

# Evaluation of the effect of intrauterine injection of platelet-rich plasma on the pregnancy rate of patients with a history of implantation failure in the *in vitro* fertilization cycle

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## ABSTRACT

**Objectives:** Implantation failure is a major problem in reproductive medicine, and despite the various methods described for treatment, there is little consensus on the most effective method. This study was conducted to investigate the effect of intrauterine injection of platelet-rich plasma (PRP) on the pregnancy rate of patients with a history of implantation failure in the *in vitro* fertilization (IVF) cycle. **Study Design:** In this study, women attending the infertility clinic of Ali ibn Abi Taleb Hospital, who had a history of implantation failure and were candidates for frozen embryo transfer (FET), were examined in Zahedan (Iran) in 2019. The patients were divided into two groups of PRP recipients and the control group. IVF was performed routinely, and in the PRP-receiving group, an intrauterine injection was given 48 h before embryo transfer (ET). The number of gestational sacs, the rate of implantation, the frequency of chemical and clinical pregnancies as well as the frequency of abortion were compared in the two groups. The collected data were analyzed by the SPSS software version 21. **Results:** Ninety patients with a history of implantation failure participated in the study, and finally, the information of 85 patients was studied. The frequency of chemical pregnancy was 40% in the experimental group, 27% in the control group, and regarding clinical pregnancy, 33% in the experimental group and 24% in the control group, but there was no significant difference between the two groups. The rate of implantation, the mean thickness of the endometrium, and the frequency of abortion did not differ significantly between the two groups. **Conclusion:** In patients with endometrial thickness greater than 8 mm with a history of recurrent implantation failure, intrauterine injection of PRP had no effect on the fertility outcome.

**Keywords:** Implantation, *in vitro* fertilization, infertility, platelet-rich plasma

## Introduction

Successful implantation is a phenomenon that requires a healthy fetus, a healthy receptive endometrium as well as a proper maternal immune response.<sup>[1]</sup> Recurrent implantation failure is one of the main controversial topics in infertility treatment and is defined as the failure of pregnancy after at least three cycles

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of fresh or frozen embryo transfer (FET) in a woman under the age of 40.<sup>[2]</sup> Repeated causes of implantation failure include low fetal quality, uterine anomalies, immunological factors, and inaccurate coordination of the developing fetus with the endometrium also plays an important role in this field.<sup>[3-5]</sup> Despite many advances in assisted reproductive techniques, the rate of implantation has not yet increased significantly after ET. It is estimated that 85% of the embryos by assisted reproductive techniques do not implant after transfer.<sup>[6-8]</sup> Studies have shown that different methods have been used to manage recurrent implantation failures, but there is little consensus on the most effective ones. The common methods used include blastocyst transmission, pre-transplant genetic screening, hatching, co-culture system, sequential transmission, hysteroscopy, endometrial scratch, salpingectomy, additional ET, egg donation, and immunotherapy, but there is no proven evidence for these treatments.<sup>[9-13]</sup> Recently, intrauterine injection of PRP has been described to increase endometrial growth and acceptance. PRP is made from a person's blood and has a platelet concentration of four to five times more than the normal, and contains several growth factors and cytokines, such as platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF- $\beta$ ), vascular endothelial growth factor (VEGF), insulin-like growth factors I, II (IGFs-I, II), and interleukin 8 (IL-8).<sup>[14,15]</sup> PRP is almost safe, non-invasive, and easy to use as a treatment for several medical disorders, including neurological damage, ocular epithelial defect, alopecia and skin therapies, myocardial infarction, osteoarthritis, and tendonitis. However, despite the widespread use of PRP in several medical fields, its effectiveness in obstetrics and gynecology (OB/GYN) is limited.<sup>[16-19]</sup>

For the first time, Chang reported the effect of intrauterine PRP injection for endometrial growth in women with thin endometrium. In this trial, PRP was injected into five women with endometrial dysfunction who had a poor therapeutic response in the FET cycle. A proper response to the treatment was reported in all of them, and eventually, four women experienced a normal pregnancy.<sup>[16,20]</sup> Some limited studies have shown that PRP can increase the endometrial thickness, especially in patients with resistant endometrium, and also, increase the endometrial uptake, and thus, increase the rate of implantation.<sup>[21]</sup> Therefore, due to the limited cases mentioned above, this study was conducted to investigate the effect of intrauterine injection of PRP on the pregnancy rate of patients with a history of implantation failure in the IVF cycle.

