) from stimulating Sertoli cells. Maintaining the reproductive axis to increase testicular T is the aim of treatment for most known causes of

male infertility. However, in a subset of males with primary testicular failure or idiopathic male infertility, no specific medical therapy has been demonstrated to be beneficial; empirical medical care is often used instead.¹¹ Besides pharmacological therapy, non-pharmacological therapy such as surgery and acupuncture is used to treat male infertility.

Acupuncture

Acupuncture is a medical technique that involves inserting needles into certain body parts to provide therapeutic outcomes. The effectiveness of acupuncture treatment is supported by clinical evidence in a variety of applications.¹² In the past, acupuncture was based on the concepts of qi, meridians, yin and yang. Currently it has developed into Medical Acupuncture which is based on the concepts of neuroanatomy and physiology body.¹²

Multiple studies have reported favorable effects of acupuncture on sperm parameters. It raised the proportion of viable sperm, total motile sperm per ejaculation, total functional sperm fraction, and axoneme integrity overall.¹³ Acupuncture has been studied in numerous clinical trials as a potential treatment for the principal conditions that cause male infertility. These diseases mostly include varicocele, idiopathic infertility, immune system disorders, genital inflammation, and sexual dysfunction. A growing number of human and animal studies are being carried out these days to assess the effectiveness of acupuncture for male infertility and investigate its processes.¹³

Acupuncture for Male Infertility Male sexual dysfunction

Male sexual dysfunction is most commonly related to premature ejaculation (PE). Ninety individuals with premature ejaculation were recruited by Sunay et al, and were assigned to four weeks of acupuncture, paroxetine, or placebo. Following therapy, the groups receiving acupuncture and paroxetine had significantly reduced Premature

Ejaculation Diagnostic Tool (PEDT) ratings. Acupuncture was far superior to a placebo, even though it was less successful in delaying ejaculation than paroxetine. Effective sexual functioning is a multifaceted process that involves vascular, neurological, and metabolic processes in addition to social and psychological reactions.¹⁴

Varicocele

Men with varicocele have drastically reduced testicular arterial blood flow because varicocele causes hypoxic-ischemic degenerative alterations in all cellular types at the sperm production site as well as stagnation in the testicular microcirculation. Recent studies show an increase in cytokines, namely IL6, TNF- α , IL37, IL18 and oxidative stress in VC patients.^{15,16} Due to the increased oxidative stress in VC patients, it can mediate immune cell changes in the testes, further causing permanent damage to the testes and affecting the normal spermatogenesis process.²⁴ TNF- α damages the testes by altering mitochondrial function, increasing NO production and stimulating oxidative stress. A recent study by Moretti et al. showed a positive correlation between IL-6 levels and malondialdehyde (MDA) levels in semen. Malondialdehyde (MDA) levels in seminal plasma and semen are negatively correlated with sperm parameters.¹⁶

A prospective, randomized investigation revealed that testicular blood flow was enhanced by 10-Hz electroacupuncture stimulation of ST29 (guilai).⁸ Zhang Y et al. case report of a 40-year-old male patient experiencing heaviness and left-sided scrotal pain due to subclinical varicocele (SCV). After ten sessions of acupuncture treatments (acupuncture at Zhongji (CV3), Guanyuan (CV4), Qihai (CV6), and bilateral Guilai (ST29), Hegu (LI4), Taichong (LR3), Zusanli (ST36), Sanyinjiao (SP6)), the patient was symptom-free, and an ultrasound reexamination revealed no obvious

abnormalities in either of the patient's bilateral spermatic veins.²⁵

Genital inflammation

Poor spermatogenesis can result from scrotal heat in patients with genital tract inflammation. For men who have extremely low sperm density and a history of genital tract irritation, acupuncture may be helpful.¹³

Since the etiology and pathophysiological mechanism of chronic prostatitis remain unclear, current research suggest that the pathogenesis of CP/CPPS may be connected to a normal immunological response, central sensitivity, oxidative stress, pelvic floor muscular spasm, and neuropsychology. There isn't currently a clinically viable treatment for CP/CPPS. The standard treatment for CP/CPPS involves using α receptor blockers, antibiotics, and anti-inflammatory drugs.^{26,27} Long-term use of these medications, however, can result in negative side effects such as nausea, vertigo, gastrointestinal distress, and hypotension, and some of them may not even seem to have any therapeutic benefit²⁸. In light of this, patients look for complementary therapies like acupuncture and cognitive behavioral therapy, with the latter being particularly sought after due to its excellent efficacy and high acceptability.²⁹

