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Efficacy of the Intrauterine Infusion of Platelet-Rich Plasma on Pregnancy Outcomes in Patients With Repeated Implantation Failure: A Randomized Control Trial

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Abstract

Objectives: The aim of the present study was to evaluate the effect of the intrauterine administration of platelet-rich plasma (PRP) before embryo transfer (ET) on pregnancy outcomes in women with repeated implantation failure (RIF).

Materials and Methods: This randomized controlled trial included 120 RIF women who were candidates for frozen-thawed ET. In the PRP group (n=60), the intrauterine infusion of 0.5 mL PRP was performed 48 hours before ET, and the control group (n=60) underwent ET without intrauterine administration.

Results: The implantation rate (28% vs. 11.9%, $P<0.001$), clinical pregnancy (51.6% vs. 26.6%, $P=0.005$), and live birth rate (58.3% vs. 28.3%, $P=0.001$) in PRP group were significantly higher compared to the control group. Based on the results, there was no significant difference with regard to miscarriage (12.5% vs. 12.9%, $P=0.97$) and multiple pregnancy rate (0.133% vs. 0.05%, $P=0.11$) between the two groups. Finally, preterm delivery was significantly higher in the PRP group ($P<0.001$).

Conclusions: According to this study, the result revealed that PRP is effective in the improvement of pregnancy outcomes in RIF patients. Further studies are needed to identify the group of patients who would benefit from this intervention.

Keywords: Repeated implantation failure, Platelet-rich plasma, Clinical pregnancy, In vitro fertilization

Introduction

Approximately 10% of couples following in vitro fertilization (IVF) treatment experience repeated implantation failure (RIF) causing a deep impact on the quality of life and a heavy financial burden. Despite the lack of uniform definition, RIF is generally defined as the failure to achieve a clinical pregnancy after three or more transfers of at least four or more high-quality embryos in a woman below 40 years old (1,2).

To date, many treatment modalities have been utilized to improve the pregnancy outcomes of the couple with RIF, including blastocyst transfer, preimplantation genetic screening, assisted hatching, salpingectomy for tubal disease, hysteroscopy, and endometrial scratching. However, these approaches have not gained wide acceptance, and the pregnancy rate after these approaches remains unsatisfactory. Thus, there is a need for alternative treatments for patients with repeated IVF failure (3-8).

The successful implantation requires synchronized interaction between a receptive endometrium and a good-quality embryo mediated by several cytokines, chemokines, growth factors, and adhesion molecules that are produced by endometrial and immune cells in the feto-maternal interface (9,10).

It seems that two-thirds of implantation failures can be explained by the lack of adequate uterine receptivity. The imbalance between pro- and anti-inflammatory cytokines and several molecules was probably associated with RIF (11-14).

Platelet-rich plasma (PRP) is prepared from fresh whole blood that has a platelet count 4-5 times higher than the baseline concentration. After the activation of the platelet in PRP, platelets release many cytokines, growth factors, and other molecules that stimulate cell proliferation, differentiation, angiogenesis, and tissue regeneration. Hence, it may help modulate endometrial cell migration, attachment, and neoangiogenesis, consequently, resulting in beneficial effects on endometrial receptivity (15,16).

Recently, the use of autologous PRP has gained great attention in human-assisted reproductive medicine and the gynecology field. Some studies showed that the intrauterine infusion of autologous PRP is effective in improving endometrial growth and implantation rate in women with the cancellation history of a previous embryo transfer (ET) cycle due to thin endometrium after infertility treatment (17-23).

To the best of our knowledge, this is the first clinical trial study that evaluated the efficacy of the intra-uterine

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Key Messages

- PRP is effective in the improvement of pregnancy outcomes in RIF patients.
- PRP improve implantation rate, clinical pregnancy and live birth rate.

administration of autologous PRP on implantation and clinical pregnancy rate and live birth before frozen-thawed embryo transfer (FET) in women with normal endometrial growth who failed to conceive after three or more ET in the ART cycle.

Materials and Methods

This randomized controlled trial was performed at the Infertility Department of Shariati Hospital and Omid Fertility Center, Tehran, Iran from October 2017 to April 2020.

A total of 120 infertile women within the age range of 20-40 years old were enrolled in this study. These women had failed to conceive after three or more ET with high-quality embryos and had at least one frozen good-quality blastocyst-stage embryo, and were candidates for FET.

