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Original Article

Effects of intrauterine infusion of platelet-rich plasma on hormone levels and endometrial receptivity in patients with repeated embryo implantation failure

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Abstract: Objective: To analyze the effect of intrauterine infusion on platelet-rich plasma on hormone levels and endometrial receptivity of patients with repeated embryo implantation failure (RIF). Methods: A total of 64 patients with repeated implantation failure and re-fertilization-embryo transfer who were admitted to our hospital from January 2019 to December 2021 were analyzed retrospectively. Among them were 30 patients who did not receive the platelet-rich plasma perfusion therapy. This became the control group (CG). The 34 patients who received the therapy were regarded as the research group (RG). The changes of hormone levels before and after the treatment and endometrial receptivity after the treatment were evaluated. The outcomes of IVF assisted pregnancy, including rates of embryo implantation, clinical pregnancy, and early miscarriage, were compared after the treatment. Risk factors for clinical pregnancy were analyzed by logistic regression. Results: After treatment, the estradiol (E2) level increased and the follicle stimulating hormone (FSH) level decreased ($P<0.05$), but there was no marked difference in luteinizing hormone (LH) before or after the treatment ($P>0.05$). The E2 level in the RG was higher than that in the CG, and FSH in the RG was lower ($P<0.05$). In comparison to CG, the endometrial thickness on the day of human chorionic gonadotropin (hCG) injection and embryo transfer in the RG increased dramatically ($P<0.05$). The uterine artery pulsation index (PI) and uterine artery resistance index (RI) decreased ($P<0.05$). The embryo implantation and clinical pregnancy rates in the RG increased markedly ($P<0.01$), and the early abortion rate decreased significantly ($P<0.05$). The logistic regression analysis identified that age, number of transplant failures, treatment regimens, and FSH were risk factors for clinical pregnancy outcomes in patients. Conclusion: Intrauterine infusion of platelet-rich plasma can improve the hormone levels in RIF patients, increase endometrial thickness, and enhance endometrial blood flow, increasing the pregnancy rate of patients and improving clinical pregnancy.

Keywords: Platelet-rich plasma, intrauterine infusion, repeated embryo implantation failure, endometrial receptivity

Introduction

With the advocacy of the two-child policy, a new round of fertility boom has followed. The number of infertile people in our country has exceeded 40 million, accounting for 12.5%-15% of the total number of married women, and it continues to rise [1]. Since its birth, in vitro fertilization and embryo transfer has undergone rapid development. With the maturity of superovulation program and the substantial improvement of embryo laboratory culture conditions, the clinical pregnancy rate of patients receiving embryo transfer has been greatly improved [2]. Effectively improving the clinical pregnancy rate and reproductive health of the offspring of patients is one of the most important issues and the goal of this technology [3]. Although assisted reproductive technology has made great progress, repeated embryo implantation failure (RIF) is a common problem faced by patients and clinicians [4]. This means that after repeated embryo implantation, the intrauterine pregnancy sac cannot be identified by ultrasound [5]. Scholars believe that in the process of in vitro fertilization and embryo transfer, the incidence of RIF is 7.7% to 11.1%, and the implantation failure is related to

maternal and embryonic factors. Maternal factors include abnormal uterine anatomy, thrombosis, reduced endometrial receptivity, and immune factors [6]. Data show that implantation failure due to decreased endometrial receptivity accounts for 2/3 of the total [7]. Taking effective measures to improve patients' endometrial receptivity has become the key to RIF.

Platelet-rich plasma is a platelet concentrate obtained by centrifugation [8]. Platelets release a large amount of different types of growth factors and proteins after activation. These factors play different roles. Although their roles are different, they can markedly accelerate cell mitosis, promote angiogenesis and endothelial cell chemotaxis, and boost osteoblast and cartilage tissue proliferation [9, 10]. Growth factors released from platelets bind to target cell surface receptors and activate protein signals on the cell membrane surface. They then enter the cell through transporting and again activate second signaling receptors to promote the synthesis of various proteins by various intracellular organelles. Cytokines, which in turn form abundant procollagen, can promote wound healing [11, 12]. Platelet-rich plasma technology is not only simple, but it is beneficial to the wound healing of patients and easy to operate. It has been tried in the field of assisted reproduction. There is a lack of research on platelet-rich plasma on the pregnancy outcomes of RIF patients.