According to a systematic evaluation, the group receiving acupuncture therapy for chronic nonbacterial prostatitis/chronic pelvic pain syndrome showed considerably greater effectiveness and cure rates. Acupuncture or electroacupuncture has been shown in numerous clinical trials to alleviate the symptoms of chronic prostatitis, including pain, voiding symptoms, quality of life, and overall scores on the NIH CPSI. Prostaglandin E2 was found in the post-massage urine, confirming the analgesic efficacy of electroacupuncture. During the course of treatment, no patient reported any adverse acupuncture-related events.⁸ Yuan et al investigated how acupuncture

affected individuals who had persistent pelvic pain symptoms. The findings showed that in prostate fluid, the amounts of interleukin-8 (IL-8), interleukin-10 (IL-10), and tumor necrosis factor-alpha (TNF- α) were significantly reduced.¹³

Immunological infertility

Acupuncture has the ability to modify and improve the immune system and affect the body's specific and non-specific immunity in both directions. One hundred and one men individuals with positive antisperm antibody (AsAb) were randomized to receive oral prednisone, acupuncture, or acupuncture combined with herbal medications. The findings demonstrated that serum positive AsAb level and sperm density compared to the control group, those in the acupuncture use group showed a considerable improvement. All groups had a decline in the positive rate of AsAb, but the acupuncture-drug group showed a more pronounced negative-turning rate.¹³ The mechanism by which electroacupuncture treats male immunological infertility may involve controlling nitric oxide levels and trace metals like zinc, copper, and iron. Furthermore, it has the ability to influence the nerve-endocrine-immunity network, enhance the internal reproductive environment, remove external allergens, and elicit both antigen and anti-allergic reactions.¹⁷

Idiopathic Male Infertility

One explanation for its occurrence Oxidative stress in the male reproductive system is the cause of idiopathic male infertility. An imbalance between pro-oxidant and antioxidant concentrations might lead to oxidative stress. Increased testicular temperature is one of the many causes of oxidative stress. Because spermatogenesis is sensitive to temperature fluctuations, temperature plays a critical role in this process. The body uses the vascular heat exchange system in the pampiriform plexus, which is a direct connection between arteries and veins, as one of its methods for

maintaining low testicular temperature.
18

Based on research by Pei Jian et al, in idiopathic male infertility who underwent acupuncture there was an increase in sperm quality, especially in the ultrastructural integrity of spermatozoa. An increase in the median percentage and total number of healthy sperm in the ejaculate, a statistically significant increase was seen in the position and shape of the acrosome, an increase in nuclear shape although chromatin condensation remains. This statistically significant increase in motility was correlated with improvements in axonemal pattern, axonemal shape, and accessory fibers.
19 (Figure 2)

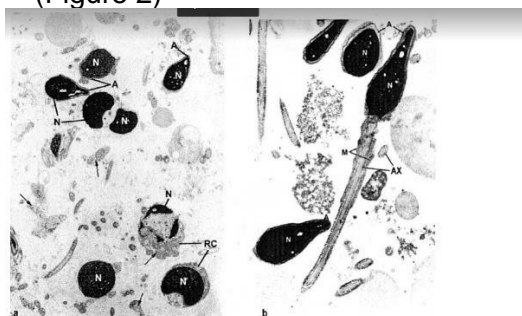


Figure 2. (a) Semen's structural properties prior to acupuncture treatment.

The nuclei (N) and acrosomes (A) of spermatozoa were typically malformed, with uncondensed, necrotic, or marginated chromatin, cytoplasmic residues (CR), and coiled axonemes (arrow). 8 times magnification. (b) Semen's structural properties following acupuncture treatment. Spermatozoa in semen were identified by consistently arranged mitochondria (M), regular acrosome (A) and nuclei (N) with well-condensed chromatin, and typical cytoskeletal structures (AX). Acrosomes and nuclei in certain sperm were changed, and their chromatin was not compacted.

Abnormal semen parameters

The intricate process of spermatogenesis is governed by a variety of regulatory and endocrine variables. Fifty percent of guys undergoing infertility evaluations had

abnormal semen parameters, with oligoasthenoteratozoospermia being the most frequently detected abnormality. There is ongoing discussion over the impact of acupuncture on male infertility, specifically with regard to idiopathic oligospermia, asthenozoospermia, and azoospermia.¹³ An azoospermic male patient, who had previously failed PESA + ICSI, was treated by Bidouee et al. After two rounds of acupuncture, the patient's sperm count in his ejaculation was 18 million/mL. This is the first account of acupuncture successfully treating idiopathic non-obstructive azoospermia in Iran.²⁹

