The Effect of Intrauterine Injection of Platelet-Rich Plasma on Pregnancy Outcomes in In-Vitro-Fertilization Candidates With Recurrent Implantation Failure

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Abstract

Background: Platelet-rich plasma (PRP) contains over 20 growth factors and protein molecules that play a role in cell proliferation, differentiation, and regeneration. This study was designed to evaluate the impact of intrauterine PRP injection on women who have experienced recurrent implantation failure (RIF).

Methods: The present clinical trial involved 94 patients with RIF who were scheduled for in vitro fertilization (IVF). For the intervention (PRP) group, PRP was injected into the uterus using an intrauterine insemination catheter 24 to 48 hours before embryo transfer. The study then assessed and compared pregnancy rates between the intervention and control groups.

Results: This study found no significant baseline differences between the two groups. Endometrial thickness (ET) was comparable, measuring 7.50 ± 0.41 mm in the PRP group and 7.53 ± 0.56 mm in the control group. The PRP group exhibited significantly higher rates of both biochemical and clinical pregnancy. Specifically, the biochemical pregnancy rate was 64.6% (n = 39) in the PRP group compared to 19.6% (n = 9) in the control group ($p < 0.001$). Similarly, the clinical pregnancy rate was significantly higher in the PRP group at 50% (n = 24) versus 17.4% (n = 8) in the control group ($p = 0.001$).

Conclusion: The findings of this study reveal that the intrauterine injection of PRP prior to embryo transfer is a safe and affordable intervention that improves the pregnancy rate, with no major adverse effects observed.

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Keywords: Platelet-Rich Plasma, Infertility, Implantation, In-Vitro-Fertilization

Introduction

Recurrent implantation failure (RIF) is defined as a minimum of three failed cycles of high-quality embryo transfer (frozen embryo transfer [FET]) in women under the age of 40 (1). Successful implantation requires a receptive endometrium, which is characterized by the up-regulation of specific cytokines and adhesion molecules. Key factors in this process include secreted growth factors, particularly when activated by agents such as thrombin and calcium chloride, which stimulate their release from alpha granules. The resulting rise in growth factors and inhibition of apoptosis can significantly improve the chances of fertility (2-6).

In order to manage RIF during in vitro fertilization (IVF) cycles, various treatment methods have been employed. These include assisted hatching, endometrial scratching, hysteroscopy, and subcutaneous administration of granulocyte colony-stimulating factor (G-CSF). More recently, intrauterine infusion of autologous platelet-rich plasma (PRP) has also been used for this purpose (7-9).

As a critical blood derivative, PRP is a highly significant substance. This bioactive material contains more than 20 protein molecules, including binding molecules, chemokines, and growth factors, which are integral to processes such as proliferation, differentiation, and cell regeneration. The presence of these biological components and factors within PRP is what confers its therapeutic potential (8, 10).

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Upon binding to their cognate receptors, growth factors present in PRP initiate a downstream signaling cascade that modulates cellular proliferation and viability (11). A key step in this process is the activation of the signaling molecule protein kinase B (AKT) by phosphoinositide 3-kinases (PI3K). Besides its anti-apoptotic properties, activated AKT is also crucial for promoting cell growth, metabolism, and angiogenesis (2).

While some earlier studies (12-14) have demonstrated the effectiveness of PRP infusion in improving pregnancy rates, other research has reported no such benefits. For instance, a study by Tehraninejad et al. (15) found that applying PRP before embryo transfer in women with RIF and normal endometrial thickness (ET) did not impact the outcomes of assisted reproductive technology. Similarly, Allahveisi et al. (16) showed that intrauterine infusion of PRP before a FET had no significant effect on pregnancy outcomes in infertile women with a history of failed implantation, concluding that this method is not effective for improving patient infertility.

Consequently, this study was undertaken to investigate the effects of intrauterine PRP injection on pregnancy success rates in IVF patients experiencing RIF.

