ORIGINAL ARTICLE

Platelet-rich plasma versus granulocyte colony-stimulating factor in addressing recurrent implantation failure: A randomized, double-blind clinical trial

Hatav Ghasemi Tehrani, Elnaz Mostajeran, Reihaneh Dehghani-Mohammadabadi, Elham Naghshineh
Department of Gynecology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Background: The aim of the study is to evaluate the effect of platelet-rich plasma (PRP) versus granulocyte colony-stimulating factor in addressing recurrent implantation failure. **Materials and Methods:** Fifty patients were randomly assigned to two treatment groups: PRP and granulocyte colony-stimulating factor (GCSF). All patients were followed up to 12 weeks after implantation. The rate of positive pregnancy tests (chemical pregnancy), implantation rate (clinical pregnancy), and pregnancy reaching 12 weeks old (ongoing pregnancy) in these two groups was compared. **Results:** Biochemical pregnancy, gestational sac formation, fetal heart formation, and 12-week pregnancy occurred in 6 (24%), 6 (24%), 6 (24%), and 5 women (20%) in the PRP group and occurred in 7 women (28%), 5 women (20%), 5 women (20%), and 5 women (20%) in the GCSF group. There was no statistically significant difference regarding biochemical pregnancy, gestational sac formation, fertile heart formation, and 12-week-old pregnancy between study groups ($P = 0.747$, 0.737, 0.737, and 1, respectively). **Conclusion:** Our study showed no difference in the efficacy of plasma-rich platelets and GCSFs in treating recurrent implantation failure.

Key words: Granulocyte colony-stimulating factor, infertility, platelet-rich plasma, recurrent implantation failure

How to cite this article: Tehrani HG, Mostajeran E, Dehghani-Mohammadabadi R, Naghshineh E. Platelet-rich plasma versus granulocyte colony-stimulating factor in addressing recurrent implantation failure: A randomized, double-blind clinical trial. J Res Med Sci 2026;31:14.

INTRODUCTION

Although many protocols have been introduced to treat repeated implantation failure (RIF), this remains a challenge for patients and clinicians.[1-4] Several managements have been introduced throughout history, including blastocyst transfer, assisted hatching, preimplantation genetic screening, hysteroscopy, removal of hydrosalpinges, and endometrial scratch, alongside some empirical treatments.[5-7] Chang *et al*. first described the infusion of intrauterine platelet-rich plasma (PRP) for treating patients with thin endometrium experiencing infertility.[8] Later, some more studies approved the benefits of PRP in patients with infertility, with improvements in pregnancy rate.[9-11] Based on the presence of granulocyte colony-stimulating factor (GCSF) receptors in placental tissues, trophoblastic cells, and endometrial cells, we know that this cytokine has a vital role in implantation. The use of GCSF in treating thin endometrium in assisted reproductive technology has been well shown. It has also been indicated that intrauterine or systemic administration of GCSF can improve pregnancy rate in patients with RIF.[12-15] Therefore, given the few studies on infertility in cases of recurrent implantation failure, the high success rate, efficacy, and safety of PRP and G-CSF injections, and the contradictory results, we decided to investigate the effectiveness of PRP and G-CSF. The present study will investigate the success rate of PRP and GCSF in patients with RIF.

Access this article online

Quick Response Code:

Website: https://journals.lww.com/jrms

DOI: 10.4103/jrms.jrms_736_23

Address for correspondence: Dr. Elham Naghshineh, Shahid Beheshti Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: naghshineh@med.mui.ac.ir
Submitted: 08-Nov-2023; **Revised:** 18-Jul-2025; **Accepted:** 16-Sep-2025; **Published:** 13-May-2026

