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# The Effect of Acupoint Stimulation on Pregnancy Outcome after Reapted Implantation Failure: A Systematic Review and Meta-Analysis

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***Abstract:*** *Objective: To systematically evaluate the effectiveness of acupoint stimulation in improving pregnancy outcome of patients with repeated implantation failure. METHODS: From the establishment to December 2020, CNKI, VIP, Wanfang database, PubMed and Cochranelibrary were retrieved by computer, and the literatures of randomized controlled trials (RCTs) on acupoint stimulation therapy for repeated implantation failure were screened. The Cochrane bias risk assessment tool was used to assess the quality of the included studies and ReviewManager5.3 software was used to perform a meta-analysis of the results. RESULTS: A total of 9 literatures were included, involving 979 patients. The results of Meta-analysis showed that acupoint stimulation was superior to the western medicine treatment group in improving the clinical pregnancy rate and embryo implantation rate, and in improving the clinical pregnancy rate, embryo implantation rate and RI, and in improving the embryo implantation rate and RI, the placebo acupoint stimulation group was superior to the blank group. Conclusion: Acupoint stimulation can improve the pregnancy rate of RIF patients.*

***Keywords:*** *Reapted Implantation Failure, Acupoint Stimulation, Pregnancy Outcome, Meta-analysis*

## 1. Introduction

Nowadays, infertility has become another important disease that seriously affects the quality of human life after malignant tumors and cardiovascular or cerebrovascular diseases [1].IVF-ET has become the most effective method to treat infertility, but since the birth of the world's first IVF baby in 1978, the clinical pregnancy rate of IVF-ET still remains at only 30% [2] .Studies have shown that repeated implantation failure (RIF) is an important cause of in vitro fertilization infertility [3]. At present, there is no unified diagnostic criteria for RIF, but the commonly adopted definition is: at least 3 consecutive IVF cycles and 1-2 high-quality embryos are transplanted in each cycle without a pregnancy [4] .Acupuncture is gaining popularity as a complementary therapy to the ART cycle due to its potential benefits and safety. In addition, studies have shown that acupuncture can improve blood circulation and affect the microenvironment of the endometrium. Thus, Endometrial Receptivity (ER) can be improved [5]-[9] .At present, the data of evidence-based medical evidence on the effect of acupuncture on the pregnancy outcome of RIF is still insufficient, and most of them are the combination of acupuncture and medicine, lack of pertinence, lack of scientific analysis and evaluation of other acupoint stimulation methods related to acupuncture. Therefore, this study aims to systematically evaluate the safety and effectiveness of acupoint stimulation for RIF pregnancy outcomes, so as to provide evidence-based medicine evidence and further research direction for the clinical application of acupoint stimulation.

## 2. Methods

### *2.1 Literature Retrieval*

Computer search of CNKI, VIP, WANFANG, Pub Med, Cochrane Library, and the keywords included "repeated embodyo implementation failure", "acute", "electroacupuncture" and "transcutanous electrical acupoint stimulation". The retrieval time is from the establishment of the database to December 2020. The retrieval method of subject words combined with free words is adopted,

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supplemented by references included in the literature.

### *2.2 Inclusion and Exclusion Criteria*

#### *2.2.1 Inclusion Criteria*

Subjects were infertile after 3 or more previous embryo transfer (ET).Intervention: The experimental group received acupoint stimulation, including acupuncture, TEAS, acusector, etc. The control group was treated with western medicine and acupoint stimulation. There is no limitation on the amount of stimulation, the time of use and the course of treatment. Outcome indicators: The primary outcome indicators were clinical pregnancy rate, while the secondary outcome indicators were embryo implantation rate, biochemical pregnancy rate, endometrial thickness, endometrial volume, and uterine artery blood flow resistance index (RI).Type of study: Clinical randomized controlled trial (RCT).

#### *2.2.2 Exclusion Criteria*

(1)Conference papers, animal experiments, reviews and other literature; (2) Unable to obtain the full text of the literature; (3) The study without clear diagnostic criteria and therapeutic evaluation criteria; (4) Repeated publications.

### *2.3 Screening and Extraction of Literature Data*

Two researchers independently read the titles and abstracts of the preliminary literatures to screen out the literatures that might meet the inclusion criteria, and then read the full text and conduct secondary screening according to the inclusion criteria to determine the included literatures. If there is an objection in this process, it will be solved through discussion and analysis. If it persists, it will be ruled by a third party. The last two researchers extracted the data according to the preset literature data extraction table. The extraction contents included the article name, author, year, sample size, infertility years, intervention measures, control methods, random methods, outcome indicators, etc., and then use the Excel software to sort these data.