## Methods

This study was a clinical trial conducted in 2019 in the Ali ibn Abi Taleb Hospital in Zahedan in which 90 infertile women attending the infertility clinic of this hospital entered the study, and finally, 85 of them were studied. This study was approved by the Ethics Committee of Zahedan University of Medical Sciences with the code IR.ZAUMS.REC.1397.486 and registered at the Iranian Center for Clinical Trials Registration IRCT20180425039418N9. Also, it has been performed in accordance with the ethical

standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

The criteria for entering the study included age under 40 years and a history of two to three IVF failures, and the exclusion criteria included any uterine anomalies in the performed analyses, having an underlying disease, taking any specific medication, not having proper fetus for transfer on the day of ET, insufficient endometrial thickness for ET, and reluctance toward participation in the study. The patients were randomly divided into two groups of 45. Sampling was performed by the blocked randomization method. Thus, according to the sample size, which was 90 people (45 people in the experimental group and 45 people in the control group), 9 blocks (each of 10 people) were identified. In each block, an equal number of cards from each group was placed. The card was then selected from the first block and the next patient was selected from the same card block, so by completing each block, 10 patients were assigned equally (5 people per group). Before the start of the study, the patients were given information about the objectives of the study, the measures taken, and the consent form. The patients were then placed in one of the two groups—experimental (intrauterine platelet injection) and control. For both groups, estradiol valerate 6 mg/d was started on the second or third day of the menstrual cycle and continued until the endometrial thickness was greater than or equal to 8 mm. During the course, when the endometrial thickness exceeded 8 mm, the vaginal progesterone suppository (Abureihan pharmaceutical co. Fretigest 400 mg) was started at a dose of 400 mg twice daily. Three days after the start of progesterone, good-quality eight cell embryos (grade A or B based on the embryological score) were transferred to all the participants.

PRP intrauterine infusion was performed 48 h before the ET in the experimental group. PRP was prepared using autologous blood as well as in two stages of the centrifugation process. In the experimental group, on the day of the PRP infusion, 8 mL of peripheral intravenous blood was taken from the participants in the syringe containing 2.5 mL of citrate acid (anticoagulant solution) and immediately separated at 1200 rpm for 12 min. The blood cells were centrifuged, then plasma was reabsorbed at 3300 rpm for 7 min to produce PRP containing four or five times more platelets than the intravenous blood. An amount of 0.5 mL of the PRP by the infertility fellowship was injected into the uterine cavity with an intra uterine insemination (IUI) catheter (Takvin, Iran). The ET was performed using ultrasound guidance by an infertility fellowship under the guidance of the American Society of Reproductive Medicine 2013 (two to three eight-celled embryos per participant).

Estradiol valerate and progesterone suppositories were continued for 2 weeks after the ET. If any pregnancy occurred and human chorionic gonadotropin ( $\beta$ -HCG) was positive, the progesterone suppository continued up to 12 weeks of gestation.

Chemical pregnancy and clinical pregnancy were detected using positive serum  $\beta$ -HCG levels 2 weeks after the ET and the

presence of a heart rate on transvaginal ultrasound 5 weeks after the ET, respectively. The information obtained was entered into the SPSS software version 21 and reviewed and analyzed.