This research retrospectively analyzed whether intrauterine infusion of platelet-rich plasma could improve endometrial receptivity in RIF women, increasing the clinical pregnancy rate after repeated in vitro fertilization-embryo transfer and provide a reference for clinical treatment.

Methods and materials

Clinical data

A total of 64 RIF patients who were admitted to our hospital from January 2019 to December 2021 were analyzed retrospectively. Among them were 30 patients who did not receive the platelet-rich plasma perfusion therapy, the control group (CG). The 34 patients who received the therapy were regarded as the research group (RG). This research was ratified by the Medical Ethics Committee of our hospital (2018-1103). All patients knew about this research and signed an informed consent form.

Inclusion and exclusion criteria

Inclusion criteria: The patients who had 3 or more embryo transfers with at least 4 high-quality embryos (All patients received fresh embryo transfer), but failed to achieve clinical pregnancy, patients with an age of 25 to 40 years old, patients without endometrial mass and the thickness of endometrium was 7-14 mm, and patients with negative blocking antibody in peripheral blood.

Exclusion criteria: Patients with a previous history of estrogen-related tumors; adenomyosis; bilateral hydrosalpinx, or systemic diseases such as abnormal thyroid function and hematological diseases.

Preparation of PRP

On the third day after menstruation, 15 mL of the patient's venous blood was collected to prepare PRP. PRP was prepared as follows: PRP was prepared from autologous blood by a two-step centrifugation method. Then, 8.5 mL of peripheral venous blood was drawn from a syringe, preloaded with 1.5 mL of citrate anticoagulation solution (ACDA) and centrifuged for 10 min. The blood was divided into three layers: red blood cells at the bottom, plasma in the supernatant, and brown ESR in the middle. The plasma layer and brown layer of the ESR were collected into another centrifuge tube and centrifuged again for 15 min to obtain the final PRP (about 1.5 mL), which was approximately 4 to 5 times the concentration of circulating blood.

Treatment schemes

The treatment was divided into two steps, with both groups undergoing conventional treatment with the following protocol: We collected the embryos. When the diameter of dominant follicles reached 18-22 mm, recombinant human chorionic gondotropin (hCG; Saizen, Germany registration number: s20130087) 250 (250 0 50 0 30087) 250 stration number: (s20130087) 250 following protocol: n as the Baiyunshan Mingxing Pharmaceutical Co., Ltd., (h44020562) 60 mg/d was performed for luteal support Three days later, the eggs were col-

lected for embryo transfer. Based on the number and shape score of embryos, the 2-3 embryos with the highest score were selected for transfer.

The drug treatment scheme was as follows: 0.1 mg long-acting gonatropin-releasing agonist (GnRH-a) was internally injected through the mid preluteal phase for 14 days (triptorelin for injection, Germany, registration number: h20140123). After 2 weeks, the endometrial thickness of the uterus was measured by ultrasound. If the endometrial thickness did not reach 7 mm, the dosage of estradiol valerate was increased to 8 mg/d. After the endometrial thickness exceeded 7 mm, endometrial transformation was induced with 400 mg progesterone suppositories (Cyclogest; Actavis, UK) 2 times/d for 3 days. Embryo transfer was performed (at least 1 high-quality embryo), and recombinant human FSH (Gonal-F, Merck, shirano, Italy, registration no. S20110004) 75-150 u/D was administered. The follicle development was monitored by ultrasound, and hormone levels (serum estradiol 2: E2, follicle stimulating hormone: FSH, luteinizing hormone: LH) were measured by immunochemiluminescence.

