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Meta-Analysis of the Clinical Efficacy of Acupuncture in the Treatment of Male Immune Infertility

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Abstract

Objective: Exploring the therapeutic effects of acupuncture for male immune infertility using Meta-analysis. **Methods:** The literature related to clinical randomized controlled trials (RCTs) on acupuncture for male immune infertility published from the establishment of the database (journal) to 2021 was searched for RR values or OR values and 95% CI as effect indicators. RevMan 5.3 software was applied for meta-analysis. **Results:** Acupuncture or combination of acupuncture and herbal medicine (hereafter referred to as acupuncture and medicine) or electro-acupuncture, the total effective rate was significantly better than the control group, and the difference was statistically significant [RR = 1.29, 95% CI (1.20, 1.38), p < 0.00001]; In addition, the efficiency of the combined acupuncture and medicine treatment was better than that of the herbal medicine group alone, and the difference was statistically significant [RR = 1.05, 95%, CI (0.94, 1.16), P = 0.42]; The sperm viability in the combined acupuncture and medicine treatment group was significantly better than that in the herbal medicine treatment group alone, and the differences were all statistically significant [MD = 0.04, 95% CI (−0.20, 0.28), P0.74]; Sperm forward motion was significantly better in the combination of acupuncture and medicine than in the herbal medicine alone group, and the differences were all statistically significant [MD = 0.66, 95% CI (−0.04, 1.36), P = 0.06]; ACP indexes were significantly higher in the combination of acupuncture and medicine than in the herbal medicine alone group, with a statistically significant difference [MD = 20.47, 95% CI (−65.31, 106.25), P = 0.64]; The AsAb content in the seminal plasma of either needle medicine or acupuncture was lower than in the homogeneous prednisone group, and the difference was statistically significant [MD = −7.00, 95% CI (−11.19, −2.81), P = 0.001]; The index of AsAb content in the serum of either needle medicine

or acupuncture was lower than that of prednisone group, and the difference was statistically significant [MD = −5.00, 95% CI (−9.53, −0.47), P = 0.03]. **Conclusion:** Based on current evidence, acupuncture is more effective than Western medicine (prednisone) alone in the treatment of male immune infertility, and is more effective when combined with Chinese medicine.

Keywords

Acupuncture, Immune Infertility, Male, Meta-Analysis

1. Introduction

Immune infertility is one of the causes of male infertility. One study found that 25% of male immune infertility is caused by anti-sperm antibodies AsAb, which inhibit sperm formation and reduce the viability of sperm, leading to infertility. The incidence of immune infertility has gradually increased in recent years [1]. There is no specific treatment, the main treatment methods are isolation therapy, immunosuppressive therapy and in vitro fertilization treatment, etc. As traditional medicine in China, acupuncture and herbal medicine have a long history of treating infertility-related diseases. The Emperor's Classic of Internal Medicine mentions the name "infertility" for the first time and systematically discusses the law of male fertility and reproductive development. This article evaluates the clinical trial of acupuncture for male immune infertility by conducting a Meta-analysis of a clinical randomized controlled trial (RCT) of acupuncture for male immune infertility. This study has been registered with PROSPERO, registration number: CDR42021292465.

2. Materials and Methods

2.1. Search Methods

Computer search of domestic databases: China Knowledge Network (CNKI), Vipshop database (VIP), Wanfang database, search strategy for free words combined with subject terms, The Chinese search logic is ("male" AND "infertility") AND ("acupuncture OR acupuncture OR electro-acupuncture OR fire acupuncture OR warm acupuncture OR ear acupuncture OR abdominal acupuncture OR trigeminal acupuncture OR skin acupuncture OR intradermal acupuncture OR acupuncture knife"), Foreign Databases: Embase, PubMed, Web of Science, The search logic is (Male AND Infertility) AND (Acupuncture OR Needle therapy OR Electroacupuncture OR Warm Needling OR Walming Needle Moxibustion OR Ear Acupuncture OR Auricular Needle OR Auricular Acupuncture OR Dermal Needle OR Intradermal Needle OR "Three-edged Needle Therapy" OR Needle Knife OR Fire Needling OR Abdomenal Acupuncture OR Abdominal Acupuncture), The language is limited to Chinese and English, and the search time limit is from the establishment of the database to October 4, 2021.

2.2. Inclusion Criteria

1) Study type: Clinical randomized controlled trial.

