Acupuncture benefits to women with recurrent implantation failure: A propensity score-matched cohort study

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ABSTRACT

Objectives: The current study aims to assess the effectiveness of acupuncture in improving the live birth rate (LBR), ongoing pregnancy rate (OPR), clinical pregnancy rate (CPR), biochemical pregnancy rate (BPR), and pregnancy loss (early abortion rate, late abortion rate, ectopic pregnancy rate) in patients with recurrent implantation failure (RIF).
Design: This retrospective study compares the outcomes of patients with RIF who underwent frozen embryo transfer (FET) with or without acupuncture.
Setting: The medical records of patients diagnosed with RIF and visiting Chengdu Xi'nan Gynecological Hospital between January 2018 and June 2021 were reviewed. The Chengdu Xi'nan Gynecological Hospital Ethics Committee approved this retrospective study (No. 2021–029).
Participants: A total of 923 patients with RIF who underwent FET were included in this study. The patients were divided into two groups: the Acupuncture ($n = 303$) and the Non-acupuncture groups ($n = 620$).
Exposure: The Acupuncture group consisted of 303 RIF patients who received acupuncture therapy in addition to standard hormone replacement therapy (HRT)/delayed hormone replacement therapy (*d*-HRT) for FET. The Non-acupuncture group consisted of 620 RIF patients who received only standard HRT/d-HRT for FET.
Primary and secondary outcome measures: The primary outcome was the LBR. The secondary outcome referred to OPR, CPR, BPR, and pregnancy loss.
Results: The Acupuncture group had significantly higher BPR ($P = 0.08$) and CPR ($P = 0.049$) than the Non-acupuncture group. A potentially higher LBR ($P = 0.16$) and OPR ($P = 0.248$) were observed in the Acupuncture group than in the Non-acupuncture group. However, the survival analysis did not show that acupuncture significantly promoted live birth.
Conclusions: Acupuncture is an appropriate adjunctive technique in the *in vitro fertilization* process as it improves biochemical and clinical pregnancies. Therefore, it is necessary to be cautious about the role of acupuncture throughout the whole pregnancy cycle.

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Strengths and limitations of this study

● Acupuncture was a practical, adjunctive technique to improve biochemical and clinical pregnancies.
● Acupuncture may not be effective for all patients, and it needs to be cautious about using acupuncture throughout the whole pregnancy cycle.
● More attention should be paid to treatment-related side effects, and long-term follow-up before further clinical trials of acupuncture for RIF can be conducted.

1. Introduction

Recurrent implantation failure (RIF), although a widely accepted definition is not available, can be interpreted as patients who show no quantifiable signs of implantation undergoing repeated assisted reproductive technologies (ART) [1]. RIF has an estimated prevalence of 15% in *vitro fertilization* (IVF) embryo transfer couples [2] and is one of the most pressing challenges in ART that needs to be addressed [3]. But whether three [4] or four [5] times embryo implantation failures [6], RIF can cause physiological and psychological stress. Giving the embryo implantation process is complex and includes an active interaction between the embryo and the receptive uterus [7], understanding the healthcare burdens of couples facing RIF is necessary. Studies have now demonstrated that implantation failure may result from embryonic or uterine factors to address this situation. Pathophysiological mechanisms of RIF include but are not limited to immunological, infection [1], inadequate culture conditions, and suboptimal embryo [8]. The complex pathogenesis suggests that the treatment of RIF is limited, and no single intervention has been identified that can substantially improve RIF [9]. Acupuncture may be a beneficial solution for this condition.

As a physical therapy, acupuncture was proven to have multiple mechanisms for health regulation. When filiform metal needles were inserted into specific acupoints on the body, nerves, muscles, and connective tissue was stimulated to generate effects. Since the first study on acupuncture for ART was conducted [10], acupuncture has become a widely accepted complementary alternative therapy during infertility. Acupuncture could improve endometrial receptivity by altering neuroendocrinological factors, circulating the blood flow of the uterus, and mediating the immune response [11]. Another review showed that acupuncture therapy improves clinical pregnancy rate (CPR), biochemical pregnancy rate (BPR), embryo implantation rates, and endometrial thickness in patients with RIF [12]. Nevertheless, better quality and adequate sample size research are needed to obtain robust evidence. Propensity score matching (PSM) is a complementary tool to mimic randomized study characteristics partly [13], achieve balance comparability, and control for confounding bias in estimating treatment effects [14]. It provides an appropriate methodology for the development of this study.