On the other hand, participants with chromosomal and genetic disorders, hematological and immunological disorders, hormonal disorders, uterine abnormality (congenital or acquired), body mass index above 30 kg/m^2, severe endometriosis, and patients with cancellation history of the previous ET due to a thin endometrium (≤7 mm) in hormone replacement therapy cycles were excluded from the study.

The patients were randomized into two equal groups through balanced block randomization, including PRP (intervention) and control groups.

In both groups, endometrial preparation was initiated with 4-6 mg daily oral estradiol valerate (Aburaihan, Iran) on day 2 of the patient's menstrual cycle after performing a transvaginal ultrasound.

The dose of estradiol was increased according to the endometrial response up to a maximal dose of 12 mg per day after observing a triple line endometrial pattern and approximately thickness of 8 mm on ultrasound.; Afterward, 100 mg endometrin vaginal suppositories (Ferring, Switzerland) twice a day plus a daily intramuscular injection of 50 mg progesterone (Aburaihan, Iran) was administrated for 5 complete days before ET and continued until 12 weeks in the cased of pregnancy occurrence.

In the PRP group, 48 hours before ET, 8.5 mL of peripheral venous blood (cubital vein) was drawn from the 10 mL syringe pre-filled with 1.5 mL of acid citrate as an anticoagulant solution (Rooyagen, Iran) based on the manufacturer's instruction and immediately centrifuged at 1600 rpm for 10 minutes to separate red blood cells. Then, plasma was re-centrifuged at 3500 rpm for 6 minutes at room temperature (18C) to obtain 1.5 mL lympho PRP with a platelet concentration of 4-5 times higher than the basal blood sample and 2000 lymphocyte/μL.

Next, 0.5 mL of PRP was gently infused into the uterine cavity with an intrauterine insemination (IUI) catheter under ultrasound guidance in sterile conditions, and a control group undergoing ET without the intrauterine infusion of PRP.

For all participants, based on each patient's profile, one to three good-quality blastocyst(s) (Grade A or B) were transferred by two physicians having an infertility fellowship under abdominal ultrasound guidance. Embryo quality was evaluated by an expert embryologist using an inverted microscope. Chemical pregnancy was defined as a positive beta human chorionic gonadotropin (β-hCG) 14 days after the ET, and clinical pregnancy was defined as the presence of a gestational sac with fetal heart pulsation on transvaginal ultrasound 4 weeks following the ET. The implantation rate was defined as the number of gestational sac on transvaginal ultrasound by the number of the transferred embryos.

Ongoing pregnancy is defined as a pregnancy beyond 12 weeks of gestation. Live birth was defined as the delivery of one or more living infant(s), and the miscarriage rate (MR) (per clinical pregnancy) is defined as a fetal loss before 20 weeks of gestation. Multiple pregnancy rate per cycle is defined as the presence of more than one gestational sac on transvaginal ultrasound. Preterm delivery was considered as the birth between 23–36+ 6 weeks of gestation.

Statistical Analysis

Qualitative and quantitative data were presented as the frequency and percentage, as well as mean and standard deviation. The normality of data was assessed with the Kolmogorov-Smirnov test. Continuous variables between the two groups were compared using an independent *t* test. On the other hand, categorical variables were compared using the chi-square test or Fisher's exact test when more than 20% of cells with expected counts of less than 5 were observable. All analyses were done using SPSS (version 23, SPSS Inc., Illinois, USA), and a *P* value less than 0.05 was considered statistically significant.

Results

Totally, 120 patients with RIF history (60 patients in the PRP group and 60 patients in the control group) were included in this study (Figure 1).

The baseline and clinical characteristics of participants are shown in Table 1. Based on the results, there were no significant differences in terms of age, body mass index (BMI), anti-Müllerian hormone (AMH), number of embryos, and the duration and etiology of infertility between the groups ($P > 0.05$). In addition, there was no significant difference between the two groups with regard to gravidity, parity, abortion, and ectopic pregnancy