2) Study population: male patients with immunogenic infertility.

3) Intervention: The intervention method was acupuncture treatment (such as milli-needle, electro-acupuncture, fire acupuncture, warm acupuncture, abdominal acupuncture, trigeminal acupuncture and other acupuncture therapies or combined with other therapies), and the control group was western medicine therapy.

2.3. Exclusion Criteria

Duplicate publications, non-RCT studies, experimental animal studies, literature with incomplete data, summaries of clinical experience or review articles, guidelines, non-Chinese and English literature, interventions that do not include acupuncture, and inaccessible complete literature.

2.4. Literature Screening and Data Acquisition

Using EndnoteX9.1 literature management software for literature processing, two researchers first read the titles and abstracts of the literature independently for initial screening, and carefully read all the literature that matched the titles and abstracts to determine whether they were finally included in the study, If there is any disagreement, the corresponding author will make a decision after discussion between the two. Data were extracted including authors, date of publication, study population and age, interventions (treatment and control), duration of treatment, overall effectiveness, and adverse effects.

The literature search was conducted according to the above criteria, and a total of 660 articles were retrieved. 387 articles were obtained after eliminating duplicates, and the full text was carefully read after the initial screening by reading the titles and abstracts, and 7 articles were finally included. The detailed process is shown in **Figure 1**.

2.5. Quality Evaluation

Two researchers evaluated the risk of bias according to the Risk of bias tool recommended in the Cochrane reviews handbook5.1, including the generation of random sequences, the execution of random concealment, the implementation of blinding, the implementation of blinding of outcome measures, incomplete information, selective reporting, and other biases, respectively. The evaluation was performed, and if the evaluation resulted in disagreement the corresponding author ruled.

2.6. Statistical Analysis

Meta-analysis using Revman 5.3 software, Relative risk ratio (RR) or ratio of ratios(OR) and 95% confidence intervals (CI) were used as effect indicators for the count data; The weighted mean difference (MD) and its 95% CI were used as