Thus, the current study aims to evaluate the effectiveness of acupuncture in improving live birth rate (LBR), ongoing pregnancy rate (OPR), CPR, BPR and pregnancy loss (early abortion rate, late abortion rate, ectopic pregnancy rate) in patients with RIF undergoing frozen embryo transfer (FET).

2. Materials and methods

This retrospective study followed the strengthened reporting of observational studies in epidemiology reporting checklist [15] (Supplementary Table 1).

2.1. Participants

This retrospective cohort study was based on the medical records of patients diagnosed with RIF who visited Chengdu Xi'nan Gynecological Hospital. The FET of RIF patients started between January 5th, 2018 and June 14th, 2021. The first patient completed implantation on December 15th, 2018, and the final patient completed implantation on October 8th, 2021. The Chengdu Xi'nan Gynecological Hospital Ethics Committee approved this retrospective study (No. 2021–029). The RIF patients were divided into two groups according to whether they received acupuncture treatment during IVF cycles. All participants signed informed consent before their data were used in the study. Otherwise, the records would be excluded from this study. Participants who met all inclusion criteria and did not meet the exclusion criteria were included.

The inclusion criteria: (1) aged 22–40 years, female; diagnosed as RIF [16]; (3) having enough frozen embryos; and (4) undergoing hormone replacement therapy (HRT) or down-regulate HRT (d-HRT) for FET.

The exclusion criteria: (1) having an anatomical abnormality of the uterus, including but not limited to the unicornuate uterus, bicornuate uterus or untreated septum uterus; (2) undergoing preimplantation genetic diagnosis (PGD)/preimplantation genetic screening (PGS); (3) oocyte or sperm donation; (4) having untreated endocrine disorders, including but not limited to hyper/hypo-thyroidism, diabetes mellitus, hypertension; (5) having a diagnosed medical or surgical severe primary or secondary disease in progress, and (6) suffering from a diagnosed psychiatric disorder.

2.2. Exposure

This study reported acupuncture as an exposure (Supplementary Table 2) The RIF patients were divided into the Acupuncture and Non-acupuncture groups. The RIF patients in both groups received standard HRT/d-HRT for FET, and only RIF patients in the

Acupuncture group received acupuncture therapy.

2.2.1. Acupuncture therapy

The acupuncture therapy was started from the previous IVF-ET (*in vitro* fertilization-embryo transfer)/FET failure until the day before the implantation day. The therapy was conducted 3–4 times a week for 30 流产的min each session. All acupuncture records were exported by the appointment system. The filiform metal needle was used, and acupoints were punctured 1.5 *cun*, and *deqi* is required during acupuncture. Each acupuncturist has been trained and has more than eight years of clinical experience. Two acupuncture prescriptions (Prescriptions 1 and 2) were used each time alternatively, which is proven to be safe according to previous studies. The acupoints prescriptions were shown as follows.

● Prescriptions 1: *Shenting* (DU24), bilateral *Benshen* (BG13), *Zhongwan* (RN12), bilateral *Tianshu* (ST25), *Guanyuan* (RN4), bilateral *Daimai* (GB26), bilateral *Zigong* (EX-CA1), bilateral *Zusanli* (ST36), bilateral *Sanyinjiao* (SP6), and bilateral *Taichong* (LR3).
● Prescriptions 2: bilateral *Shenshu* (BL23), bilateral *Ciliao* (BL32), bilateral *Taixi* (KI3).