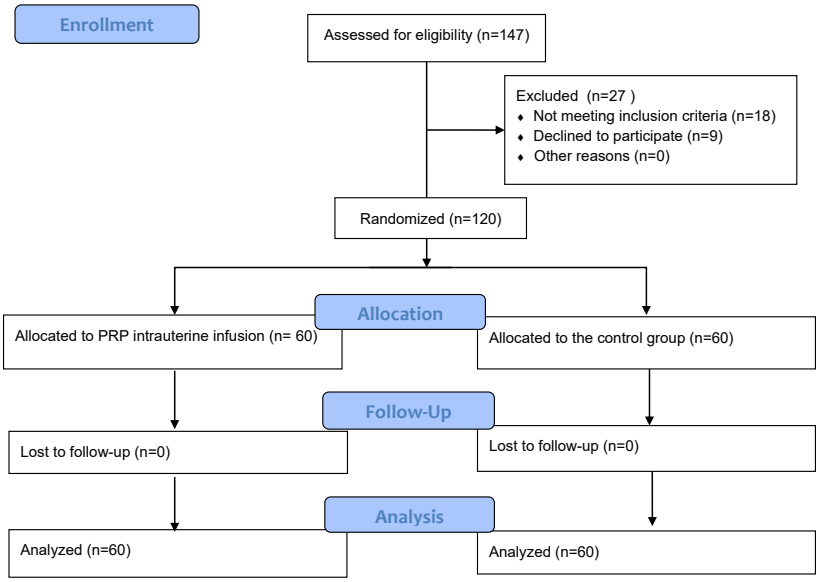

Figure 1. CONSORT Flow Diagram.

($P > 0.05$).

The etiology of infertility between intervention and control groups is compared in Table 2. In both groups, the main etiology of infertility was mixed and belonged to both genders (55% in the intervention group and 56.77% in the control group).

Table 3 provides the clinical outcomes of patients in the intervention and control groups. There was a significant difference between the two groups in relation to β-hCG, clinical pregnancy rate (CPR), ongoing pregnancy rate (OPR), and live birth rate (LBR). In other words, 51.67%, 51.67%, 48.33%, and 58.33% of cases in the intervention group were β-hCG, CPR, OPR, and LBR positive compared to 30%, 26.67%, 25%, and 28.33% of them in the control group respectively ($P < 0.05$). The implantation rate was significantly higher in the intervention group (28% vs. 11.9%, $P < 0.001$). There was no significant difference regarding the multiple pregnancy rate (0.133% vs. 0.05%, $P = 0.11$). Further, no significant difference was found in terms of chemical pregnancy, delivery type, grade of the embryo, and MR per clinical pregnancy between the two investigated groups ($P > 0.05$) although preterm delivery was significantly higher in the PRP group ($P < 0.001$).

The etiology of cesarean section in PRP and control groups is shown in Figure 2. Elective choosing cesarean and twin pregnancy were two common causes of caesarian in both groups.

Table 1. Baseline Demographic and Clinical Characteristics of Patients in the Two Groups

Variable		PRP Group	Control Group	*P* Value
Age (y)		33.4±4.9	34±3.73	0.45*
BMI (kg/m²)		24.85±2.84	25.24±2.71	0.45*
AMH		2.51±1.22	2.64±2.99	0.76*
Infertility	First	50 (83.33)	47 (78.33)	0.49
	Second	10 (16.67)	13 (21.67	
	Zero	36 (60)	41 (68.33)	
	One	16 (26.67)	11 (18.33)	
	Second	6 (10)	5 (8.33)	0.67
	Third	2 (3.33)	2 (3.33)	
	Fourth	0	1 (1.67)	
Parity	Zero	53 (85.83)	50 (83.33)	0.35
	One	6 (13.33)	10 (16.67)	
	Second	1 (1.67)	0	
Duration of infertility	1-3 year	24 (40.00)	17 (28.33)	0.18
	4-7 year	36 (60.00)	43 (71.67)	
	Zero	44 (73.33)	49 (81.67)	
	One	11 (18.33)	8 (13.33)	0.6
	Second	4 (6.67)	3 (5)	
	Third	1 (1.67)	0	
Ectopic pregnancy	Zero	55 (91.67)	51 (85)	0.29
	One	5 (8.33)	7 (11.67)	
	Second	0	2 (3.33)	

Note. PRP: Platelet-rich plasma; BMI: body mass index; AMH: anti-Müllerian hormone. *t test.

Discussion

Successful implantation requires a good quality embryo and a receptive endometrium. The window of implantation is a restricted time during the mid-secretory phase when the endometrium is receptive to blastocyst under the control of estrogen and progesterone and is characterized by the up-regulation of several cytokines, growth factors, and adhesion molecules, and other proteins (1).