The observation group was treated with PRP based on the control group treatment as follows: On the day after preparation, PRP was activated for intrauterine perfusion. The patient was instructed to lay in the lithotomy position on examination bed. The cervix was exposed with an endoscope. The vulva and vagina were disinfected. PRP was absorbed with a syringe and connected with the graft tube. The implantation tube was passed through the open cervical and the PRP was slowly pushed into the uterine cavity. After perfusion, the patient was told to remain lying in this position for 30 min.

Serological test

The serum levels of FSH, LH, and E2 were tested by immunochemiluminescence assay (Siemens, CENTARU XP, Germany) before and after treatment (14 days after treatment).

Outcome measures

Main outcome measures: The FSH, LH, and E2 changes were observed before and after the treatment. Uterine artery pulsation index (PI) and uterine artery resistance index (RI) in patients were compared. Embryo implantation rate = the number of intrauterine sac/total number of transferred embryos ×100%. Clinical pregnancy rate = number of patients with clinical pregnancy/total number of patients ×100%.

Secondary outcome measures: The differences in clinical data between the two groups were compared. The independent risk factors affecting clinical pregnancy rate were analyzed by logistics regression, and the predictive curve was drawn.

Statistical analysis

The collected data were statistically analyzed using SPSS20.0, and the pictures were rendered by GraphPad 7. The data were expressed by mean ± standard deviation (Meas ± SD). Independent sample t-test was used for intergroup comparison, and paired t-test was used for intra-group comparison. The counting data were represented as percentage (%) and analyzed through Chi-square test. The independent risk factors of clinical pregnancy were assessed by Logistics regression. The value of independent risk factors in predicting pregnancy outcomes was assessed by ROC curve. $P<0.05$ revealed a significant difference.

Results

Clinical data

We found that there was no marked difference in age, time of infertility, number of transplant failures, and causes of infertility between the two groups (**Table 1**, $P>0.05$).

Changes of FSH, LH, and E2 before and after treatment

After treatment, the E2 level increased and the FSH level decreased in both groups ($P<0.05$), but there was no obvious difference in luteinizing hormone (LH) before and after the treatment ($P>0.05$). After treatment, the E2 level in the RG was higher than that in the CG. FSH was lower (**Table 2**, $P<0.05$).

Comparison of endometrial thickness and uterine artery blood flow parameters after treatment

The changes of endometrial thickness and uterine artery blood flow parameters between

Table 1. Baseline data

Factors	Control group (n=30)	Research group (n=34)	*P*-value
Age			0.215
≥35 year (n=45)	19	26	
<35 year (n=19)	11	8	
Time of infertility			0.950
≥4 year (n=36)	17	19	
<4 year (n=28)	13	15	
Number of transplant failures			0.156
≥5 times (n=20)	12	8	
<5 times (n=44)	18	26	
Causes of infertility			0.779
Fallopian tube factor (n=34)	15	19	
Decrease of ovarian reserve (n=18)	8	10	
Other factors (n=12)	7	5	

both groups after treatment revealed that on the day of embryo transfer, the endometrial thickness in the RG was higher than that in the CG (P<0.05). The PI and RI indexes were lower than those in the CG (**Figure 1**, P<0.05).

Analysis of embryo transfer and pregnancy outcomes of patients

The pregnancy outcomes after treatment were compared between both groups. The successful embryo implantation rate and clinical pregnancy rate in the RG were higher than those in the CG (**Table 3**, P<0.05).