### *2.4 Quality Assessment*

The quality of the included RCTs was assessed by the Cochrane bias risk assessment tool. Two reviewers asses the following items as "high," "low," and "unclear,": ①generation of random sequences; ②distribution hiding; ③blinded the researchers and the subjects; ④outcome indicators were evaluated by blind method; ⑤ incomplete report outcome; ⑥ selective outcome report; ⑦ Other biases.

### *2.5 Statistical Methods*

The software RevMan5.3 was used for systematic evaluation. The dichotomous outcomes were analyzed by relative risk (RR) index, the continuous variables were analyzed by mean difference (MD), and the 95% confidence interval (95%CI) was calculated. The significance was set at $P<0.05$, and heterogeneity was assessed using $I^2$. The Cochrane Handbook suggested that "0-40% may not be important; 30-60% may represent moderate heterogeneity; 50-90% may represent significant heterogeneity; "75 to 100% may represent considerable heterogeneity" to explain the value of $I^2$.

## 3 Results

### *3.1 Literature Retrieval*

A total of 878 literatures were retrieved from 5 databases by using search terms, including PubMed (n=11), the Cochrane Library n=15, CNKI n=278, Wanfang n=549, VIP n=25 and 3 literatures from other methods. After carefully reading the titles, abstracts and full texts, 9 literatures were included. The literature screening process is shown in Figure 1.

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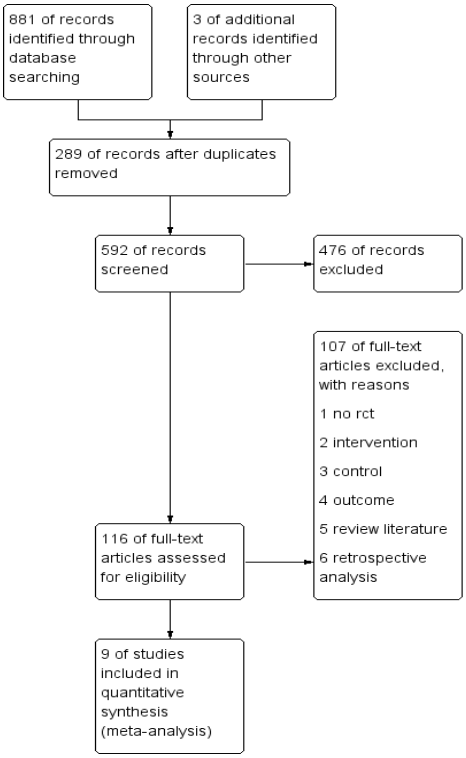


*Figure 1: Flow chart of the systematic literature search*

### *3.2 Main Features of the Included Studies*

#### *3.2.1 Basic Characteristics*

A total of 9 RCTs studies were included, with a sample size of 979 cases, aged between 24 and 44 years, the course of disease was between 1 and 9 years, and the course of treatment was 1-3 menstrual cycles. The characteristics of the included studies are shown in Figure 2.

| Included literatures | Stochastic Method | Treatment group | | | | Control group | | | | Course of treatment | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Sample size | Age | Infertile duration | Interventions | Sample size | Age | Infertile duration | Interventions | | |
| XujinLong2018[30] | ① | 36 | 34.56±4.83 | 4.92±1.92 | acupuncture+Gn RH-a/t-FSH/HMG/HCG long program in IVF-ET hyperstimulation | 36 | 38.81±4.31 | 4.53±1.93 | Gn RH-a/t-FSH/HMG/HCG long program in IVF-ET hyperstimulation | 3 menstrual cycles | a,b,d,e |
| LiangYing2020[31] | ③ | 43 | 31.86±4.53 | - | TEAS+estradiol valerate+micronized progesterone+dydrogesterone | 40 | 31.98±5.58 | - | estradiol valerate+micronized progesterone+dydrogesterone | 2 days before and on the day of transplantation | a,b,e |
| XuMei2014[32] | ② | 82 | 32.5±4.6 | 5.1±3.7 | TEAS+estradiol valerate+Progesterone injection | 94 | 31.9±4.3 | 4.8±3.6 | estradiol valerate+progesterone injection | From the 10th day of menstruation to 24h before transplantation | a,b,e,e |
| Zhenhong Shuai 2014[33] | ③ | 34 | 29.47±3.24 | 4.56±3.25 | TEAS+natural cycles induced by HCG heg | 34 | 29.65±2.60 | 3.88±2.29 | MTEAS+natural cycles induced by HCG heg | 3menstrual cycles | a,e,d,e,g |
| Zhenhong Shuai 2019[34] | ③ | 61 | 31.23±3.78 | 5.09±2.78 | TEAS+IVF | 61 | 31.58±3.07 | 5.71±3.59 | MTEAS+IVF | From the fifth day of ovarian stimulation cycle to the seventh day of transplantation | a,e,d,e |
| DengChao2020[35] | ② | 49 | 35.52±6.74 | - | electroacupuncture+estradiol valerate+progesterone injection+dydrogesterone | 51 | 31.68±7.25 | - | estradiol valerate+progesterone injection+dydrogesterone | 1 menstrual cycle, after menstruation clean to transplant day | a,e |
| MajuanJuan2019[36] | ① | 35 | 30.04±2.98 | 4.4±1.8 | acupuncture+estradiol valerate+progesterone injection+dydrogesterone | 35 | 30.55±3.71 | 4.9±1.5 | estradiol valerate+progesterone injection+dydrogesterone | From the second day of menstruation to the day of transplantation | a,e,e,f,h |
| CaiLiang2020[37] | ① | 108 | 31.05±5.33 | 4.44±0.58 | acupuncture+estradiol valerate+noroxone +CC+HCG+dydrogesterone+progesterone injection+estradiol tablets | 108 | 30.46±5.18 | 4.36±0.55 | estradiol valerate+noroxone +CC+HCG+dydrogesterone+progesterone injection+estradiol tablets | From the third day of menstruation to 0.5h after transplantation | a,e,f |
| ZhaoMeng2019[38] | ① | 38 | 32.57±4.25 | 6.11±1.62 | electroacupuncture combined with infrared radiation | 34 | 33.71±4.22 /32.10±4.54 | 6.40±1.31/ 5.30±1.75 | placebo acupuncture group/ blank control group | After menstruation to the day before transplantation | a,b,e,e,g,h |