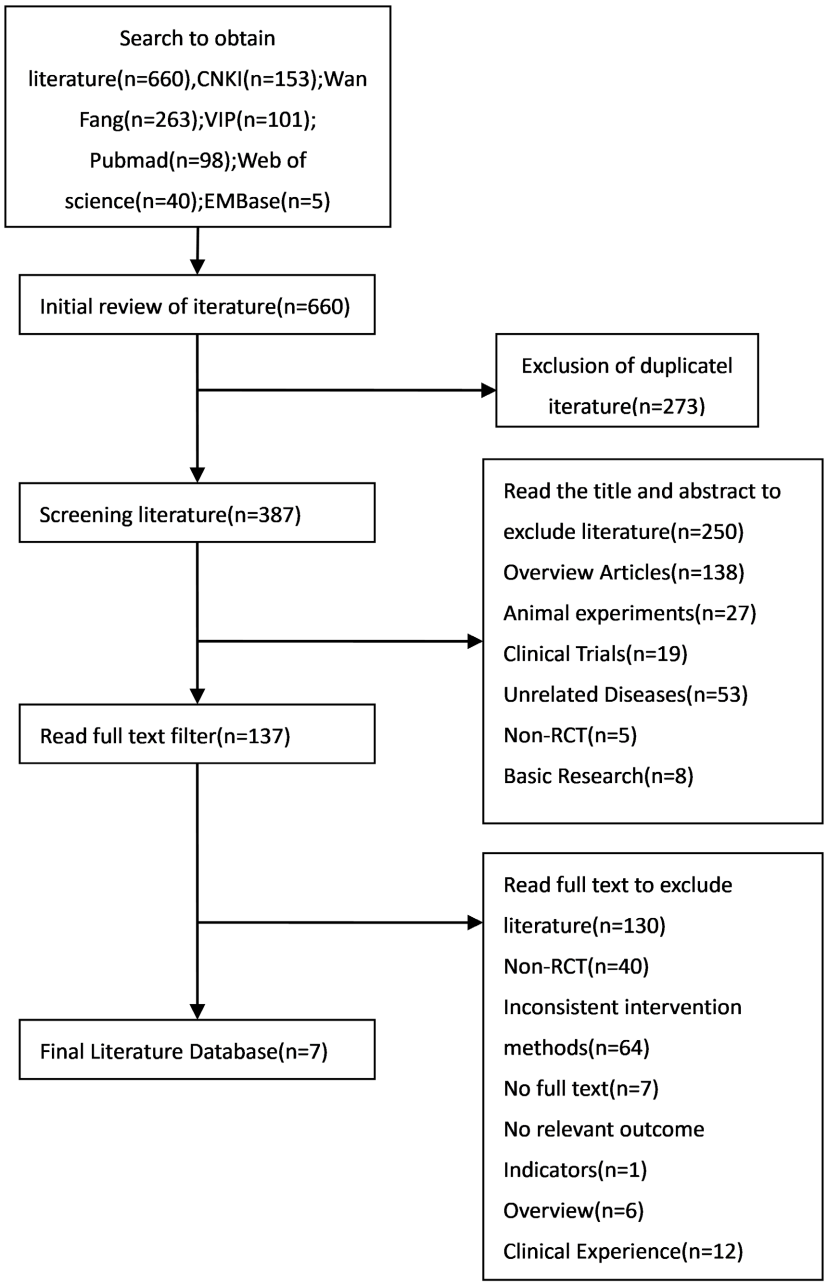

Figure 1. Literature selection process.

effect indicators for the measures. Due to the clinical characteristics of acupuncture therapy, its clinical heterogeneity is generally large, so this study was all analyzed using a random effects model.

3. Results

3.1. Characteristics of the Included Literature

A total of 7 included papers with a total of 515 patients with immune infertility. Two of the papers were different outcome indicators for the same investigator. Six studies were combined and included, all in the journal literature, with a total

of 515 patients with immune infertility, a total of 300 patients in the treatment group and 215 patients in the control group, The basic characteristics of the included literature are shown in Table 1.

3.2. Literature Quality Assessment

Of the seven included papers (six studies), only five mentioned the word randomization but did not describe the specific randomization method [2] [3] [4] [5] [6]; 2 papers were randomly grouped according to the order of consultation [7] [8]; only 1 article mentions blindness [2]. The rest of the literature refers to blinded methods; all cases did not mention cases of interruption and dislodgement; 1 literature mentions follow-up [3]. Other offsets are not available, and the specific evaluation results are shown in Figure 2.

4. Meta-Analysis

4.1. Comparison of Total Efficiency

The included literature (6 studies) [2] [3] [4] [5] [7] [8] compared the total

Table 1. Table of basic characteristics of the included literature.

Research	Number of cases (control/treatment)	Interventions		Treatment	Closing indicator
		Treatment group	Control group		
Lun X2004 [2]	100 (50/50)	Electroacupuncture	Prednisone	Acupuncture once a day; 2 months as a course of treatment	Total efficiency Rate of change of seminal plasma and serumAsAb positivity
Yan WG2004 [3]	318 (159/159)	Electroacupuncture	Prednisone	Acupuncture once a day; 30 times as a course of treatment	Total efficiency Rate of change of seminal plasma and serumAsAb positivity
He YP2007 [4] [5]	105（35/35/35）	Acupuncture and GuiShengWan GuiShengWan	Prednisone	Chinese medicineonce a day Acupuncture twice a week; 3 months as a course of treatment	Total efficiency Seminal plasma ACP
Luo QW2005 [6]	110 (40/40/30)	Acupuncture and GuiShengWan GuiShengWan	Prednisone	Chinese medicine once a day; Acupuncture every other day; 2 months as a course of treatment	Total efficienc; Sperm viability Forward motion of sperm
Fu B2004 [7]	100 (50/50)	Electroacupuncture	Prednisone	Acupuncture once a day; 2 months as a course of treatment	Total efficiency Rate of change of seminal plasma and serumAsAb positivity
Xu HG2014 [8]	100 (50/50)	Acupuncture and LiuWeiDiHuangWan	Prednisone	Acupuncture once a day; 2 months as a course of treatment	Total efficiency Rate of change of seminal plasma and serumAsAb positivity

effective rate with acupuncture/acupuncture/electro-acupuncture in the treatment group and prednisone in the control group, and the differences were statistically significant [RR = 1.29, 95% CI (1.20, 1.38), p < 0.00001]. The results are shown in **Figure 3**, indicating that the overall efficiency of the needle-drug combination or acupuncture or electroacupuncture alone was better than that of the prednisone group; Subgroup analysis by combining acupuncture and herbal treatment [4] [5] are shown in **Figure 4**, the difference was statistically significant [RR = 1.05, 95% CI (0.94, 1.16), P = 0.42]. The overall efficiency of the