2.2.2. Standard HRT/d-HRT protocols

The HRT/d-HRT protocols were administered as in previous studies [17,18]. Patients with RIF who received the *d*-HRT protocol for endometrial preparation received pretreatment with intramuscular long-acting gonadotropin-releasing hormone agonist (GnRH-a) (2.0–3.75 mg, Triptorelin, Ferring GmbH, France) from 2 to 3 days of menstruation. Hypopituitarism ($E_2 < 180$ pmol/L, LH < 5 U/L, P < 5.0 nmol/L, endometrial thickness<5 mm) would be confirmed in this RIF patient based on an ultrasound scan and blood tests performed after 28 days.

All RIF patients undergoing HRT or *d*-HRT had to be examined by transvaginal ultrasound and blood tests to determine their ovarian status and baseline hormone on the 2–3 days of menstruation. And then, they received oral estradiol valerate (3 mg bid, Progynova, DELPHARM Lille S.A.S., France) for endometrial preparations. The dosage of estradiol valerate would be increased when the thickness of the endometrium was below 8 mm appropriately when the thickness of the endothelium was more than 8 mm, intramuscular injection of progesterone (60 mg/d; Zhejiang Xianju, Chinad received oral dydrogesterone (10 mg bid, Abbott Biologicals B·V., Netherlands). After the endometrial transformation, embryo transfer was performed in 2–3 days or five days later.

2.3. Clinical outcomes

Clinical information was obtained from the clinical database of Xi'nan Gynecological Hospital, including pregnancy follow-up information. In case of inconsistencies or incomplete data, patients were contacted for additions. In this study, the primary outcome was the LBR. The secondary outcome referred to OPR, CPR, BPR, and pregnancy loss. Clinical pregnancy and ectopic pregnancy were diagnosed by transvaginal ultrasound four weeks after the patient underwent embryo transfer; ongoing pregnancy rate was diagnosed 12 weeks after embryo transfer, and live birth was diagnosed 40 weeks after embryo transfer. Early abortion was diagnosed at 12 weeks, and late abortion within 12–28 weeks after embryo transfer.

2.4. PSM procedure

PSM [19,20] was used to enable balance and comparability of potential risk factors between the Acupuncture and Non-acupuncture groups. In brief, Individuals in the Acupuncture and Non-acupuncture groups are screened based on a conditional probability of scoring, the size of which represents the probability of being selected into a particular group. The control unit that has not yet been matched but is closest in distance measurement to the processed unit is selected during each step. The ratio of the Acupuncture group to the Non-acupuncture group was 1:1. The following covariate factors were included in this study: 1) Baseline characteristics: name, age, body mass index (BMI), previous implantation cycle, previous IVF-ET/FET cycle, FET therapy. 2) infertility years, type of infertility.

2.5. Statistics

Continuous variables were presented as Mean $\pm$ Standard difference or meridian (first quartile, third quartile); categorized variables were presented as N (%). For inter-group comparison, the independent two-sample *t*-test or Mann–Whitney *U* test was applied to continuous variables; the Chi-square test or Fisher's exact test was used to categorize variables. All statistical analyses were performed as two-sided tests ($P < 0.05$). Log-rank test and Kaplan-Meier method were applied to compare time to live birth between groups. Cox regression models were used for stratified separate risk sets (baseline), and intergroup HR (hazard ratio) was calculated. Inter-group AHR (adjusted hazard ratio) values were obtained using embryo transfer numbers as covariates. R software version 4.1.3 (https://www.r-project.org/) was applied to complete PSM ("MatchIt" Package), statistical analysis, and survival analysis ("survival" and "survminer" Packages).

3. Results

3.1. Clinical characteristics

Altogether 19,087 cycles of RIF patients undergoing FET were extracted from the databases. Then, 303 RIF patients in the Acupuncture group met the inclusion criteria, and 620 RIF patients in the Non-acupuncture group were ready for PSM. Following PSM in a 1:1 ratio, 300 RIF patients treated with acupuncture treatment matched 300 RIF patients treated without treatment during FET. The flow chart of patients' screening is shown in Fig. 1. No significant differences were obtained in the baseline characteristics of the two groups ($P > 0.05$). The included RIF patients' average age was 32.65 years, with 5.77 average infertility years. In this study, 445 (74.2%) RIF patients had two embryo transfers failed; 113 (18.8%) RIF patients had three embryo transfers failed; and 42 (7.0%) RIF patients had four embryo transfers failed. The average BMI of the included RIF patients was 22.0 kg/m^2, and the average AMH was 4.18 ng/ml. See Table 1 for more details.