Analysis and predictive value evaluation of risk factors of clinical pregnancy

To assess the risk factors of clinical pregnancy, we divided the patients into two groups according the pregnancy outcome and explored the risk factors by logistic regression (**Table 4**). Univariate analysis revealed that there were obvious differences in age, number of transplant failures, FSH, and E2 before treatment and treatment regimens (**Table 4**, P<0.05). Afterwards, we assigned the difference factors (**Table 5**). Multivariate logistic regression analysis found that age (OR: 0.069, 95% CI: 0.011-0.442, P=0.005), number of transplant failures (OR: 7.478, 95% CI: 1.249-44.759, P=0.028), treatment regimens (OR: 7.513, 95% CI: 1.184-47.664, P=0.032), and FHS (OR: 0.361, 95% CI: 0.203-0.643, P=0.001) were independently tied to clinical pregnancy (**Table 6**). We analyzed the predictive value of various indexes in clinical pregnancy by ROC curve and found that age, transplant failure times, treatment regimens, and FSH were effective in predicting clinical pregnancy. The combined detection of various indexes had the highest value (**Figure 2**) (**Table 7**).

Discussion

Embryo implantation is a gradual process in which the embryo migrates and invades through the epithelium of the uterine cavity, attaching to the surface of the endometrium [13]. RIF is defined as failure to conceive after multiple embryo transfers in the *in vitro* fertilization cycle. There are no specific criteria [14]. According to the European Federation of Human Reproductive and Embryological Associations, RIF is defined as the absence of gestational sac 5 weeks or more after embryo transfer, followed by transfer of 3 high-quality embryos or multiple transfers of 10 or more embryos [15]. The implantation process involves many factors, including embryo quality, endometrial receptivity, and immune role.

Rich platelet blood is part of autologous plasma. Its platelet concentration is higher than the baseline concentration [16]. Platelets store various growth factors and cytokines in their cytoplasmic granules, which undergo exocytosis in the presence of activating factors such as extracellular matrix collagen [17]. Platelet-rich blood is prepared from peripheral blood without the risk of viral infection and immune responses. Platelet-rich blood has been used in gynecological diseases including Asherman syndrome [18], wound healing after cesarean section [19], treatment of thin endometrial lining after embryo transfer hormone therapy, and premature ovarian failure [20]. Tehraninejad et al. found that platelet-rich blood is not an effective adjuvant therapy for patients with RIF and normal endometrial thickness undergoing IVF-embryo implantation [21]. Another research found that platelet-rich plasma can improve

Table 2. Changes of FSH, LH and E2 before and after treatment

Groups	FSH (m IU/m L)		LH (m IU/m L)		E2 (pg/ml)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=30)	8.51±2.18	7.01±1.03*	5.68±2.01	5.90±2.06*	42.46±20.83	138.55±13.37*
Research group (n=34)	8.45±2.04	6.29±0.98*	5.78±2.49	5.08±1.77*	50.29±14.30	152.08±19.53*
T value	0.126	2.854	0.175	0.093	1.770	2.305
P-value	0.901	0.006	0.862	1.708	0.082	0.025

Note: *indicates that compared with that before treatment, P<0.05. Estradiol 2: E2; follicle stimulating hormone: FSH; luteinizing hormone: LH.

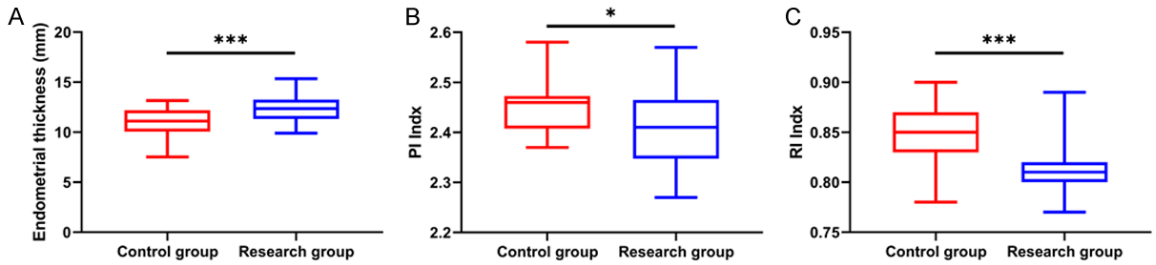

Figure 1. Changes of endometrial thickness and uterine artery blood flow parameters after treatment. A. Comparison of endometrial thickness between both groups on the day of embryo transfer; B. Comparison of PI index between two groups of patients on the day of embryo transfer; C. Comparison of RI index between both groups on the day of embryo transfer; Note: *P<0.05, ***P<0.001. pulsation index: PI; resistance index: RI.