notes: a.Clinical pregnancy rate b.Biochemical pregnancy rate c.Embryo implantation rate d.Live production rate e.Endometrial thickness f.Positive rate of endometrial blood flow distribution g.Endometrial volume h.RI TEAS:transcutaneous electrical acupoint stimulation
①Random number table②Random words only③Computer random

*Figure 2: Characteristics of included studies*

#### *3.2.2 Acupoints Usage*

There are 37 body acupoints and 7 auricular points, and the statistical results of frequency are as follows.A total of 6 body acupoints were used more than 4 times. The name and frequency are: Zigong (EX-CA1,10) Sanyinjiao (SP6,8) Guanyuan (RN4,7) Zusanli (ST36,5) Guilai (ST29,4) Taixi (KI3,4) Diji (SP8,4). A total of 3 acupuncture points (Shenshu(DU12), Zhongji(RN3) and Taichong(LR3) are used 3 times. There are 5 acupoints that are used twice (Luanchao Shenshu, Ciliao, Xuehai, Qihai,). A

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total of 20 acupoints with a frequency of 1 use (Neiguan, Pishu, Zhongwan, Xinshu, Yanglingquan, Fuliu, Tianshu, Hegu, Baliao, Baihui, Gongsun, Neiguan, Rangu, Hou Xi, Zhiyang, Geshu, Lieque, Zhaohai).One study [10] used auricular points: Neifenmi, Neishengzhiqi, Shenmen, Naogan, Shen, Pizhixia, and Jiaogan.

### *3.3 Quality Assessment*

Nine papers [10] - [18] included all applied randomization. Among them, 4 literatures [10,16,17,18] were rated as "low risk" by random number table method, 3 literatures [11,13,14] were rated as "low risk" by computer random method, and 2 literatures [12,15] mentioned the word "random" but did not specify the random method as "unclear"; Nine papers did not mention the hidden distribution results, so they were rated as "unclear"; One paper[14]adopted a single blind method , and one paper [13] adopted the double-blind method and was therefore rated as "low risk", and the remaining articles did not involve blind method; One article [15] mentioned that the dropped subjects were rated as "high risk", and the others were not mentioned, so they were rated as "low risk"; The results of 9 papers were consistent with the preset outcome indicators, so the selective results were rated as "low risk"; Nine articles could not find other sources of bias, so they were rated as ' unclear ', as shown in Figure 3.