3.2. Clinical outcomes

There was no significant difference in the follow-up duration between the Acupuncture and Non-acupuncture groups ($P = 0.175$). The BPR ($P = 0.08$) and CPR ($P = 0.049$) of the Acupuncture group were significantly higher than those in the Non-acupuncture group. A potentially higher LBR ($P = 0.16$) and OPR ($P = 0.248$) were observed in the Acupuncture group than in the Non-acupuncture group.
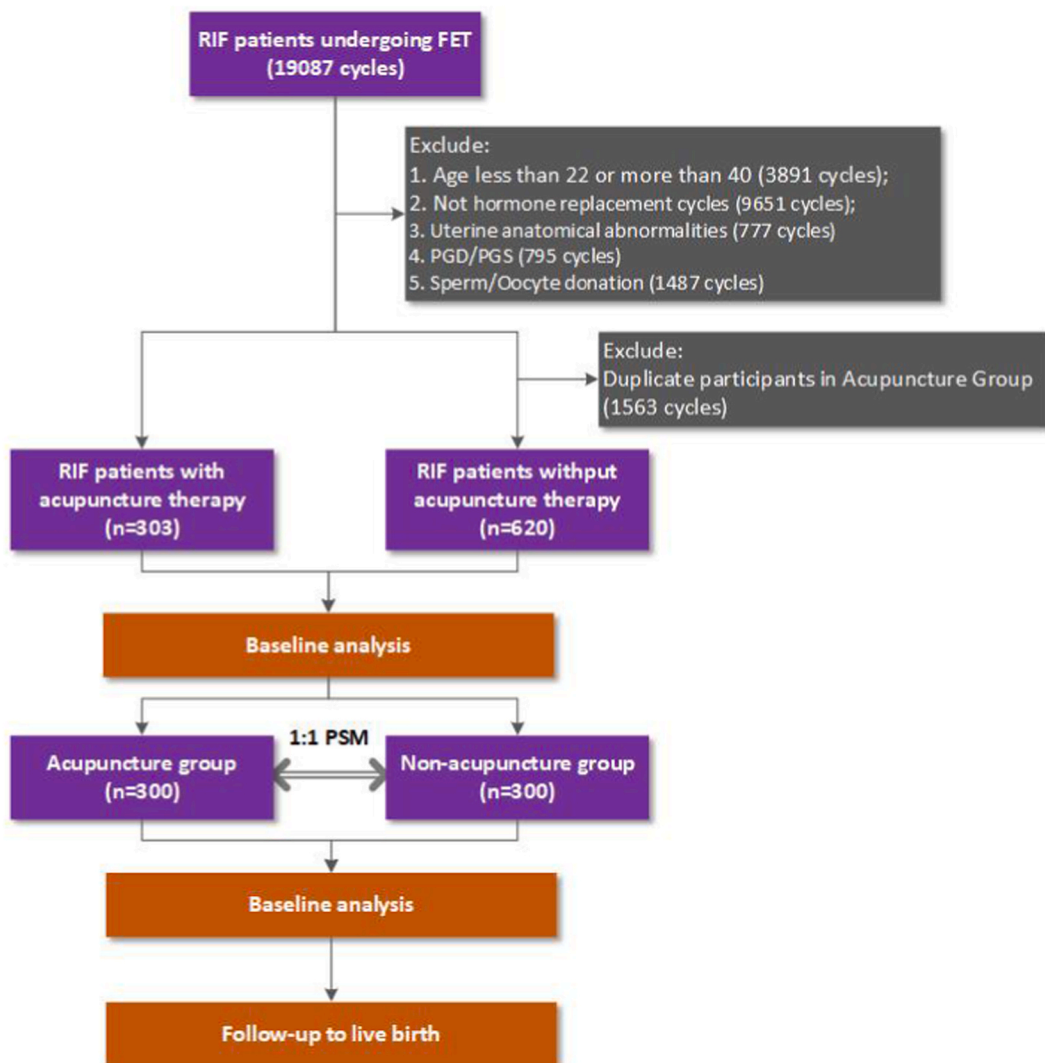

Fig. 1. Study flowchart. Abbreviations: RIF, recurrent implantation failure; FET, frozen embryo transfer; PGD, preimplantation genetic diagnosis; PGS, preimplantation genetic screening.