Table 3. Comparison of embryo transfer and pregnancy outcomes

Group	Embryo implantation rate	Clinical pregnancy rate
Control group (n=30)	10.60 (7/66)	20.00 (6/30)
Research group (n=34)	25.00 (18/72)	44.12 (16/34)
x^2 value	4.809	5.173
P-value	0.028	0.023

pregnancy outcomes in RIF patients [22]. The application of platelet-rich blood in RIF patients has been controversial. We retrospectively analyzed the effect of platelet-rich blood on their clinical pregnancy.

The serum FSH and E2 levels exert vital effects in the occurrence and development of premature ovarian failure. The reserved follicles were consumed in large amounts, the secretion of E2 decreased, which weakened its feedback inhibition on the pituitary gland. The secretion of FSH increased and changed in its expression directly reflecting the degree of premature ovarian failure [23]. In this research, the serum FSH level decreased, and the E2 level increased after platelet-rich blood therapy. It suggested that patients' ovarian function improved after treatment. In this research, we found an increase in LH levels after treatment in both groups, but no difference between the groups. We think this was due to the small sample size. We speculated that PRP has little effect on LH, resulting in no difference between the groups. We need to explore its specific mechanism in more detail. We evaluated the endometrial receptivity of patients after treatment. Endometrial receptivity is defined as a temporary and unique sequence of factors for endometrial embryo transfer. It is the time window for the uterine environment to accept embryos and subsequent implantation [24]. Currently, high-resolution transvaginal ultrasonography, three-dimensional ultrasonography, and endometrial tissue blood flow are mainly used in clinical practice. In this research, we analyzed and compared the endometrial thickness and uterine artery blood flow parameters of patients after treatment. It demonstrated that the thickness of endometrium on the day of embryo transfer in the RG was higher than that in the CG, and the PI and RI indexes in the RG was lower. This denotes that the uterine

Table 4. Univariate analysis

Factors	Pregnancy group (n=22)	Non-pregnancy group (n=42)	*P*-value
Age			0.002
≥35 years (n=45)	10	35	
<35 years (n=19)	12	7	
Time of infertility			0.842
≥4 years (n=36)	12	24	
<4 years (n=28)	10	18	
Number of transplant failures			0.019
≥5 times (n=20)	11	9	
<5 times (n=44)	11	33	
Causes of infertility			0.838
Fallopian tube factor (n=34)	11	23	
Decreased ovarian reserve (n=18)	6	12	
Other factors (n=12)	5	7	
Treatment regimens			0.023
Platelet-rich plasma treatment group (n=34)	16	19	
Non-platelet-rich plasma treatment group (n=30)	6	24	
FSH (m IU/m L)	7.07±1.67	9.22±1.92	<0.001
LH (m IU/m L)	5.70±2.14	5.805±2.52	0.172
E2 (pg/ml)	57.31±13.62	41.23±17.47	0.001

Note: estradiol 2: E2; follicle stimulating hormone: FSH; luteinizing hormone: LH.

Table 5. Assignment table

Factors	Assignment
Age	≥35 year =1, <35 year =0.
Number of transplant failures	≥5 times =1, <5 times =0.
Treatment regimens	Platelet-rich plasma treatment group =1, non-platelet-rich plasma treatment group =0.
FSH (m IU/m L)	The original data are used as continuous variables.
E2 (pg/ml)	The original data are used as continuous variables.
Clinical pregnancy	Pregnancy =1, non-pregnancy =0.

Note: estradiol 2: E2; follicle stimulating hormone: FSH.