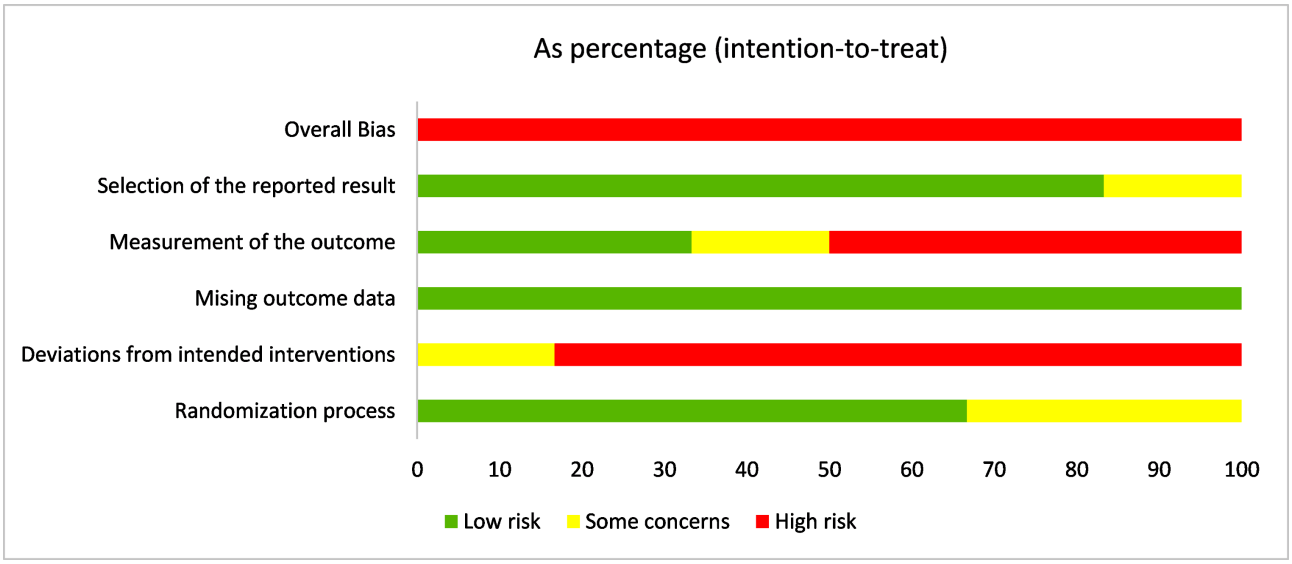

Figure 2. Offset analysis percentage chart.

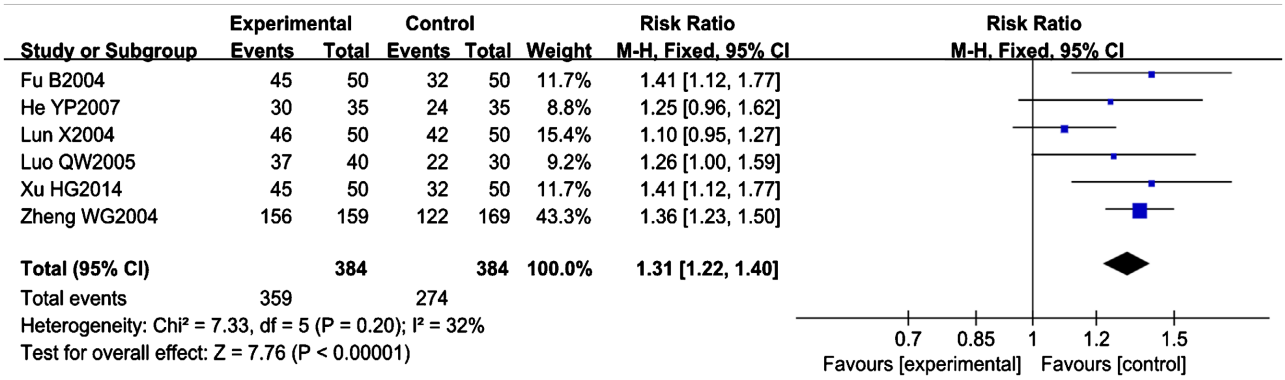

Figure 3. Total efficiency comparison forest diagram.