MATERIALS AND METHODS

This randomized, double-blinded clinical trial was conducted at Shahid Beheshti Hospital, Isfahan, between January 2020 and January 2021 in Isfahan, Iran. We enrolled patients aged 20–45 who had at least three implantation failures or had an unsuccessful transfer of 10 embryos with informed consent. Patients with hematological disorders (leukemia and thrombocytopenia), immunological disorders (antiphospholipid syndrome and thrombophilia), hormonal disorders (diabetes, thyroid conditions, and hyperprolactinemia), chromosomal and genetic abnormalities (hereditary or congenital), and renal failure were excluded from the study. All eligible participants were divided into the PRP treatment group or the GCSF group [Figure 1]. Before entering the microinjection cycle, patients performed follicle-stimulating hormone and anti-Mullerian hormone tests. The cycle of microinjection began with the administration of human chorionic gonadotropin (hCG), pyruvate–dehydrogenase (PDH) at a dose of 300 IU/d, and ultrasound stimulation was repeated on the 5th day. If a follicle of 12–14 µm was observed, the patient was prescribed cetrotide (0.25).[16] When two or more than two follicles with a size of 18 or more than 18 µm were seen in the ultrasound, the final follicle stimulation was done by prescribing HCG 10,000 to the patient. Thirty-six hours after the final stimulation of the follicle, an ovarian puncture was performed, and after the puncture, 2.5 cc of PRP obtained from the patient's blood was injected into the uterus 48 h before embryo transfer in the group receiving PRP. The other group received GCSF in 300 micrograms subcutaneously 1 h before embryo transfer.[16] Finally, the rate of positive pregnancy tests (chemical pregnancy), implantation rate (clinical pregnancy), and pregnancy reaching 12-week-old (ongoing) pregnancy in these two groups were compared.

Table 1: Demographic information of study groups

Factor	PRP (*n*=25), *n* (%)	GCSF (*n*=25), *n* (%)	*P**
Age (mean±SD)	31.15±2.18	33.42±3.76	0.88
Education			
Illiterate	3 (12)	2 (8)	0.91
Diploma and less	13 (52)	14 (56)	
Bachelor's degree or more	9 (36)	9 (36)	
Occupation			
House-keeping	15 (60)	16 (64)	0.45
Employee	7 (28)	8 (32)	
Freelancer	3 (12)	1 (4)	

*Statistical significance is based on a one-way ANOVA test or Chi-square/Fisher's exact tests, where applicable. PRP=Platelet-rich plasma; GCSF=Granulocyte colony-stimulating factor; SD=Standard deviation

Statistical analysis

We analyzed the data using the Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., Chicago, Illinois, USA). The continuous variables were expressed as mean ± standard deviation, and the categorical values were expressed as percentages and were analyzed using the Chi-square test. An independent sample *t*-test was used to measure continuous variables with a normal distribution. We used the odds ratio to evaluate the association of outcomes across the groups. P <0.05 was considered statistically significant.

RESULTS

In total, we enrolled 50 patients. Twenty-five patients were treated with PRP (Group 1), and 25 patients were treated

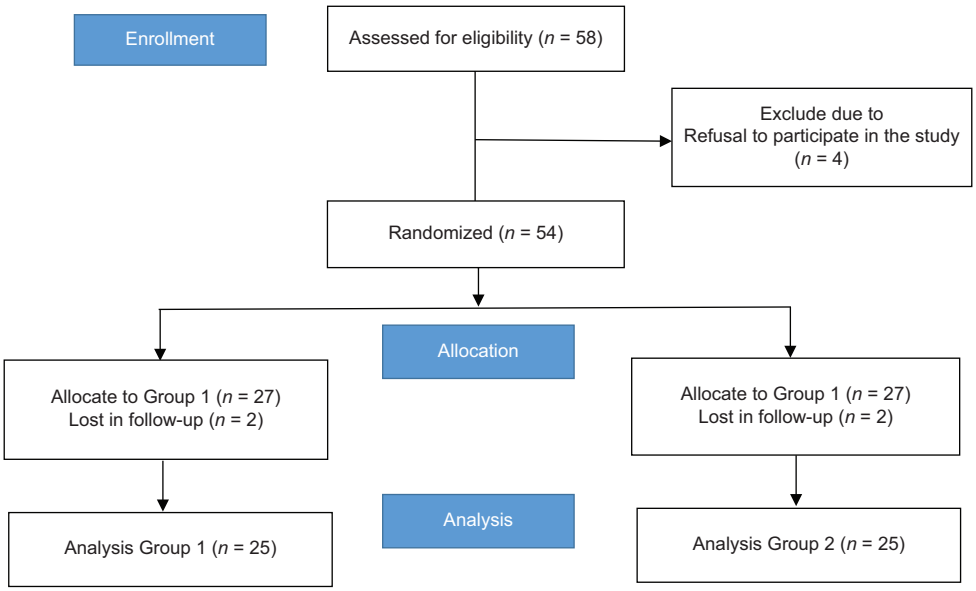

Figure 1: The study process is shown in the CONSORT flow diagram

Table 2: Frequency distribution of embryo type

Embryo type	PRP				GCSF			
	Fresh 3-day-old embryo	Frozen 3-day-old embryo	Fresh 5-day-old embryo	Frozen 5-day-old embryo	Fresh 3-day-old embryo	Frozen 3-day-old embryo	Fresh 5-day-old embryo	Frozen 5-day-old embryo
n (%)	3 (12)	15 (60)	1 (4)	6 (24)	2 (8)	17 (68)	1 (4)	5 (20)