Table 6. Multivariate logistics regression analysis

Factors	B value	S.E	Wals	*P*-value	Exp (B)	95% CI of EXP (B)	
						Lower limit	Upper limit
Age	-2.674	0.949	7.950	0.005	0.069	0.011	0.442
Number of transplant failures	2.012	0.913	4.856	0.028	7.478	1.249	44.759
Treatment regimens	2.017	0.943	4.577	0.032	7.513	1.184	47.664
FSH	-1.019	0.294	11.985	0.001	0.361	0.203	0.643
E2	0.086	0.178	0.234	0.628	1.090	0.769	1.543

Note: estradiol 2: E2; follicle stimulating hormone: FSH.

perfusion of platelet-rich plasma can increase the thickness of endometrium, enhance the endometrial blood flow, and improve the endometrial receptivity. This is mainly because platelet-rich plasma is rich in a large amount of growth factors. When a large amount of growth factors are released, the increase of E2 in patients promotes the proliferation of endome-

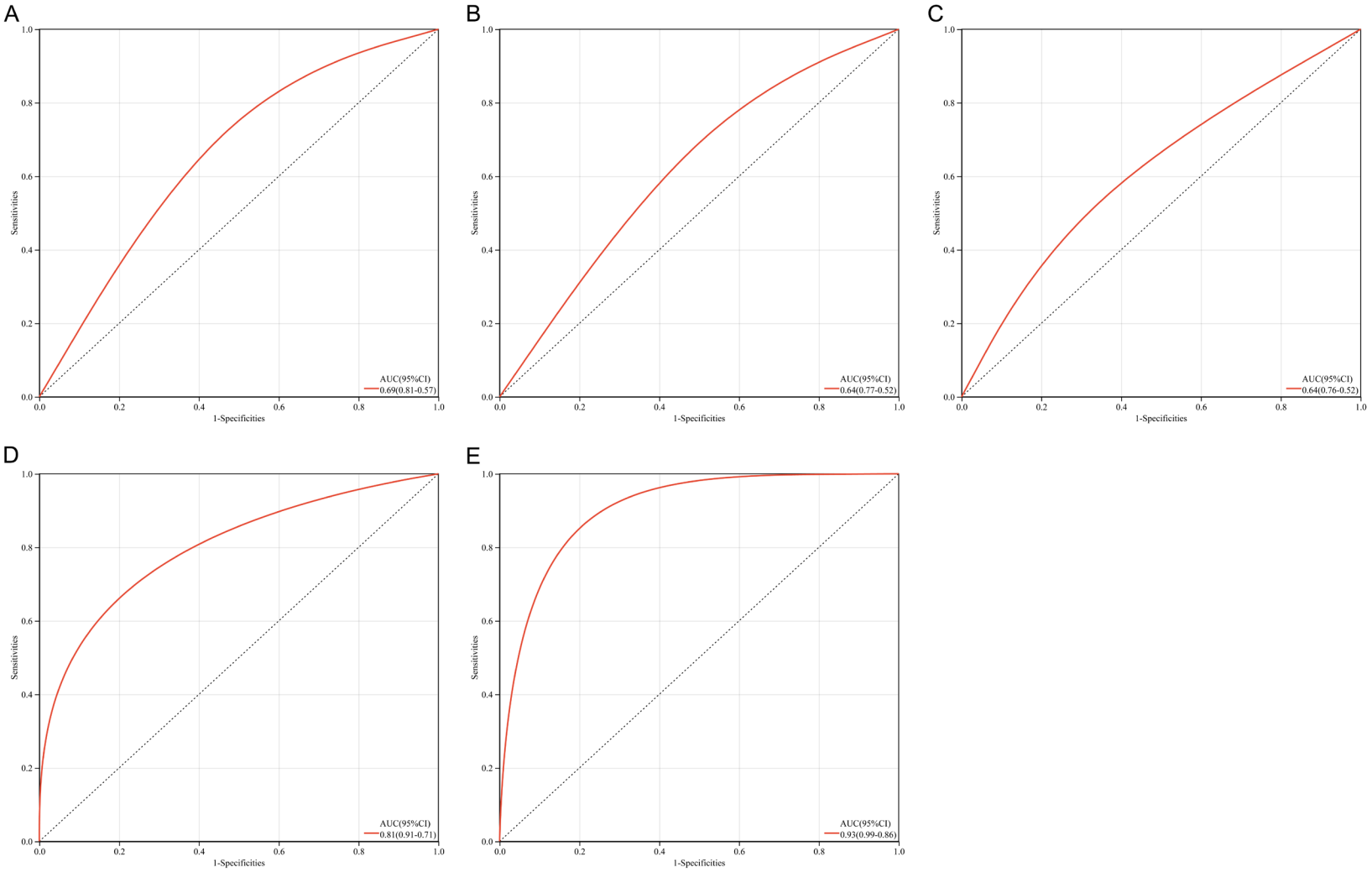

Figure 2. Age, number of transplant failures, treatment regimens, and FSH combined to predict the ROC curve of clinical pregnancy. A. ROC curve of age in predicting clinical pregnancy of patients; B. ROC curve of clinical pregnancy predicted by the number of transplant failures; C. ROC curve of treatment regimens in predicting the clinical pregnancy of patients; D. ROC curve of FSH in predicting the clinical pregnancy of patients; E. ROC curve of combined indexes in predicting the clinical pregnancy in patients. Note: follicle stimulating hormone: FSH.

Table 7. ROC curve parameters

Factors	AUC	95% CI	Specificity	Sensitivity	Youden index
Age	0.689	0.569-0.810	0.545	0.833	0.379
Number of transplant failures	0.643	0.519-0.767	0.500	0.786	0.286
Treatment regimens	0.637	0.515-0.759	0.727	0.548	0.275
FSH	0.812	0.710-0.914	0.955	0.619	0.574
Combination	0.925	0.859-0.992	0.818	0.952	0.771

Note: follicle stimulating hormone: FSH.

trial functional layer, improving the endometrial receptivity of patients [25]. A previous study [24] found that autologous platelet-rich plasma transfusion improved clinical pregnancy rates in women with embryo transfer cycles, which is similar to our findings. This could indicate that platelet-rich plasma has a promising effect in improving clinical pregnancy rates in women. Relative to their study, we assessed the risk factors affecting patients' pregnancy.