Table 1

Characteristics of RIF patients in the Acupuncture and the Non-acupuncture groups.

	Before PSM			After PSM		
	Overall (N = 923)	Acupuncture group (N = 303)	Non-Acupuncture Group (N = 620)	Overall (N = 600)	Acupuncture Group (N = 300)	Non-Acupuncture Group (N = 300)
Age (years, %)						
< 30	194 (21.0)	60 (19.8)	134 (21.6)	123 (20.5)	59 (19.7)	64 (21.3)
30-35	445 (48.2)	161 (53.1)	284 (45.8)	308 (51.3)	159 (53.0)	149 (49.7)
≥35	284 (30.8)	82 (27.1)	202 (32.6)	169 (28.2)	82 (27.3)	87 (29.0)
Mean ± Standard difference	32.62 ± 3.98	32.48 ± 3.85	32.68 ± 4.04	32.65 ± 3.94	32.51 ± 3.85	32.79 ± 4.03
BMI (kg/m2, %)						
< 18.5	105 (11.38)	37 (12.21)	68 (10.97)	67 (11.32)	37 (12.5)	30 (10.14)
18.5–25	682 (73.89)	212 (69.97)	470 (75.81)	426 (71.96)	205 (69.26)	221 (74.66)
≥25	136 (14.73)	54 (17.82)	82 (13.23)	99 (16.72)	54 (18.24)	45 (15.2)
Mean ± Standard difference	21.85 ± 3.08	21.95 ± 3.15	21.8 ± 3.05	22.0 ± 3.18	22.03 ± 3.18	21.97 ± 3.18
AMH (ng/ml,%)						
< 2	260 (28.2)	91 (30.0)	169 (27.3)	167 (27.8)	90 (30.0)	77 (25.7)
2–6.8	508 (55.0)	159 (52.5)	349 (56.3)	330 (55.0)	158 (52.7)	172 (57.3)
≥6.8	155 (16.8)	53 (17.5)	102 (16.5)	103 (17.2)	52 (17.3)	51 (17.0)
Mean ± Standard difference	4.14 ± 3.47	4.16 ± 3.70	4.13 ± 3.36	4.18 ± 3.71	4.18 ± 3.87	4.18 ± 3.55
Infertility year (years, %)						
< 3	143 (15.5)	43 (14.2)	100 (16.1)	85 (14.2)	43 (14.3)	42 (14.0)
3-7	500 (54.2)	165 (54.5)	335 (54.0)	337 (56.2)	164 (54.7)	173 (57.7)
≥7	280 (30.3)	95 (31.4)	185 (29.8)	178 (29.7)	93 (31.0)	85 (28.3)
Mean ± Standard difference	5.56 ± 3.31	5.63 ± 3.20	5.53 ± 3.36	5.77 ± 3.48	5.63 ± 3.21	5.92 ± 3.72
Endometrial thickness (cm,%)						
< 0.8	160 (17.3)	58 (19.1)	102 (16.5)	107 (17.8)	58 (19.3)	49 (16.3)
0.8–1	349 (37.8)	124 (40.9)	225 (36.3)	236 (39.3)	122 (40.7)	114 (38.0)
≥1	414 (44.9)	121 (39.9)	293 (47.3)	257 (42.8)	120 (40.0)	137 (45.7)
Mean ± Standard difference	0.94 ± 0.21	0.92 ± 0.22	0.94 ± 0.21	0.93 ± 0.21	0.93 ± 0.22	0.93 ± 0.21
Previous failed cycles (%)						
Two cycles	669 (72.5)	227 (74.9)	442 (71.3)	445 (74.2)	224 (74.7)	221 (73.7)
Three cycles	184 (19.9)	54 (17.8)	130 (21.0)	113 (18.8)	54 (18.0)	59 (19.7)
Four cycles	70 (7.6)	22 (7.3)	48 (7.7)	42 (7.0)	22 (7.3)	20 (6.7)
FET therapy (%)						
d-HRT	220 (23.8)	68 (22.4)	152 (24.5)	136 (22.7)	68 (22.7)	68 (22.7)
HRT	703 (76.2)	235 (77.6)	468 (75.5)	464 (77.3)	232 (77.3)	232 (77.3)
Type of Infertility (%)						
Primary infertility	444 (48.1)	150 (49.5)	294 (47.4)	318 (53.0)	147 (49.0)	171 (57.0)
Secondary infertility	479 (51.9)	153 (50.5)	326 (52.6)	282 (47.0)	153 (51.0)	129 (43.0)
ET embryo number (%)						
Transfer one embryo	340 (36.8)	113 (37.3)	227 (26.4)	231 (38.5)	112 (37.3)	119 (39.7)
Transfer two embryos	583 (63.2)	190 (62.7)	393 (63.4)	369 (61.5)	188 (62.7)	181 (60.3)
Follow-up (days, median [IQR])	36.00 [7.00, 251.00]	42.00 [7.00, 253.00]	35.00 [7.00, 249.00]	35.00 [7.00, 251.00]	42.00 [7.00, 253.00]	30.00 [7.00, 247.75]