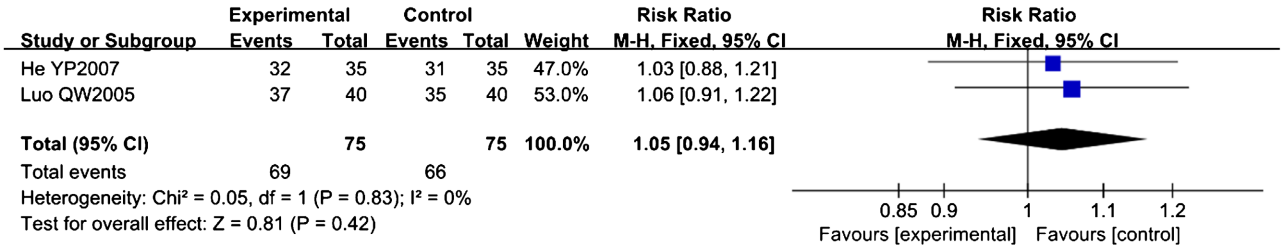

Figure 4. Forest plot of needle medicine and Chinese medicine subgroup analysis.

combined needle and drug group was better than that of the herbal medicine group alone.

4.2. Comparison of Sperm Viability and Forward Motion of Sperm

Only one of the included papers deals with sperm viability and sperm forward motion index [5]. A subgroup analysis with the combination of Chinese herbal medicine and acupuncture within the group showed that the differences in indicators between the two groups were statistically significant [MD = 00.04, 95% CI (−0.20, 0.28), P = 0.74], [MD = 0.66, 95% CI (−0.04, 1.36), P = 0.06]. The results are shown in Figure 5 and Figure 6.

4.3. Comparison of Seminal Plasma ACP Changes

ACP is one of the main components of immunosuppressive factors in seminal plasma, and the decrease of ACP causes the production of AsAb. In the present study there was only one paper involving the comparison of changes in ACP indicators before and after treatment [4], and the difference was statistically significant [MD = 20.47, 95% CI (−65.31, 106.25), P = 0.64], The results showed that the efficacy of the needle and medicine group was better than that of the Chinese medicine group. The results are shown in Figure 7.

4.4. Changes of AsAb Antibodies in Seminal Plasma and Serum before and after Treatment

Three papers [2] [7] [8] discussed the rate of change of AsAb antibodies in serum and seminal plasma before and after treatment. Figure 8 shows the comparison

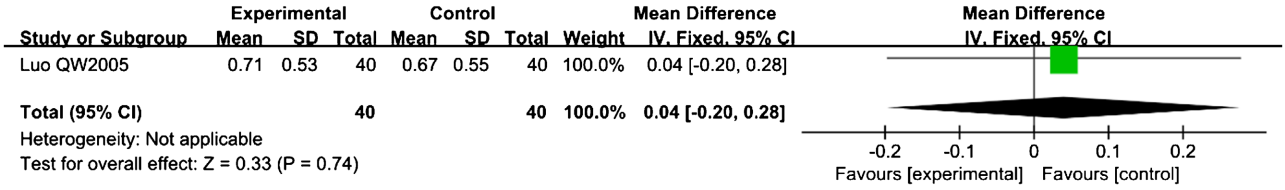

Figure 5. Forest plot of sperm viability.

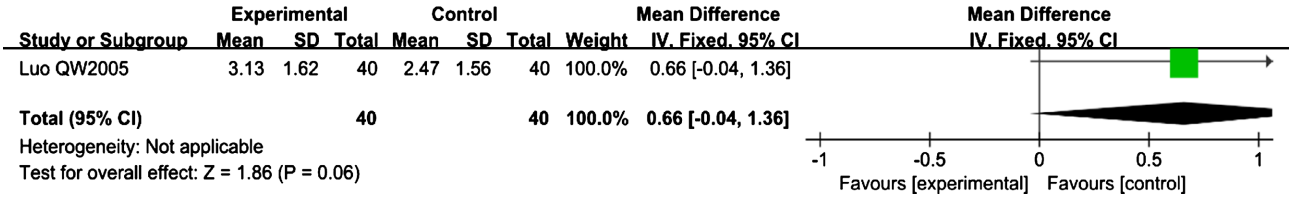

Figure 6. Forest diagram of forward motion of sperm.