PRP=Platelet-rich plasma; GCSF=Granulocyte colony-stimulating factor

Table 3: Assessment outcomes between study groups using the Chi-square test

	PRP, *n* (%)	GCSF, *n* (%)	*P**
Biochemical pregnancy	6 (24)	7 (28)	0.74
Gestational sac formation (clinical pregnancy)	6 (24)	5 (20)	0.73
Fatal heart formation	6 (24)	5 (20)	0.73
12-week-old pregnancy	5 (20)	5 (20)	1

*Chi-square test. Values <0.05 are considered significant. PRP=Platelet-rich plasma; GCSF=Granulocyte colony-stimulating factor

with GCSF (Group 2). There was no statistically significant difference between study groups regarding background data [Table 1]. The frequency distribution of embryo type and endometrial history is shown in Table 2. Regarding endometrial history, 9 (36%) of the patients in the PRP group and 11 (44%) patients in the GCSF group had endometrial scratching history. Biochemical pregnancy, gestational sac formation, fetal heart formation, and 12-week pregnancy occurred in 6 (24%) and 7 women (28%) and 6 (24%) and 5 women (20%) and occurred in 6 (24%) and 5 women (20%) and 5 (20%) and 5 women (20%) in Groups 1 and 2, respectively. There was no statistically significant difference regarding biochemical pregnancy, gestational sac formation, fertile heart formation, and 12-week-old pregnancy between study groups (P = 0.747, 0.737, 0.737, and 1, respectively) [Table 3]. No complications were observed in both groups.

DISCUSSION

Our study compared the pregnancy outcomes of patients with RIF treated with PRP versus GCSF. Our results showed no significant difference between the two groups regarding biochemical pregnancy, gestational sac formation, fertile heart formation, and 12 weeks of pregnancy.

Platelets in PRP store various growth factors and cytokines in their cytoplasmic granules that undergo exocytosis in the presence of activating factors such as collagen in the extracellular matrix.[17] Previous studies showed that endometrial epithelial and stromal cells synthesize many cytokines and growth factors necessary for implantation during the implantation process in response to hCG. Furthermore, platelets in PRP activate many cytokines and growth factors affecting endometrial receptivity, thus improving the implantation rate.[18,19] Several studies investigated the effect of intrauterine or systemic GCSF on pregnancy outcomes.[12,20] The impact of GCSF on pregnancy outcomes in RIF patients has been evaluated in a study by Davari-Tanha *et al*.[16] The study showed significant improvement in the rate of implantation and chemical pregnancy in RIF patients undergoing 300 µg/mL GCSF compared with the control group.[16] In another study by Aleyasin *et al*., subcutaneous administration of GCSF in patients with RIF showed statistically significant improvement in the implantation rate and chemical and clinical pregnancy.[21]

Few studies with similar designs have been published. In a survey by Mehrafza *et al*., they retrospectively studied 123 patients with a history of more than two repeated failed embryo transfers.[5] Participants were divided into two groups: intrauterine infusion of PRP and systemic administration of GCSF. They showed that the clinical pregnancy rate was significantly higher in the PRP group than in the GCSF group. This different finding can be related to our smaller sample size.

The limitation of our study was a relatively small sample size and a lack of patient satisfaction evaluation

CONCLUSION

Our study showed the same results regarding biochemical pregnancy, gestational sac formation, fertile heart formation, and 12-week-old pregnancy in patients with RIF treated with PRP and those treated with GCSF, demonstrating similar effects. More extensive studies with a control group are suggested to evaluate our findings and choose the best treatments for patients with RIF.