Note: Continuous variables are presented by median[IQR]; categorical variables are given by n(%). There were no significant differences among baseline characteristics between the Acupuncture group and the Non-acupuncture group before ($P > 0.05$) or after PSM ($P > 0.05$). **Abbreviations:** PSM, propensity score matching; RIF, recurrent implantation failure; BMI, body mass index; AMH, Anti-Mullerian hormone; HRT, hormone replacement therapy; d-HRT, down-regulate hormone replacement therapy.

And there was no significant difference in pregnancy loss between the two groups ($P > 0.05$). See Table 2.

3.3. Time-to-event analysis

During the follow-up period, the median survival time was 254 (252, 256) days in the Acupuncture group and 251 (248, 254) days in the Non-acupuncture group. The Multifactorial Cox regression model and the log-rank test showed that acupuncture was not significantly associated with live birth outcome ($P = 0.67$, 95%CI HR = 0.947 [0.739, 1.21], 95%CI AHR = 0.969 [0.599, 1.24]) See Fig. 2.

4. Discussion

This study investigated the effects of acupuncture on patients with RIF undergoing FET. By analyzing data from 300 patients with

Table 2

Clinical outcomes between the Acupuncture and the Non-acupuncture groups after PSM.

	Overall (N = 600)	Acupuncture group (N = 300)	Non-acupuncture group (N = 300)	P
Pregnancy status				
Biochemical pregnancy rate (%)	409 (68.2)	215 (71.7)	194 (64.7)	**0.08**
Clinical pregnancy rate (%)	329 (54.8)	177 (59.0)	152 (50.7)	**0.049**
Ongoing pregnancy rate (%)	261 (43.5)	139 (46.3)	122 (40.7)	0.188
Live birth rate (%)	254 (42.3)	136 (45.3)	118 (39.3)	0.16
Pregnancy loss				
Ectopic pregnancy rate (%)	4 (0.7)	1 (0.3)	3 (1.0)	0.616
Early abortion rate (%)	42 (7.0)	20 (6.7)	22 (7.3)	0.873
Late abortion rate (%)	23 (4.1)	12 (4.3)	11 (4.0)	0.999