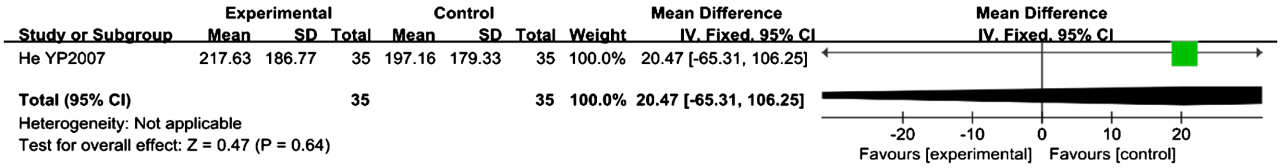

Figure 7. Forest plot of seminal plasma ACP variation.

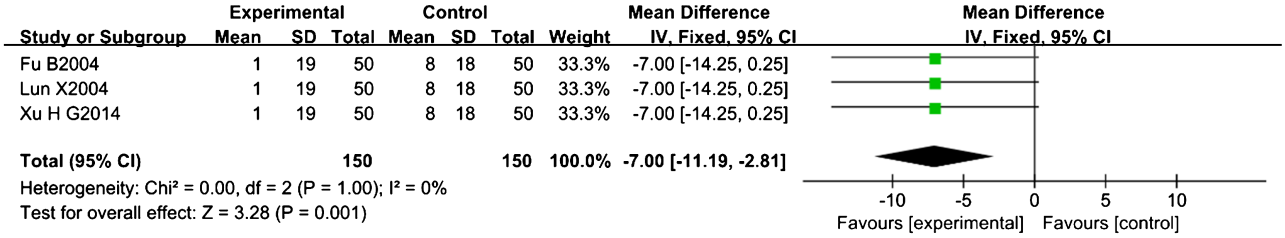

Figure 8. Forest plot of seminal plasma AsAb.

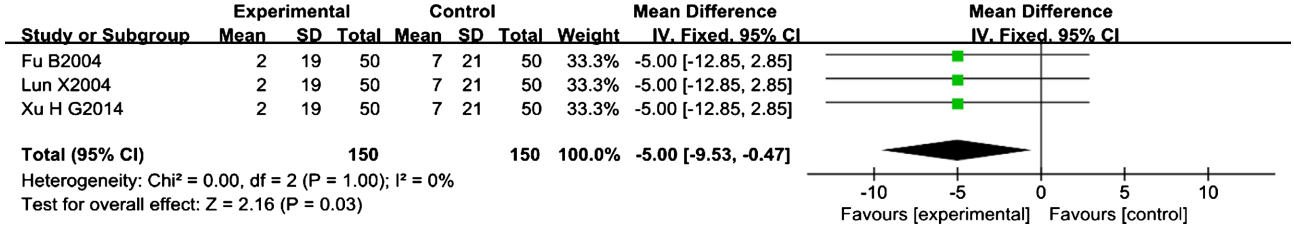

Figure 9. Forest plot of serum AsAb.

of AsAb indicators in seminal plasma before and after treatment, and the difference is statistically significant [MD = −7.00, 95% CI (−11.19, −2.81), P = 0.001]. The results showed that seminal plasma AsAb was significantly lower than that of the prednisone group after treatment in both the needle-drug combination and electroacupuncture alone groups; **Figure 9** shows the comparison of AsAb indicators in serum before and after treatment, and the difference is statistically significant [MD = −5.00, 95% CI (−9.53, −0.47), P = 0.03]. The serum AsAb was significantly lower than that of the prednisone group for both acupuncture and drug combination treatment or acupuncture alone.

5. Publish Offset

Publication bias of the included literature tests. In this study, funnel plots were drawn using the indicator of total efficiency. Since Fu Bing [7] and Xu Guanghua [8], with the same overall effective rate, this **Figure 10** shows similar publication distribution on both sides and no publication bias, but due to the small number of literature included in this study, there may be deviations from the real situation.