## Results

In this study, 90 patients participated in the study and 5 people were excluded from the study due to reasons, such as lack of proper embryo or insufficient endometrial growth, and finally, 85 people were studied. An independent t-test was used to compare the mean age and body mass index (BMI) and endometrial thickness of the patients before the transfer, and the results showed that the mean age and BMI and endometrial thickness in the experimental and control groups were not significantly different [Table 1]. With the independent t-test, the mean number of embryos transferred in the two groups did not differ significantly [Table 2]. The independent t-test also showed that the mean number of gestational sacs seen on ultrasound and the implantation rates in the two groups did not differ significantly [Table 2].

In this study, the frequency of chemical pregnancy was 40% in the experimental group and 27% in the control group, which was not significantly different between the two groups according to the Chi-square test [Table 3]. Also, the frequency of clinical pregnancy was 33% in the experimental group and 24% in the control group, which was not significantly different between the two groups based on the Chi-square test [Table 3]. In this study,

**Table 1: Demographic information of patients in the two study groups**

Parameter	Experimental group	Control group	P
Age	313±43	312±4.8	0.917
Body mass index	26.5±3.2	27.7±30	0.088
Endometrial thickness	9.12±1.29	9.5±1.20	0.139

**Table 2: Comparison of embryo transfer cycle characteristics in the two study groups**

Parameter	Experimental group	Control group	P
Number of embryos	2.5± 0.5	2.53±0.5	0.762
Number of gestational sacs	0.87±0.5	1± 0.24	0.493
Implantation rate	0.36±0.24	0.38± 0.16	0.769

**Table 3: Comparison of chemical pregnancy, clinical pregnancy, and abortion in both experimental and control groups**

Parameter	Group	Status		P
		Positive	Negative	
Chemical pregnancy	Experimental	16 (40%)	24 (60%)	0.192
	Control	12 (27%)	33 (73%)	
Clinical pregnancy	Experimental	13 (33%)	27 (67%)	0.410
	Control	11 (24%)	34 (76%)	
Abortion	Experimental	5 (31.25%)	11 (68.75%)	0.196*
	Control	1 (8.33%)	11 (91.66%)	

\*Fisher's exact test

the frequency of abortion was 31.25% in the experimental group and 8.33% in the control group. According to Fisher's exact test, the difference between the two groups was not statistically significant [Table 3].

## Discussion

Despite the expansion of experience and skills in advanced reproductive technologies and significant improvements in infertility treatment, insufficiency and implantation failure in the IVF cycle is one of the most important challenges.<sup>[22]</sup> There is ample evidence that PRP is a safe treatment and can have many potential effects in a variety of medical fields.<sup>[23]</sup> The aim of this study was to investigate the effect of intrauterine injection of PRP on the pregnancy rate of patients with a history of implantation failure in the IVF cycle.

The results of our study showed that the number of gestational sacs as well as the rate of implantation in the two groups did not differ from each other. Also, it was found that the frequency of chemical pregnancy in the experimental and control groups was 40 and 27%, respectively, and the frequency of clinical pregnancy was 33 and 24% in both, respectively, but no significant relationship was observed between the two variables in the two groups. In a study by Nazari *et al.*<sup>[24]</sup> of 97 patients, intrauterine injection of 0.5 mL of PRP was performed 48 h before the blastocyst transmission. In their study, similar to the present study, in terms of age, body mass index, and previous ET number, there was no significant difference between the two groups of experimental and control. However, the rate of chemical pregnancy in the PRP group was higher than in the control group (53.6%, respectively, compared to 27.08%). Also, the rate of clinical pregnancy in the PRP group was higher than in the control group (44.89%, respectively, compared to 16.6%). Therefore, they concluded that intrauterine PRP may be effective in improving the outcome of pregnancy in recurrent implantation failure. In another study, Hakan Coksuer and colleagues conducted a study in 2019 in Turkey in which the success rate of IVF was studied by 34 patients in the PRP group and 36 patients in the control group. They reported that after 48 h of platelet injection, the mean endometrial thickness increased significantly as compared before the injection (10 mm compared to 6.25 mm). The rate of clinical pregnancy (35% in the PRP group and 22% in the control group) as well as the birth rate of the live infant (41% in the PRP group and 17% in the control group) in the PRP-receiving group was significantly higher than the control group. The results of their study were inconsistent with our study.<sup>[25]</sup> In another study conducted by Fatemeh Aghajanzadeh and her colleagues.<sup>[4]</sup> There was no significant difference in the implantation rate, chemical pregnancy rate, clinical pregnancy, and abortion rate in the IVFs with and without PRP, and our study also confirmed the results of this study. In another study conducted by Anju Madhavan and colleagues<sup>[3]</sup> in 2018 in India, 98 patients with a history of at least one failed IVF with an endometrial thickness of at least 7 mm reported that the pregnancy rate was 43% in the control group and 48% in the PRP-receiving group, which