Methods

The present controlled, open-label, parallel-group, phase 3 clinical trial involved 90 women who were candidates for IVF and had both RIF and a thin endometrium. Prior to participation, all subjects provided both verbal and written consent. The Ethical Board of Tehran University of Medical Sciences approved the study (IR.TUMS.MEDICINE.REC.1402.364), and it was registered with the Iranian Registry of Clinical Trials (IRCT) (IRCT20240119060732N1).

Inclusion criteria for this study were women aged between 20 and 38 who had a history of IVF failures because of inadequate ET despite hormonal therapy, and possessed embryos of good quality (graded A or B). Exclusion criteria included a history of diabetes, immunosuppressant drug use, and the presence of malignancy, myomatous uterus, adenomyosis uterus, hydrosalpinges, severe endometriosis (stage 4), acute pelvic infection, blood and platelet disorders, as well as unwillingness to participate in the study.

Eligible women were randomly assigned (using a computer-generated random sequence) to one of two equally sized groups, each with 50 participants: An intervention group and a control group. In the intervention group, 5 mL of PRP was introduced into the uterus using an intrauterine insemination (IUI) catheter 24 to 48 hours before embryo transfer, adhering to strict sterile and standard conditions. The control group received no additional intervention.

To prepare PRP, 45 mL of the patient's venous blood was collected into a 5 mL anticoagulant-containing tube. The sample was then subjected to two-step centrifugation: an initial spin at 1200 rpm for 12 minutes to separate the upper two-thirds of the plasma from the dense middle layer and red blood cells, followed by a second spin at 3300 rpm for 7 minutes to concentrate the platelets. This process yielded approximately 10 mL of concentrated platelets at a concentration of 900,000 platelets/mL. The final PRP samples were then verified for platelet concentration using an automated hematology analyzer.

The sample size was determined using G*Power 3.1 software. This calculation was based on the projected differences in clinical pregnancy rates between the study groups, with a statistical power of 80% and a significance level of 0.05. The results indicated that a sample size of 100 patients (50 per group) was necessary.

The patient-related variables recorded were age, body mass index (BMI), the number of previous pregnancies, the number of previous abortions, and the history and treatment of any underlying medical conditions. The primary outcomes investigated were chemical and clinical pregnancy rates, which were evaluated six weeks post-intervention by assessing the beta subunit of human chorionic gonadotropin (βHCG) titer and performing a transvaginal ultrasound. Additionally, changes in ET were also examined.

Descriptive statistics (mean, standard deviation, and relative frequency) were employed to characterise the data. For inferential analysis, the correlation between qualitative variables was assessed using the chi-square test, while the t-test was applied to examine the correlation between quantitative variables. All analyses were conducted using SPSS version 23 software, with a significance level of $p < 0.05$.

Results

Of the 100 patients initially enrolled in the study, two women from the intervention group were lost to follow-up (one due to vaginal bleeding and one due to a thin endometrium), while four were lost from the control group (three due to lack of referral and one due to a thin endometrium). Ultimately, the analysis included 48 women in the intervention group and 46 in the control group (Figure 1).