6. Discussion

Chinese medicine for infertility dates back 2000 years. Chinese medicine believes that the cause of the disease is caused by congenital deficiencies, loss of nourishment, excessive labor and leisure (sexual intercourse), exposure to evil poisons, uncontrolled diet, emotional disorders, trauma, etc. [9]. The basic pathogenesis is a deficiency of the liver and kidney yin, involving the lungs and spleen, and on the basis of this deficiency, immune dysfunction occurs, resulting in further immune inflammation leading to infertility. Different doctors have different profiles of the evidence types, at present, the main evidence types are spleen and kidney deficiency, deficiency of kidney yin, dampness and heat in the

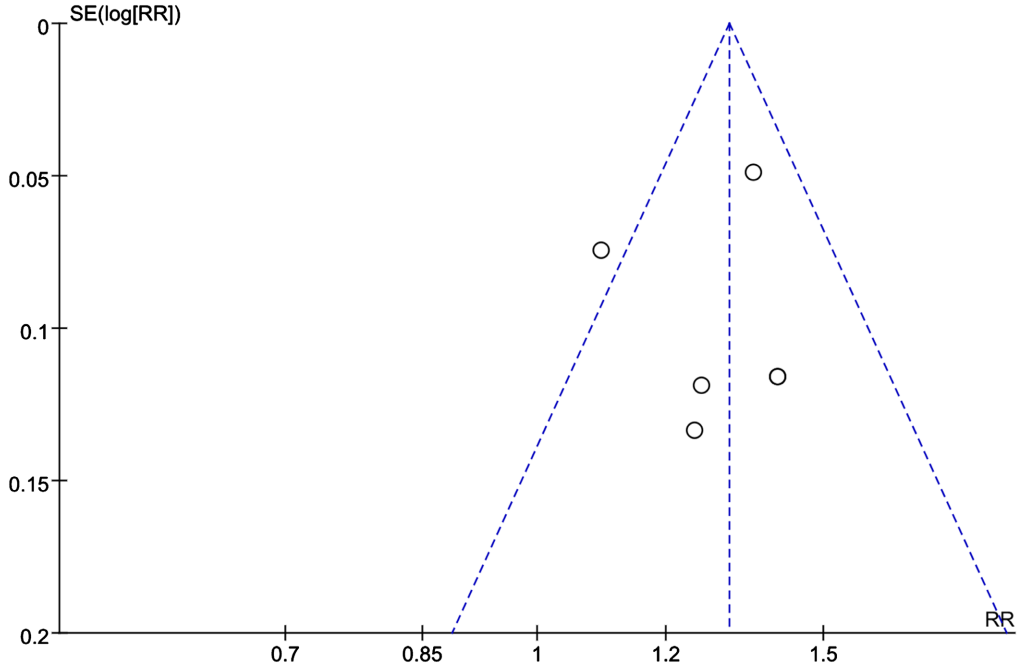

Figure 10. Published offset funnel plot.

liver meridian, stagnation of qi and blood stagnation, etc. Chinese medicine treatment is mainly through traditional Chinese medicine, combination of Chinese and Western medicine, acupuncture treatment and acupuncture-drug combination or electro-acupuncture, etc. [10].

Male immune infertility is defined as a man and a woman who have lived together for more than 2 years and both have normal reproductive function, but anti-sperm antibodies (AsAb) are detected in the male's body. Studies have shown that among the many factors contributing to immune infertility, anti-sperm antibodies (AsAb) are the most important to ignore [11]. The main reason is the presence of immune antibodies in the blood or semen [12]. The prevalence of male infertility in China is increasing year by yea [13]. There are many factors that contribute to immune infertility, and it is generally accepted that they are related to abnormalities in blood-testis barrier function, the production of AsAb, and the effect of complement-regulating proteins on fertility [14]. It is currently believed that the causes of AsAb in the body are related to the following factors: 1) Vasectomy: One Research [15] found that there is sperm phagocytosis in the lumen of the epididymis, and that vasectomy produces sperm granulomas or epididymal congestion, leading to the production of inflammation-associated cells such as plasma cells and lymphocytes, and sperm are surrounded and phagocytosed by inflammatory cells such as macrophages. 2) Factors of vas deferens injury: Damage to the vas deferens from various causes, including vas deferens defect, vas deferens obstruction or damage during hernia repair. 3) Testicular injury: Testicular injury caused by various external forces, if the external force is large and the injury is serious, the testicular tissue is destroyed and the integrity of the blood-testis barrier is also damaged, which in turn leads to the production