Note: Categorical variables are presented by n(%)—abbreviations**:** PSM, propensity score matching.
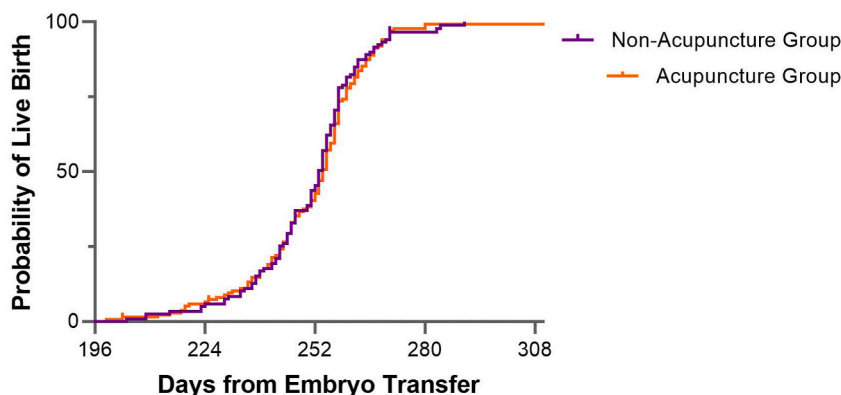

Fig. 2. The incidence of LBR between the Acupuncture group and the Non-acupuncture group. As shown in the figure, there was no significant difference between the Acupuncture and Non-acupuncture groups (log-rank test, P = 0.67).

RIF, this retrospective cohort study found significantly higher BPR and CPR in the Acupuncture group of patients with RIF than in the Non-acupuncture group, even though acupuncture did not improve the LBR or pregnancy loss in patients with RIF.

Endometrial injury, anticoagulants, and immune therapy are difficult to carry out as regular treatments for RIF [20]. The evidence's strength and quality do not support clinical use, and the side effects are doubtful. However, it is difficult to ignore the side effects, pregnancy-related and perinatal side effects, and emergencies such as ovarian hyperstimulation syndrome, ectopic and ectopic pregnancies, and ovarian torsion that arise during ART [21]. Ovarian stimulation by cancer needs to be considered separately due to the complications and the treatment of ovarian function, which requires the development of new and immediate stimulation protocols. As there is usually no time to postpone chemotherapy, in steroid-dependent cancers such as breast cancer, different methods and compounds need to be used [22]. But acupuncture applications in IVF research give insight into RIF, and non-specific effects can be applied to multiple aspects of IVF, such as analgesia undergoing transvaginal oocyte retrieval [23] and stress relief [24]. Also, as a comprehensive improvement, the side effects of acupuncture are rare. In several systematic reviews of acupuncture as a complementary therapy for IVF, the side effects that rarely occur with acupuncture are a benefit that should be considered in clinical practice. Zheng et al. [25] indicated that acupuncture improves CPR and LBR among women undergoing IVF. Still, more positive effects from using acupuncture in IVF can be expected if appropriate acupuncture sessions are used. Qu et al. [26] and Manheimer et al. [27] concluded no significant differences between the acupuncture and control groups regarding biochemical pregnancy, ongoing pregnancy, implantation rate, live birth, or miscarriage outcomes. However, a benefit in trials with lower baseline pregnancy rates has been confirmed. This suggests that various factors may influence acupuncture treatment, including IVF pathology and the dosage of acupuncture [11].

The results suggest that acupuncture treatment may have a positive impact on the success of infertility treatment, particularly in terms of BPR and CPR. Moreover, the study did not observe significant differences in miscarriage rates between the acupuncture and non-acupuncture groups. Although acupuncture showed some positive trends in improving the outcomes of LBR and OPR, the results are unclear. The results cannot yet be adequately interpreted because this study has not yet provided information on regular follow-up for the period from 12 weeks after embryo transfer until live birth. The persistent effect of acupuncture may also be another factor. Studies have shown that acupuncture treatment is continuous; however, its effects are generally maintained for about 12 weeks.