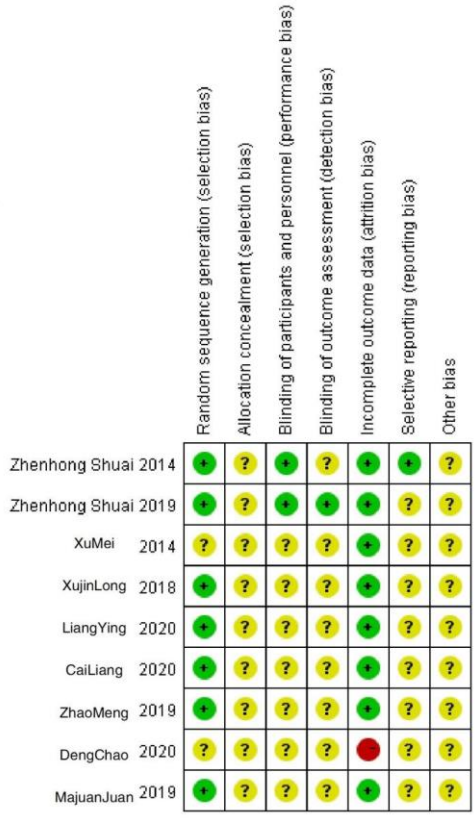


*Figure 3: Risk assessment diagram of included literatures*

### *3.4 Meta-Analysis Results*

#### *3.4.1 Clinical Pregnancy Rate*

Six studies [10,11,12,15,16,17] reported the effects of acupoint stimulation and western medicine on the clinical pregnancy rate, and the acupoint stimulation group was superior to the western medicine group in improving the clinical pregnancy rate of patients (RR=1.73;95% CI: 1.38 2.16;Z = 4.81;P < 0.00001;I ²=0%).Three studies [13,14,18] reported the effect of acupoint stimulation and comfort acupoint stimulation on clinical pregnancy rate, and the acupoint stimulation group was superior to the comfort acupoint stimulation group in improving the clinical pregnancy rate of patients (RR=2.07;95% CI: 1.34 3.18;Z = 3.30, P = 0.001;I ²=0%).One study [18] reported the effect of acupoint stimulation and blank group on the clinical pregnancy rate, and the acupoint stimulation group showed no difference in improving the clinical pregnancy rate of patients compared with the untreated group (RR=2.21;95% CI:

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0.90 5.45; Z=1.72, P=0.08).The detailed forest plot is shown in Figure 4.

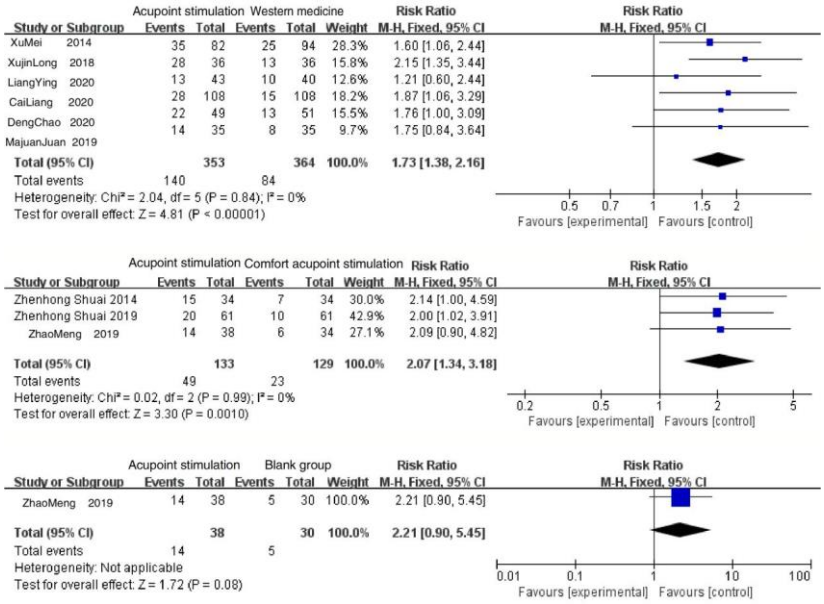


*Figure 4: MEAT analysis of clinical pregnancy rate*

### *3.4.2 Endometrial Thickness*

Five studies [10,11,12,15,16] reported the effect of acupoint stimulation and western medicine on endometrial thickness, and acupoint stimulation was superior to western medicine in increasing endometrial thickness of patients (MD=0.77;95% CI: 0.13 1.40;Z = 2.37;P = 0.02;I ²=90%, using random effects model; Fig. 5).Three studies[13,14,18] reported the influence of acupoint stimulation and comfort acupoint stimulation on the thickness of the endometrium. The acupoint stimulation group was better than the comfort acupoint stimulation group in increasing the patient's endometrial thickness. The heterogeneity is large (I ²=74%), after excluding one study [13] (MD=1.65; 95% CI: 1.23–2.07; Z=7.68; P<0.00001; I ²= 0% , Using a random effects model; Fig. 5).One study [18] reported the effect of acupoint stimulation and blank group on endometrial thickness, and acupoint stimulation was superior to untreated group in increasing endometrial thickness (MD=2.08;95% CI: 1.42 2.74;Z = 6.19;P < 0.00001;Fig. 5).