Acknowledgments
The authors would like to thank all colleagues and patients who contributed to this study.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Alssum LR. Repeated implants failure in young patient with

idiopathic nephrotic syndrome: A case report with brief review of the literature. BMC Oral Health 2024;24:25.
2. Fodina V, Dudorova A, Erenpreiss J. Reasons and Mechanisms of Recurrent Failed Implantation in IVF. InInfertility and Assisted Reproduction. IntechOpen; 2021.
3. Hajder E, Hajder M, Brkic M, Hajder E. Immune mechanisms in recurrent pregnancy loss (RPL) and recurrent implantation failure (RIF). HealthMED 2016;10:179.
4. Polanski LT, Baumgarten MN, Quenby S, Brosens J, Campbell BK, Raine-Fenning NJ. What exactly do we mean by 'recurrent implantation failure'? A systematic review and opinion. Reprod Biomed Online 2014;28:409-23.
5. Mehrafza M, Kabodmehri R, Nikpouri Z, Pourseify G, Raoufi A, Eftekhari A, *et al.* Comparing the impact of autologous platelet-rich plasma and granulocyte colony stimulating factor on pregnancy outcome in patients with repeated implantation failure. J Reprod Infertil 2019;20:35-41.
6. Simon A, Laufer N. Assessment and treatment of repeated implantation failure (RIF). J Assist Reprod Genet 2012;29:1227-39.
7. Feferkorn I, Dahan MH. How to manage recurrent implantation failure, what do we know?. InHandbook of Current and Novel Protocols for the Treatment of Infertility. Academic Press; 2024. p. 325-44.
8. Chang Y, Li J, Chen Y, Wei L, Yang X, Shi Y, *et al.* Autologous platelet-rich plasma promotes endometrial growth and improves pregnancy outcome during *in vitro* fertilization. Int J Clin Exp Med 2015;8:1286-90.
9. Nazari L, Salehpour S, Hoseini S, Zadehmodarres S, Ajori L. Effects of autologous platelet-rich plasma on implantation and pregnancy in repeated implantation failure: A pilot study. Int J Reprod Biomed 2016;14:625-8.
10. Zadehmodarres S, Salehpour S, Saharkhiz N, Nazari L. Treatment of thin endometrium with autologous platelet-rich plasma: A pilot study. JBRA Assist Reprod 2017;21:54-6.
11. Krüger JP, Freymannx U, Vetterlein S, Neumann K, Endres M, Kaps C. Bioactive factors in platelet-rich plasma obtained by apheresis. Transfus Med Hemother 2013;40:432-40.
12. Eftekhar M, Miraj S, Farid Mojtahedi M, Neghab N. Efficacy of intrauterine infusion of granulocyte colony stimulating factor on patients with history of implantation failure: A randomized control trial. Int J Reprod Biomed 2016;14:687-90.
13. Li Y, Pan P, Chen X, Li L, Li Y, Yang D. Granulocyte colony-stimulating factor administration for infertile women with thin endometrium in frozen embryo transfer program. Reprod Sci 2014;21:381-5.
14. Narayana N, Khurana A, Rai S, Poddar SD, Sharma P, Abhisheka K, *et al.* Intrauterine G-CSF in IUI cycles for women with thin endometrium may improve endometrial thickness and pregnancy rates: A randomized controlled study. Med J Armed Forces India 2025;81:410-5.
15. Lin LJ, Chen G, Xu LZ, Chen H. The effect of granulocyte colony stimulating factor (G-CSF) on the outcome of assisted reproduction technology in thin endometrium women: A meta-analysis. Clin Exp Obstet Gynecol 2023;50:85.
16. Davari-Tanha F, Shahrokh Tehraninejad E, Ghazi M, Shahraki Z. The role of G-CSF in recurrent implantation failure: A randomized double blind placebo control trial. Int J Reprod Biomed 2016;14:737-42.
17. Bos-Mikich A, de Oliveira R, Frantz N. Platelet-rich plasma therapy and reproductive medicine. J Assist Reprod Genet 2018;35:753-6.
18. Srivastava A, Sengupta J, Kriplani A, Roy KK, Ghosh D. Profiles of cytokines secreted by isolated human endometrial cells under the influence of chorionic gonadotropin during the window of embryo implantation. Reprod Biol Endocrinol 2013;11:116.
19. Dimitriadis E, White CA, Jones RL, Salamonsen LA. Cytokines, chemokines and growth factors in endometrium related to implantation. Hum Reprod Update 2005;11:613-30.
20. Würfel W, Santjohanser C, Hirv K, Bühl M, Meri O, Laubert I, *et al.* High pregnancy rates with administration of granulocyte colony-stimulating factor in ART-patients with repetitive implantation failure and lacking killer-cell immunglobulin-like receptors. Hum Reprod 2010;25:2151-2.
21. Aleyasin A, Abediasl Z, Nazari A, Sheikh M. Granulocyte colony-stimulating factor in repeated IVF failure, a randomized trial. Reproduction 2016;151:637-42.