of AsAb, even some small injuries or repeated athletic trauma may produce AsAb [14]. 4) Urinary tract infections: It has been found that semen infections caused by UU and CT also have a high potential to cause immune infertility in men [15], and additionally have a correlation with HBV infection [16]. 5) Epididymitis, prostatitis, etc. also have an effect on the production of AsAb [17]. The mechanisms by which AsAb causes immune infertility are currently thought to be as follows: 1) Effect on sperm operation: AsAb in either sperm or cervical mucus causes sperm to advance weakly and slow down. 2) AsAb also has an effect on sperm capacitation and acrosome reaction, resulting in the process not being completed properly. 3) Effect on crossing the zona pellucida and sperm-egg fusion. 4) Effect on fertilized eggs: AsAb binds to certain specific antibodies in fertilized eggs, eventually leading to lysis of the fertilized egg and causing embryonic death. Currently, Western medicine treats male immune infertility mainly with anti-immune therapy, usually using hormone therapy such as prednisone, and relevant antibiotics in case of co-infection [18].

There are more ways to treat male immune infertility in TCM. In this study, we conducted a meta-analysis of acupuncture and acupuncture-drug combination for the treatment of male immune infertility, with western prednisone as a control, to compare the results in multiple ways. The results showed that the acupuncture combined with Chinese herbal medicine or electroacupuncture group or the Chinese herbal medicine group alone were better than the western prednisone group in terms of total effective rate: In terms of seminal plasma and serum biochemical indices, AsAb antibody and ACP in seminal plasma and AsAb antibody in serum were more sensitive to the combination of needle and drug treatment. The effect of the combination of acupuncture and medicine was better than that of the Western medicine group alone; the results of the sperm viability and forward motion of sperm showed that the sperm viability of the combination of Chinese medicine or acupuncture and medicine was better than that of the Western medicine group alone, and the combination of acupuncture and medicine was better than that of the Chinese medicine group alone.

This study also provides simple statistics on the methods and acupoints of acupuncture performed. Four studies [4] [5] [7] [8] used acupuncture combined with herbal medicine, and the remaining two used electroacupuncture [2] [3]. Among the studies on electroacupuncture, two of them used sparse wave [2] [7] and one used continuous wave [3], both of which were operated by acupuncture acupuncture acupoints after obtaining qi and then connecting the electroacupuncture needle, with a frequency of 14 - 26 times/min and a stimulation intensity that was tolerated by the patient and felt obvious soreness, numbness and pain. One study used fluoroscopy [3],Used Xue Hai to penetrate Zu San Li, San Yin Jiao to penetrate Tai Xi, Yang Lin Quan to penetrate Tai Chong and Liver Shu to penetrate Kidney Shu. Among the acupoints used in acupuncture, Liver Shu, Ge Shu, Xin Shu, Diaphragm Acupoint, Tai Chong, Tai Xi, Shen Men, and Xue Hai were the most numerous, involving four studies, followed by Yang Chi,

Ci Liao, and Guan Yuan, involving two studies, and only one study using Yang ling quan [3]. The selection of acupuncture points is based on the Bladder meridian, followed by the Governor meridian, the Ren meridian, the Kidney meridian and the Spleen meridian.

7. Shortcomings and Prospects

Limitations and shortcomings of this study; 1) Fewer included literature, smaller sample size, less precise values; 2) There is a high risk of drift; 3) Follow-up was low, with only 1 study dealing with follow-up; 4) Interventions were not uniform, acupuncture treatment was not uniform in different literature in terms of acupuncture points and acupuncture techniques, the waveforms used for electroacupuncture were not uniform, and there was also no agreement in terms of stimulation intensity; 5) None of the included literature described a specific randomized grouping method, and only one mentioned a blinded method, thus creating numerous biases; 6) Inconsistent determination of outcome indicators and differences in efficacy determination; 7) Small study sample size, resulting in lower precision values and the possibility of false positives or false negatives; 8) Only one study mentioned follow-up, so it is impossible to judge the long-term effect. In order to achieve better efficacy of acupuncture in the treatment of male immune infertility, it is hoped that future studies will be conducted at a deeper level to explore more deeply the specific mechanisms of acupuncture in the treatment of male immune infertility.

In summary, from the results of this study alone, the efficacy of acupuncture combined with Chinese herbal medicine was superior to that of drugs alone or acupuncture alone. However, due to the diversity of acupuncture treatment methods, there are significant differences in the efficacy of various acupuncture methods, and the lack of uniform research standards and objective indicators may lead to poor precision of studies. Due to the low quality of the included literature and the significant heterogeneity and risk bias in the literature, it is hoped that a more objective and rigorous trial report will be conducted in the future to verify the reliability of this result.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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