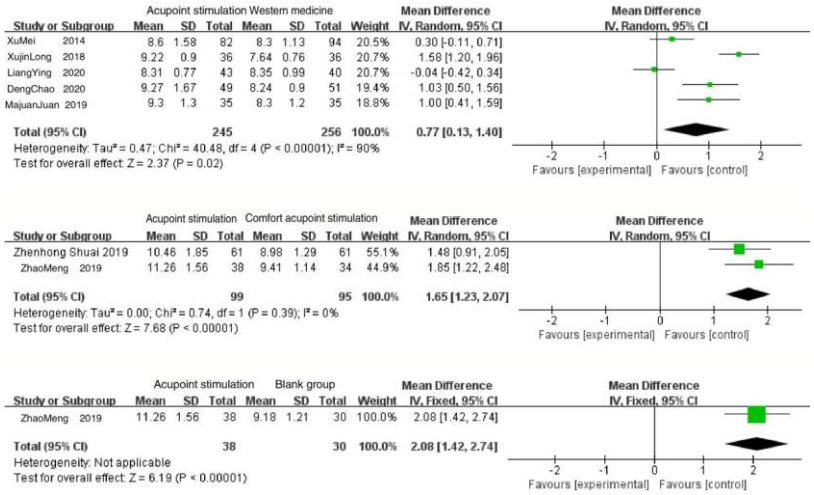


*Figure 5: MEAT analysis of Endometrial Thickness*

### *3.4.3 Embryo Implantation Rate*

Three studies[12,16,17] reported the effects of acupoint stimulation and western medicine on the embryo implantation rate. The acupoint stimulation group was better than the western medicine group in improving the embryo implantation rate of patients (RR=1.73; 95% CI: 1.27–2.34; Z=3.53; P=0.0004; I ²=0%; Fig. 6). Three studies[13,14,18] reported the effects of acupoint stimulation and

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comfort acupoint stimulation on the embryo implantation rate. The acupoint stimulation group was better than the comfort acupoint stimulation group in improving the embryo implantation rate of patients (RR=2.04; 95% CI: 1.41–2.96; Z=3.76; P=0.0002; I ²=0%; Fig. 6). One study [18] reported the effect of acupoint stimulation and blank group on embryo implantation rate,The acupoint stimulation group was better than the untreated group in improving the embryo implantation rate of patients (RR=2.37; 95% CI: 1.07–5.22; Z=2.14; P=0.03;Fig. 6).

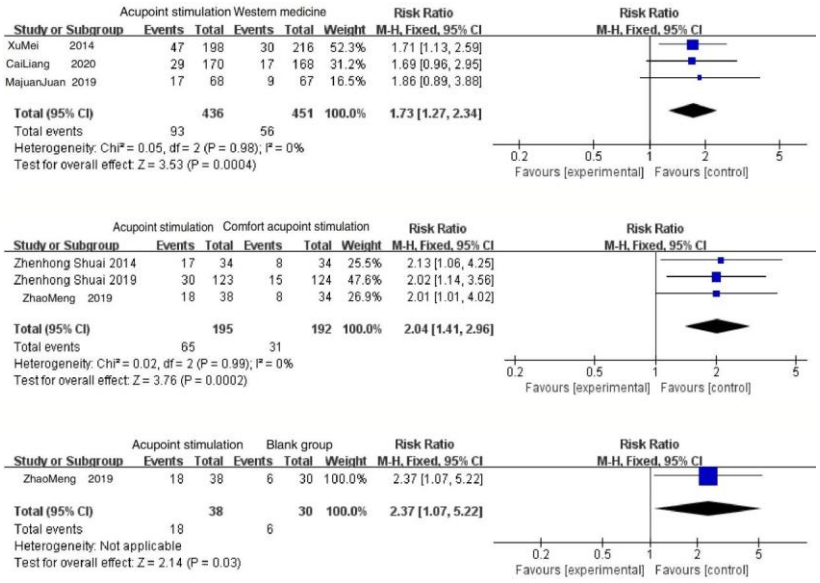


*Figure 6: MEAT analysis of Embryo Implantation Rate*

### *3.4.4 Biochemical Pregnancy Rate*

Three studies [10,11,12] reported the effects of acupoint stimulation and western medicine on biochemical pregnancy rate, and there was no difference between the acupoint stimulation group and the western medicine group in reducing patients' biochemical pregnancy rate (RR=1.22;95% CI: 0.90 1.66;Z = 1.31;P = 0.19;I ²=33%;Fig. 7).One study [18] reported the effect of acupoint stimulation and comfort acupoint stimulation on biochemical pregnancy rate, and the acupoint stimulation group showed no difference in reducing patients' biochemical pregnancy rate compared with the comfort acupoint stimulation group (RR=1.70;95% CI: 0.92 3.13;Z = 1.70;P = 0.09;Fig. 7).One study [18] reported the effect of acupoint stimulation and blank group on biochemical pregnancy rate, and the acupoint stimulation group showed no difference in reducing the biochemical pregnancy rate of patients compared with the untreated group (RR=1.67;95% CI: 0.89 3.14;Z = 1.58;P = 0.11; Fig. 7).