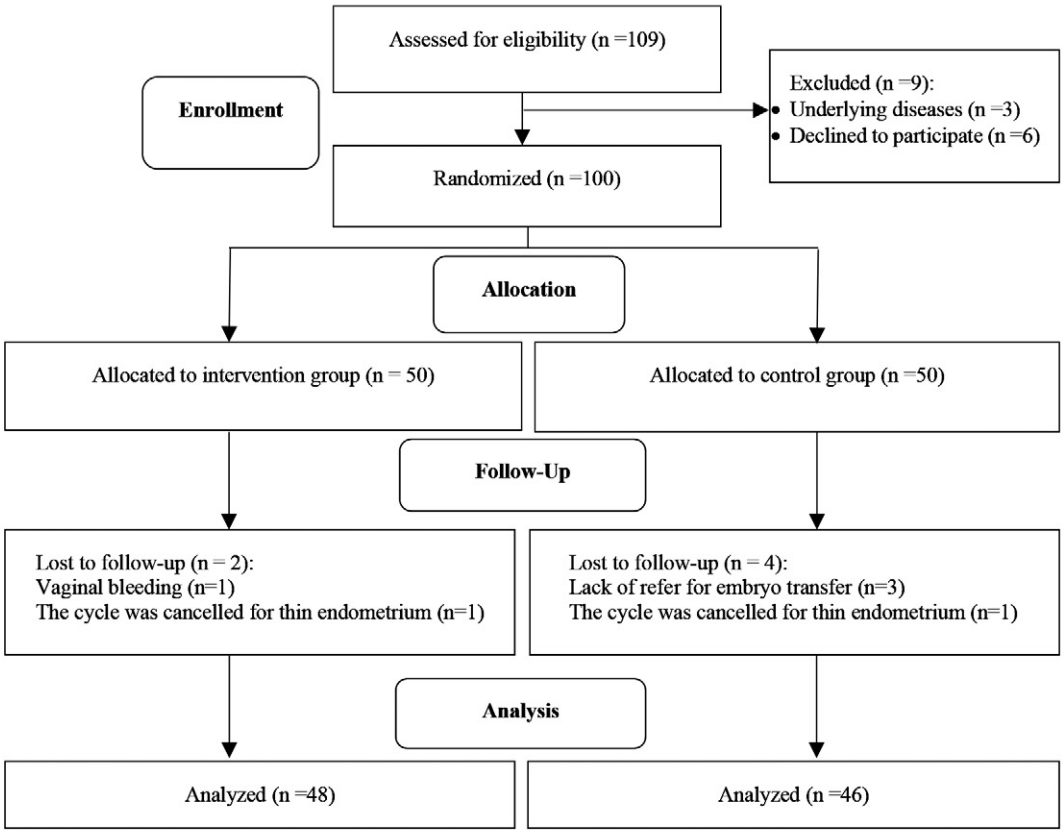

Figure 1. The flow diagram of the study

Among the 94 patients studied, the mean age of the women was 33.87 ± 4.81 years, and their mean (±SD) BMI was 26.63 ± 2.52 kg/m2. There was no significant difference observed between the two groups. The demographic and clinical characteristics for each of the two patient groups are presented in Table 1.

Table 1. The demographic and clinical history of the women, separately for the two groups of patients

Variable	PRP Group (n=48)	Control Group (n=46)	P value
Age (years), mean±SD	33.96 ± 4.48	33.78 ± 5.16	0.860
Body mass index (kg/m^2), mean±SD	26.17 ± 2.23	27.11 ± 2.73	0.070
Number of ectopic pregnancies (times), mean±SD	0.75± 0.50	0.25± 0.62	0.169
Menstrual status, n (%)			
Regular	37 (77.1)	36 (78.3)	0.393
Irregular	7 (14.6)	9 (19.3)	
Heavy Menstrual Bleeding	1 (2.1)	0 (0.0)	
Oligomenorrhea	3 (6.2)	1 (2.2)	
Hypermenorrhea	0 (0.0)	0 (0.0)	

PRP: Platelet-Rich Plasma, SD: Standard Deviation

The mean (±SD) infertility duration was found to be 3.95 ± 5.00 years. A total of 48 (51.1%) patients presented with primary infertility, while the remaining subjects had secondary infertility. The ET was measured at 7.50 ± 0.41 mm in the PRP group and 7.53 ± 0.56 mm in the control group. There was no significant difference in the number of transferred embryos between the two groups (3.76 ± 2.77 in the PRP group compared to 2.74 ± 1.37 in the control group).

The biochemical pregnancy rate was significantly higher in

the PRP group compared to the control group, with rates of 64.6% (n = 39) and 19.6% (n = 9), respectively (P< 0.001). Similarly, another finding showed that the PRP group had a significantly higher rate of biochemical pregnancy (50%, n = 24) compared to the control group (17.4%, n = 8) (P = 0.001). The obstetric and infertility findings, along with post-treatment outcomes for both patient groups, are detailed in Table 2.