In the end, we counted the pregnancy outcomes of patients. After treatment, the embryo implantation and clinical pregnancy rates in the RG were higher than those in the CG, indicating that platelet-rich plasma perfusion therapy can improve the clinical pregnancy outcomes. We also analyzed the risk factors of pregnancy outcomes by logistic regression, among which age, number of transplant failures, treatment regimens, and FHS were independently tied to clinical pregnancy. Due to the increase of patient age and implantation times, the hormone and uterine receptivity reduced, which led to a decrease in the probability of clinical pregnancy. We found that the probability ratio of clinical pregnancy treated with platelet-rich plasma was higher than patients not receiving platelet-rich plasma. It showed that platelet-rich plasma therapy can improve the clinical pregnancy outcomes. ROC curve discovered that the combined detection of risk factors could be used as an observation index to predict clinical pregnancy.

This retrospective analysis found that intrauterine infusion of platelet-rich plasma can improve hormone levels and endometrial receptivity in RIF patients. There are some limitations. Due to time constraints, we only collected data from 2019-2021, and the study population was limited. Patients were not followed up for a long time, and it's vague whether perfusion therapy influences pregnancy outcomes. We hope to conduct randomized controlled trials in future studies and follow up patients to enrich our conclusions.

To sum up, intrauterine infusion of platelet-rich plasma can improve hormone levels, increase endometrial thickness, and improve endometrial blood flow in RIF patients, improving the pregnancy rate and clinical pregnancy.

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Disclosure of conflict of interest

None.

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