The mechanism of acupuncture on RIF has not been revealed, but it can be divided into two fields. The local effect refers to the modulation of acupuncture on the morphology of the endometrium, ovarian blood flow and endometrial microcirculation. Ho et al. found that electroacupuncture significantly reduced the pulsatility index of the right and left uterine arteries [28]. The lower the blood flow index, the lower the vascular resistance and the richer the blood supply to the follicles. The arterial blood flow index on the

ovulatory side of the ovary reaches its lowest value currently. It indicates that the pulsatility index effectively predicts pregnancy outcomes in IVF. Chen et al. [29] found that acupuncture can affect progesterone levels, increase the euglycemia rate, and improve the endometrium's blood flow and endometrial morphology. The changes to endometrial-subendometrial blood flow distribution directly or potentially affect the implantation and pregnancy rate of IVF [30]. The local effect is that acupuncture causes the release of calcitonin gene-related peptide or substance P from the sympathetic efferent branch of the corresponding spinal cord segment in IVF patients and acts on the peripheral nerve endings to produce retrograde nerve impulses, thus reducing sympathetic excitability [31]. The effect of the peptide on the peripheral nerve endings has retrograde nerve impulses, thus decreasing sympathetic excitability.

Another systemic effect is that acupuncture releases endogenous opioids, modulates immune function and relaxes stress [32]. Fu et al. found that acupuncture can improve certain aspects of endometrial receptivity in rat models during the implantation period [33]. And Shuai et al. evaluated the effect of transcutaneous electrical acupuncture point stimulation (TEAS) on endometrial protein expression in women undergoing FET. The results indicated that TEAS might benefit endometrial expression and ultrasound markers of endometrial receptivity [34]. Acupuncture, electroacupuncture and TEAS are all "peripheral nervous system modulation" methods. Acupuncture points activate the nerve endings, generating action potentials, and the resulting stimulation signals travel along the nerve trunks to the central nervous system (spinal cord and brain), where they stimulate the production of specific chemicals in the brain that has some therapeutic effect on the condition [35]. In addition, anxiety in Chinese infertility patients is about 32%, and depression is about 23% [36]. Emotional abnormalities can cause excessive hyperactivity of the hypothalamic-pituitary-adrenal axis, stimulating the body to produce too much prolactin, adrenocorticotropic hormone and androgen, which inhibits pituitary gonado-tropin secretion and reduces ovarian sex hormone secretion, ultimately affecting the outcome of IVF. Acupuncture can make the sympathetic nervous system of IVF-ET patients less excitable, and feel relaxed, which can significantly relieve patients' anxiety and depression and other adverse emotions [37], reduce the stress of ART patients, and thus improve pregnancy outcomes.

In the study design, we removed potential sources of bias and confounding in the sample selection process through PSM. Also, we excluded subjects with an anatomical abnormality of the uterus and untreated endocrine disorders, as these significantly impact RIF. In PSM, we matched essential factors such as BMI, previous failed implantation cycle, last IVF-ET/FET cycle, FET therapy, and infertility years. The population was selected according to strict inclusion criteria to minimize the risk of misleading conclusions due to the high incidence of false-positive diagnoses and the resulting inappropriate treatment.

5. Conclusions and limitations

We found acupuncture a good adjunctive technique in the IVF process, as acupuncture improved biochemical and clinical preg-nancies. The survival analysis did not show that acupuncture significantly promoted live birth, and it needs to be cautious about the role of acupuncture throughout the whole pregnancy cycle. Several limitations need to be considered in interpreting the results. Although there were insufficient participants and not all confounding factors could be excluded, we focused on as many comparable patients as possible to rule out possible known causes of RIF and explore the effects of acupuncture. Further, we did not record the reasons of dropout for long-term process to live birth. More attention must be paid to treatment-related side effects, and long-term follow-up before further clinical trials of acupuncture for RIF can be conducted.

Patient and public involvement

The Chengdu Xi'nan Gynecological Hospital Ethics Committee approved this retrospective study (No. 2021–029). All participants were required to sign an informed consent for using their data for scientific purposes and agree to be contacted after the follow-up procedure.

Author contribution statement

Di Gan: Conceived and designed the experiments; Performed the experiments; Wrote the paper.
Liying Liu: Conceived and designed the experiments; Wrote the paper.
Ying Zhong; Siyi Yu; Fanrong Liang; Wenhui Hu: Contributed reagents, materials, analysis tools or data.
Jie Yang: conceived and designed the experiments.
Yongna Wu; Yuanyuan Lai; Wei; Xiaoli Guo; Rui Tian: performed the experiments.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e18193.

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