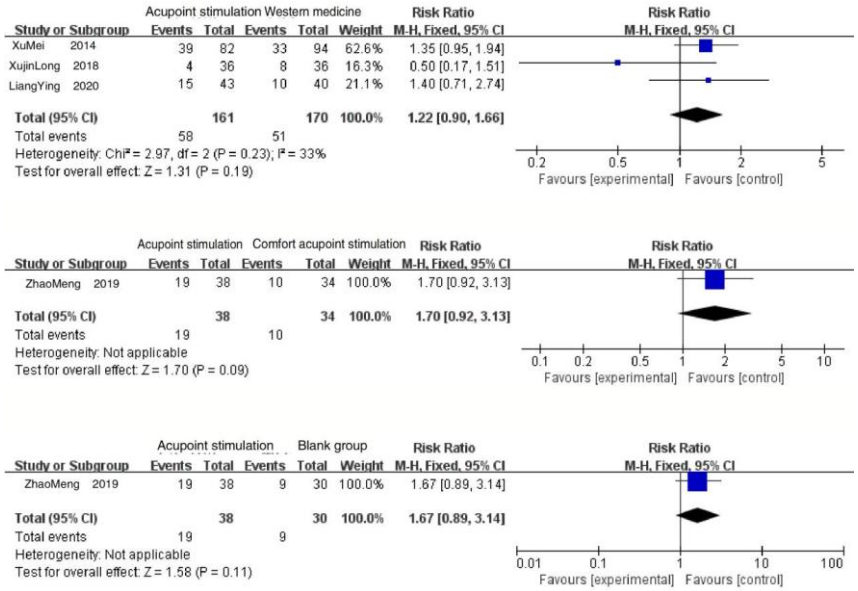


*Figure 7: MEAT analysis of Biochemical Pregnancy Rate*

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### *3.4.5 Endometrial Volume*

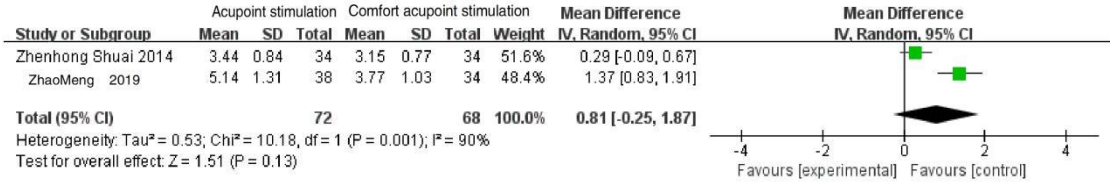


*Figure 8: MEAT analysis of Endometrial Volume*

Two studies [13,18] reported the effects of acupoint stimulation and western medicine on endometrial volume, and there was no difference in increasing endometrial volume between acupoint stimulation group and western medicine group (MD=0.81;95% CI: 0.25 1.87;Z = 7.22;P = 0.13;Parenchymal heterogeneity I ²=90%, using random effects model;Fig. 8).

### *3.4.6 RI*

One study [16] reported the effects of acupoint stimulation and western medicine on RI. There was no difference between the acupoint stimulation group and the western medicine group in improving the RI of patients (MD = -0.10; 95% CI: -0.38–0.18; Z = 0.69; P =0.49). One study [18] reported the effects of acupoint stimulation and comfort acupoint stimulation on RI. The acupoint stimulation group was better than the comfort acupoint stimulation group in improving patients' RI (MD = -0.18; 95% CI: -0.23–-0.13; Z = 0.69; P<0.00001). One study [18] reported the effect of acupoint stimulation and blank group on RI. The acupoint stimulation group was better than the comfort acupoint stimulation group in improving the RI of patients (MD = -0.18; 95% CI: -0.23–-0.13; Z = 7.63; P<0.00001). The detailed forest plot is shown in Figure 9.