Based on Dong-Mei H's review, the role of acupuncture in male infertility shows a significant effect on increasing the total functional sperm fraction, survival percentage, total motile sperm per ejaculate, axoneme integrity with increasing fertility index, increasing the number of sperm per ejaculate in azoospermia patients, increasing fertilization, improvement in sperm quality after acupuncture, particularly in the ultrastructural integrity of spermatozoa as shown by transmission electron microscopy. Increases the percentage of normal form sperm in infertile patients with oligoasthenoteratozoospermia. Increased serum concentrations of FSH, LH, and testosterone and increased serum testosterone correlate with increased sperm motility.^{20,30}

Mechanism Acupuncture for Male infertility

Stimulating the somatic afferent neurons that innervate the skin and muscles is the primary mechanism via which acupuncture functions clinically. This may impact how the somatic nervous system, endocrine systems, autonomic nervous system, and metabolic processes operate. Infertility can be directly mechanically affected by acupuncture, or it can have effects through the neurological system that fall into the general categories of local, segmental, extrasegmental, and central

impacts.²¹ The effects of acupuncture are believed to be mediated by changes in the activity of the autonomic nervous system and the stimulation of neuropeptides and neurotransmitters that may have a role in the etiology of infertility, according to experimental study.⁸

Stimulating A delta and/or C nerve fibers, which result in action potentials at histologically distinct acupuncture sites, is one way that acupuncture affects the quality of semen. The posterior column medullary level experiences a somatovisceral reflex arc as a result of this stimulation, which eventually travels to the superior center and manifests as the cerebral cortex, thalamus, and reticular formation. Moreover, it enhances vasodilation to improve testicular and epididymal circulation.²² Alterations in semen's reactive oxygen species (ROS) are another potential mechanism. It is established that ROS have a major impact on the quality of infertile men's semen, particularly in those with varicocele who have impairments in sperm motility.²³ According to recent research, ROS levels in the semen of infertile men treated with acupuncture considerably decreased, particularly in those with varicocele and genital tract irritation. When ROS production naturally occurs during regular times, it mostly comes from immature and/or injured spermatozoa and polymorphonuclear neutrophils. cells' natural antioxidant defenses are exceeded by metabolism, oxidative stress results in recurrent lipid peroxidation events that produce additional radicals, and production of ROS, which has the potential to harm other bodily organs and cells, including sperm cells with particular lipid compositions. Therefore, the morphological and functional alterations in sperm are caused by increased ROS generation in semen.³¹

One example is the vasodilation brought on by acupuncture, which will supply antioxidant supplements like

carotenoids, selenium, and vitamins C and E. antioxidants that occur naturally in a wide variety of fruits and vegetables, including lutein, beta-carotene, lycopene, and aqueous zeaxanthin, which guard against ROS-induced peroxidation damage to plasma membranes. Furthermore, sperm parameters rise when the cause of gamete recovery is allowed, particularly in the case of normal form sperm counts.¹⁸ It has been shown that acupuncture improves the activity of the ROS-lowering antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GPx).¹⁹ EA increases and releases blood flow via the vasodilation blood channels in the testis and epididymis. Testicles should be able to maintain their optimal temperature since enhanced blood flow in the reproductive organs is expected to maximize the processes of the vascular heat exchange system. Preserving the ideal temperature of the testicles enhances spermatogenesis and reduces the likelihood of oxidative damage.¹⁴

Acupuncture may lessen local inflammatory responses and alleviate edema and inflammatory infiltration. The majority of acupuncture research, however, concentrated on microcirculation and immunological control. TNF- α , interleukin-8 (IL-8), interleukin-10 (IL-10), and β -endorphin and leucine-enkephalin levels could all be decreased and elevated, respectively, by acupuncture. Acupuncture may also improve the prostate's local immune system and raise the amount of released immunoglobulin A in prostatic fluid. After acupuncture, the peripheral blood of males with immunological infertility shows beneficial alterations in the T lymphocyte subgroup. The mechanism for male immunological infertility brought on by acupuncture may also be connected to the rise in acid phosphatase (ACP) level in plasma. These findings suggest that

acupuncture may be able to control endocrine function and treat aberrant immune.¹³