Table 2. The obstetric and infertility findings and post treatment outcomes in two groups of patients

Variable	PRP Group (n=48)	Control Group (n=46)	P value
Infertility duration (years), mean±SD	5.23 ± 3.96	4.76 ± 3.97	0.568
In Vitro Fertilization number (times), mean±SD	2.92 ± 0.58	1.87 ± 2.99	0.352
Embryos transferred (number), mean±SD	3.76± 2.77	2.74± 1.37	0.330
Endometrial thickness (mm), mean±SD	7.50± 0.56	7.53± 0.56	0.782
Type of infertility, n (%)			
Primary	26 (54.2)	22 (47.8)	0.680
Secondary	22 (45.8)	24 (52.2)	
Male infertility, n (%)	14 (29.2)	13 (28.3)	1.000
Infertility due to tubal disorders	8 (16.7)	10 (21.7)	0.605
Infertility due to uterine disorders	2 (4.2)	6 (13)	0.154
Infertility due to ovarian disorders	10 (20.8)	15 (32.6)	0.246
Biochemical pregnancy	31 (64.6)	9 (19.6)	<0.001
Clinical pregnancy	24 (50.0)	8 (17.4)	0.001

PRP: Platelet-Rich Plasma, SD: Standard Deviation

In this study, no severe adverse events or systemic complications were documented. Nonetheless, 6 patients experienced mild uterine cramps following the PRP injection, which resolved spontaneously within several hours without the need for additional intervention.

Discussion

The current study found that PRP could significantly increase the pregnancy rate. Our findings are consistent with recent studies (4, 5) conducted on patients with RIF, which also reported that intrauterine infusion of autologous PRP 48 hours before embryo transfer improves pregnancy rates. Furthermore, Kim et al. (14) demonstrated that PRP infusion raised both pregnancy and live birth rates (LBR) in patients with a thin-resistant endometrium. Specifically, implantation, clinical pregnancy, ongoing pregnancy, and LBRs rose by 12.7%, 30%, 20%, and 20%, respectively.

ET is a critical factor for successful embryo implantation. PRP therapies are emerging as a promising strategy in reproductive medicine due to their ability to promote tissue repair and regeneration. In assisted reproductive technology (ART), PRP is recognized as an innovative treatment for endometrial disorders. Successful ART outcomes depend on a receptive endometrium, a viable micro-embryo, and synchronized communication between the blastocyst and the uterus. As an autologous therapy, PRP effectively promotes cell proliferation, neoangiogenesis, and anti-inflammatory responses, thereby enhancing endometrial receptivity (12).

In a study by Karadbhajne et al. (17), PRP was identified as a cutting-edge treatment for endometrial disorders within ART. The authors highlighted successful ART outcomes at every stage hinge on a receptive endometrium, a viable micro-embryo, and a synchronized communication between the blastocyst and the uterus. As an autologous therapy, PRP effectively enhances cell proliferation, neoangiogenesis, and anti-inflammatory effects, leading to promoting the endometrium's ability to accept an embryo. In a related study, Aghajanzadeh et al. (18) found that PRP therapy led to at least a 6.7% implantation success rate in women experiencing RIF.

Our findings are in contrast with several studies. For instance, Eftekhar et al. (19) found that intrauterine PRP administration before embryo transfer did not affect ART outcomes in women with RIF. Similarly, Allahveisi et al. (16) also reported that intrauterine infusion of PRP before FET had no significant effect on pregnancy outcomes in infertile women with a history of implantation failure. In agreement with these results, Tehraninejad et al. (15) concluded that intrauterine PRP infusion is not beneficial for RIF cases with an ET of ≥ 7 mm. These findings suggest that PRP may not be an effective complementary

treatment for all RIF women undergoing IVF. Therefore, careful patient selection is necessary to identify those who would benefit from this treatment.

A strong aspect of this study was its prospective clinical trial design. However, the study was limited by the absence of a placebo or sham intervention for the control group, a small sample size, and the lack of long-term follow-up to assess sustained pregnancy rates or LBRs as primary outcomes. Consequently, future research should involve larger scale, randomized controlled trials that incorporate a placebo or sham and have extended evaluation periods.

Conclusion

Our current findings demonstrate that the intrauterine administration of PRP is a safe and affordable method for enhancing pregnancy rates, with no significant side effects observed. However, larger, randomized controlled trials are required to validate these results.

Conflict of Interest

The authors declare no conflict of interest.

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