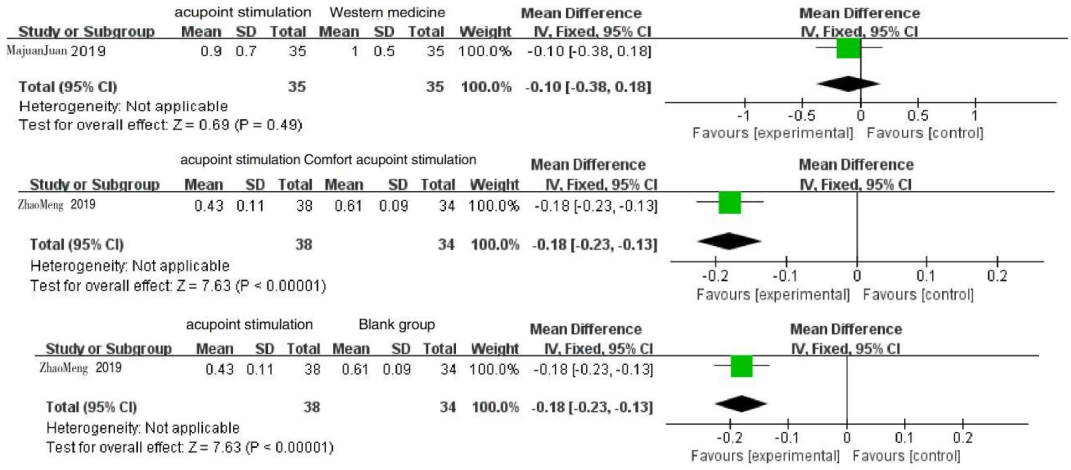


*Figure 9: MEAT analysis of RI*

### *2.4.7 Sensitivity Analysis*

Sensitivity analysis was conducted for endometrial thickness, and the references included in the Meta analysis were excluded one by one, and the MD, 95%CI, effect size and P value of the remaining references were calculated.The results showed that the acupoint stimulation group and the western medicine group had little influence on the final results after removing each literature, and the sensitivity analysis results showed that the Meta analysis results were stable and reliable.The heterogeneity of acupoint stimulation and comfort acupoint stimulation groups decreased significantly after one study was excluded [13].The sensitivity analysis of endometrial thickness was shown in Table1 and Table 2.

*Table 1: Acupoint stimulation VS western medicine*

| Excluded research | MD | 95% CI | P | I ² |
|---|---|---|---|---|
| nothing | 0.77 | 0.13,1.40 | 0.02 | 90% |
| XuMei2014 | 0.89 | 0.10,1.67 | 0.03 | 91% |
| XujinLong2018 | 0.54 | 0.02,1.06 | 0.04 | 80% |
| LiangYing2020 | 0.98 | 0.38,1.58 | 0.0002 | 85% |
| DengChao2020 | 0.71 | -0.07,1.48 | 0.07 | 92% |
| MajuanJuan2019 | 0.71 | -0.05,1.48 | 0.07 | 92% |

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*Table 2: Acupoint stimulation VS comfort acupoint stimulation*

| Excluded research | MD | 95% CI | P | $I^2$ |
|---|---|---|---|---|
| nothing | 1.31 | 0.59,2.03 | 0.0004 | 74% |
| Zhenhong Shuai2014 | 1.65 | 1.23,2.07 | <0.00001 | 0% |
| Zhenhong Shuai2019 | 1.20 | -0.11,2.50 | 0.07 | 87% |
| ZhaoMeng2019 | 1.03 | 0.09,1.97 | 0.03 | 76% |

## 3. Discussion

A total of 9 studies were included in this study, involving 979 patients. To evaluated the clinical efficacy of acupoint stimulation compared with western medicine intervention, comfort acupoint stimulation group and non-treatment group ,in terms of clinical pregnancy rate, embryo implantation rate, biochemical pregnancy rate, endometrial thickness, endometrial volume, and RI .The results showed that acupoint stimulation was superior to the western medicine treatment group in improving the clinical pregnancy rate, embryo implantation rate, and endometrial thickness. In improving endometrial thickness, embryo implantation rate, endometrial thickness and RI it was better than the comfort acupoint stimulation group, and it was better than the blank group in improving endometrial thickness, embryo implantation rate, and RI. Therefore, acupoint stimulation has a positive effect on increasing the pregnancy rate of RIF patients.

Traditional Chinese medicine does not have a definition of "repeated implantation failure", but according to its clinical symptoms, it can be classified as "infertility". In TCM, the kidney is the foundation of reproduction and the backbone of the five zang organs. The yin and yang of the five internal organs are all based on the kidney yin and yang. The yin and yang in the kidney are abundant, which is the foundation of women's gestation [19]. Chongmai can regulate the qi and blood of the twelve meridians, and is closely related to reproductive function. Ren mai is the sea of meridians and it is the foundation of the foundation of pregnancy. Unobstructed Renmai and plentiful Chongmai is a necessary condition to fetation. Congenital deficiency of kidney qi or acquired kidney qi is impaired, resulting in the inability of the Jingqi to transform blood, the deficiency of Chong and Ren, the dystrophy of the uterus, and it is difficult to get pregnant. In addition, spleen is the root of nurture .The production and transportation of qi and blood are all rely on the spleen. And the spleen can nourish the kidneys. If the spleen is weakness, it can cause the insufficient of nutrients, qi and blood .They can't nourish the kidney, chongmai, renmai, uterus, and uterine collateral. It can also lead to infertility. In addition, conception also requires the right time. In TCM, yinyunzhishi is the best time for the uterus to receive an embryo. At this time, yin and yang meet and merge, they can produce everything. If yin and yang are all filled in uterus, it will have a strongest ability to accept embryos .A famous ancient Chinese physician Fu Qingzhu believes that "If the jing is full, the uterus is easy to absorb sperm, and if the blood is enough, the uterus is easy to contain things." If the spleen-kidney deficiency, it can lead to insufficiency of jing and blood then the uterus' acceptability of the embryo will also be reduced, which is not conducive to conception.