was not statistically significant. They concluded that intrauterine PRP did not increase the rate of implantation and the rate of clinical pregnancy. In our study, similar results were obtained. In a review study by Ahmed Samy and colleagues<sup>[26]</sup> in 2020, it was reported that localized PRP injections had a significant effect on increasing pregnancy rates in women with infertility with a thin endometrium (less than 7 mm). Nazari *et al.*<sup>[13]</sup> (2016) conducted a study on the effect of PRP on fetal implantation and pregnancy in infertile patients with recurrent implantation failure following IVF. In this study, 20 women with a history of repeated IVF failures and being candidates for FET based on the entry criteria, were examined. Intrauterine infusion of 0.5 mL of PRP containing four to five times more platelets than the peripheral blood samples was performed 48 h before the blastocyst transmission. A total of 16 clinical pregnancies were reported and continued. According to their study, the injection of PRP has been shown to be effective in improving pregnancy outcomes in patients with recurrent implantation failures. The results of this study were contrary to our study. In this study, the blastocyst was transferred, but in our study, eight cell embryos were transferred. The cause of the difference in the results may be related to the type of embryo transferred. According to the results of our study, the investigation of the frequency of the abortions showed that 31.25 and 8.33% had abortions in the experiment and control groups, respectively, which was not a significant difference. But in the PRP group, it was much higher than the control group. In other words, more people became pregnant in the PRP group, but their abortion rate was higher than the control group. The lack of meaningful results was largely due to the small size of our study. In a study by Nazari *et al.*<sup>[13]</sup> 1 in 20 women with a history of recurrent IVF failure reported 1 abortion in the PRP group. In another study by Dieamant *et al.*<sup>[27]</sup> a study of PRP and G-CSF injections in the patients with implantation failure compared with the control group, the abortion rate was reported 18.2% versus 17.6%, respectively. It was not also significant statistically. Laird *et al.*<sup>[28]</sup> in their study of cytokine expression in endometriosis in women with implantation failure and recurrent abortion, stated that the presence of complex cytokine networks and the overlap between their biological activities may alter a cytokine and bring about its different effects on other compounds, and this may affect their role in implantation failure and abortion abundance.

Comparing the results of different studies and considering the results of this study, it seems that in patients with low endometrial thicknesses (less than 8 mm), PRP may increase the thickness of the endometrium, and thus, increase the pregnancy rate, but in higher thicknesses, does not have a significant effect on the fertility rates, and although it may increase the rate of chemical pregnancies to some extent, it cannot increase live birth rates.

In general, one of the limitations of our study was the small sample size and the inability to follow-up the patients to realize the live birth rate. It is recommended that studies with a larger number of participants be preferably multi-centric to achieve more conclusive results. It is also recommended that future

studies evaluate and compare the consequences of pregnancy, such as twinning, live birth rates, and abortion rates in these two groups of patients.

## Conclusion

In general, the results of this study showed that intrauterine PRP injection did not affect the pregnancy rates, and in the patients with endometrial thickness less than 8 mm with a history of recurrent implantation failure, intrauterine PRP injection may have a different effect.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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