According to related research, acupuncture can considerably lessen CP/CPPS patients' pain, enhance their NIH-CPSI symptoms, and enhance their overall quality of life.³² The subsequent three mechanisms are among the causes. (a) Modulation of Inflammatory Mediators: Acupuncture has been shown to downregulate the expression of key inflammatory molecules such as tumor necrosis factor (TNF)- α , prostaglandin E2, and interleukins (IL-6, IL-8). Additionally, it influences the balance between pro-inflammatory and anti-inflammatory cytokines, including the upregulation of IL-10, which plays a critical role in reducing inflammation at the molecular level. (b) Neuroplasticity and Central Nervous System Modulation: Chronic pain conditions, such as CP/CPPS, are associated with structural and functional changes in the brain, including reduced gray matter volume and altered activation in regions like the anterior cingulate gyrus. Acupuncture has been demonstrated to modulate these changes by influencing neurotransmitter systems, such as serotonin and dopamine, and by regulating synaptic plasticity through molecular pathways like BDNF (brain-derived neurotrophic factor) signaling. (c) Molecular Mechanisms of Analgesia: While the central analgesic effect of acupuncture is well-documented, the precise molecular mechanisms remain under investigation. Current evidence suggests that acupuncture may act through the modulation of opioid receptors (e.g., μ , δ , and κ receptors) and the inhibition of pain-related signaling pathways, such as the TRPV1 and NMDA receptor pathways.²⁹

According to a recent study, alterations in calcium, integrin binding protein 1 (CIB1), and the cell cycle regulator cyclin-dependent kinase 1 (CDK1) are the causes of low sperm parameters. Dysregulation of CDK1 or

other cell cycle regulators can lead to an imbalance between the quantity of Sertoli and developing germ cells. This imbalance can also increase germ cell mortality and cause anomalies in spermatogenesis. Therefore, alterations in the sperm CDK1 and CIB1 signaling pathways may have a role in controlling sperm parameters in oligoasthenozoospermia patients.³³

Patients with abnormalities in semen parameters associated with elevated levels of zinc and N-acetylglucosamine semen and fructose can increase sperm motility and number by receiving 30 minutes per day for two months of transcutaneous electrical acupuncture point stimulation at BL 23 (Shenshu), ST 36, CV 1 (Huiyin), and CV 4. This is according to a 2019 randomized controlled trial (RCT) by Yu et al. Greater levels of CIB1 and decreased levels of CDK1 may be the cause of this positive effect. Unfortunately, CDK1 and CIB1 levels of the patient were not measured in this case.²¹

The entire mechanism are vasodilation to improve testicular and epididymal circulation.^{24,29,30 18,21,22} Improves the activity of the ROS : lowering antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GPx).^{13,29,31 13,21,23} Preserving the ideal temperature of the testicles.^{24 18} Improve the prostate's local immune system and raise the amount of released immunoglobulin A in prostatic fluid.¹³ Decrease Tumor necrosis factor (TNF)- α , prostaglandin E2, interleukin (IL-6, IL-8), interferon (IFN)- γ , and other inflammatory factors expression level.^{13,22,24 13,18,29} Upregulation of CIB1 and downregulation of CDK1.^{24,29 18,21} Improvement of Sertoli cell function and may enhance spermatogenesis.^{30 22} Improve Sperm parameters.^{25,27,31 19,20,23} Analgeic effect.^{13,22,33}

Currently there are no journals comparing the effectiveness of manual acupuncture and electro acupuncture on male infertility.

CONCLUSION

Acupuncture has shown therapeutic potential in addressing various causes of male infertility, such as sexual dysfunction, semen analysis abnormalities, immunological infertility, genital inflammation, varicocele and idiopathic infertility. In addition to its effects in improving blood circulation and modulating the immune system, acupuncture works through molecular and cellular mechanisms that affect gene expression, cellular signaling and oxidative stress pathways. It may increase the expression of genes involved in spermatogenesis, reduce sperm DNA damage through increasing antioxidant enzymes, regulate apoptosis, and modify epigenetics and the synthesis of nitrogenous bases and RNA. Although clinical evidence is promising, further research is needed to understand in depth the specific molecular mechanisms of acupuncture in improving male fertility.

Acupuncture can be considered an effective complementary therapy to improve sperm quality, sexual function and semen parameters in men with infertility problems. Its ability to modulate molecular pathways makes it a promising intervention to treat the underlying causes of infertility. It can be particularly beneficial for conditions such as sexual dysfunction, abnormal semen analysis, immunological infertility, genital inflammation, varicocele, and idiopathic infertility, where molecular dysfunction plays an important role. However, further research is needed to elucidate the molecular mechanisms underlying how acupuncture improves fertility, including investigation of its effects on gene expression, epigenetic modifications, oxidative stress pathways, and cellular signaling in reproductive tissues. Further research is needed to compare the effectiveness between various acupuncture modalities such as manual acupuncture, electro acupuncture, laser acupuncture, etc.

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