According to the statistical results of this study, commonly used acupoints are the Zigong (10) Sanyinjiao (8) Guanyuan (7) Zusanli (5) Guilai (4) Taixi (4) Diji (4), and the Zigong is an extra point. It can regulates the qi and elevating the spleen-qi; Sanyinjiao is the junction point of the spleen meridian, kidney meridian, and liver meridian, which can nourish the liver and kidney, and regulate and harmonize qi and blood; Guanyuan is the meeting of the three yinjing and the Renmai, and is also a "women's blood storage " .It can replenish qi and blood, and strengthen the kidney; Zusanli is the foot-yangming stomach meridian's he-sea point, which can adjust the spleen and stomach, and replenish qi and blood;Taixi is the Yuan-Source acupoint of the kidney meridian, which can tonify the kidney and nourish Yin, tonify the Ren and replenish the blood; Diji is the Xi-Acupoint of the spleen meridian of Foot-Taiyin ,which is the main transport and transformation place of the spleen earth. It is the place where the meridian qi is deeply collected, and it has a strong power to help spleen and Qi's movement. The coordination of the above acupoints can treat the spleen and kidney at the same time, regulate qi and blood, build connections between meridians, improve the uterine environment, and facilitate the implantation of blastocysts. In addition, modern studies have found that acupuncture can locally increase uterine artery blood flow through the central sympathetic nerve inhibitory effect [20], reduce the resistance of uterine artery blood flow [21], and change the release of signal molecules such as chemokines, integrins and growth factors. To adjust the receptivity of the endometrium to facilitate implantation [22,23], which may be the reason why acupoint stimulation improves the clinical pregnancy rate of RIF patients.

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Limitations of this study: Embryonic factors account for 1/3 of the reasons for implantation failure, and suboptimal endometrial receptivity accounts for the remaining 2/3 [24]. In the absence of the gold standard diagnostic test for endometrial receptivity, we consider clinical pregnancy as an alternative outcome to confirm good endometrial receptivity. However, the loss of clinical pregnancy may be the result of embryo quality (aneuploidy or poor implantation potential) or other factors (for example, abnormal endometrial microbiota, uterine structural defects, or maternal immune factors), and may not truly reflect the uterus Intimal receptivity. This may reduce the accuracy of some outcome indicators included in this study, and the study lacks sufficient details related to the known sources of heterogeneity (embryo transfer stage, embryo quality, number of embryos transferred).In addition, the methods of acupoint stimulation, selection of acupoints, course of treatment, treatment timing, amount of stimulation included in the study are not same, and there are also differences in the prescription of acupoint selection among the studies.

There is no significant statistical difference between acupoint stimulation and comfort acupuncture in improving endometrial volume and biochemical pregnancy rate, which may be related to the inappropriate setting of comfort acupuncture point stimulation. A study [18] chose comfort acupuncture as the control group, while Lund I et al. [25] found that micro-acupuncture and placebo plus fake needle contact with the skin both can cause the activity of skin afferent nerves, which has a significant impact on the corresponding functional areas of the brain, resulting in a "edge contact response."

Acupoint stimulation and comfort acupoint stimulation in improving the endometrial volume and biochemical pregnancy rate has no significant statistical difference, may be associated with comfort acupoint stimulation Settings is inappropriate, a study [18] choose comfort acupuncture as a control group, and [25] such as LundI found traces of acupuncture and placebo plus fake needle contact with skin can cause skin afferent nerve activity, This activity has a significant impact on the corresponding brain regions, resulting in the "marginal contact response. "Mao Wenchao et al. [26] systematically differentiated the effects of acupuncture and sham acupuncture, and believed that the difference between the non-specific effects of treatment acupuncture and sham acupuncture could be reduced to the greatest extent through blind method, random method and other means. Therefore, in the future, more large sample, multi-center and RCTs with appropriate and rigorous acupoint stimulation control methods are needed to provide reliable evidence-based medicine evidence for further studies.

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