Table 2. The Etiology of Infertility in Both Intervention and Control Groups

	Male Only	Female Only	Mixed	Total
PRP group	9 (15)	18 (30)	33 (55)	60
Control group	9 (15)	17 (28.33)	34 (56.67)	60
Total	18 (15)	35 (29.17)	67 (55.83)	120

Note. PRP: Platelet-rich plasma.

Table 3. Clinical Outcomes of Patients in the Intervention and Control Groups

Variable		PRP Group	Control Group	*P* Value
βHCG	Positive	31 (51.67)	18 (30.00)	0.016
	Negative	29 (48.33)	42 (70.00)	
CPR	Positive	31 (51.67)	16 (26.67)	0.005
	Negative	29 (48.33)	44 (73.33)	
OPR	Positive	29 (48.33)	15 (25.00)	0.008
	Negative	31 (51.67)	45 (75.00)	
LBR	Positive	35 (58.33)	17 (28.33)	0.001
	Negative	25 (41.67)	43 (71.67)	
Delivery type	Cesarean	18 (69.23)	8 (61.54)	0.63
	NVD	8 (30.77)	5 (38.46)	
IR	0	26 (44.07)	37 (61.67)	0.21
	33.3	8 (13.56)	4 (6.67)	
	50	20 (33.90)	13 (21.67)	
	66.6	2 (3.39)	1 (1.67)	
	100	3 (5.08)	5 (8.33)	
Chemical pregnancy	Positive	0	2 (3.33)	0.49
	Negative	60 (100.00)	58 (96.67)	
Grade of embryo	Grade A	109 (78.42)	113 (71.07)	0.15
	Grade B	30 (21.58)	46 (28.93)	
Pre-term rate		13 (25.00)	2 (3.33)	<0.001
Number of embryo transfer		139	159	-
Implantation rate		39/139= 0.28	19/159=0.12	<0.001
MR per clinical pregnancy		4/31=0.129	2/16=0.125	0.97
MPR		8/60=0.133	3/60=0.05	0.11

Note. PRP: Platelet-rich plasma; β-hCG: beta human chorionic gonadotropin; CPR: Clinical pregnancy rate; OPR: Ongoing pregnancy rate; LBR: Live birth rate; IR: Implantation rate; MR: Miscarriage rate; MPR: Multiple pregnancy rate.

PRP is prepared from the patient's own fresh whole blood and contains a multitude of growth factors, cytokines, proteins, and antimicrobial properties such as the vascular endothelial growth factor, platelet-derived growth factor, hepatocyte growth factor, and interleukin 8 that release from their cytoplasm and conduct cell proliferation, differentiation, and tissue regeneration necessary for embryo implantation (15,16).

Considering that the first study of the application of autologous PRP therapy in reproductive medicine was carried out by Chang et al, numerous studies (17-24) indicated that the intrauterine infusion of PRR is a new treatment in the improvement of endometrial growth and the outcome of pregnancy in patients undergoing infertility treatment with a thin endometrium (endometrial thickness <7 mm).

Kim et al in a pilot study revealed that after the intrauterine administration of PRP in twenty women with a history of the cancellation of the previous ET cycle due to poor endometrial growth, the pregnancy outcome significantly improved even though the average of increment in endometrial thickness was not significant (20). Likewise, Tandulwadkar et al showed that after the use of the IUI of PRP, endometrial vascularity and pregnancy rate increased in patients with a history of repeated ET cancellation cycle due to suboptimal endometrial thickness and vascularity (23).

A recent in vitro study by Aghajanova et al demonstrated that PRP stimulates the cell process involved in endometrial regeneration and neoangiogenesis. Then, they also identified that PRP is effective in the treatment of Asherman's syndrome. In another study, Zhang et al found that PRP could regulate endometrial receptivity by promoting mesenchymal stem cell proliferation (25-27).

Consistent with our finding, Nazari et al investigated the effectiveness of PRP in enhancing the pregnancy rate in RIF20 women with a history of RIF and reported that 18 of 20 participants became pregnant and 16 clinical pregnancies were recorded accordingly. They further showed that the intrauterine administration of PRP was effective in improving the pregnancy rate in RIF patients (21).

To the best of our knowledge, the present study is the first clinical trial that evaluated the effectiveness of PRP on

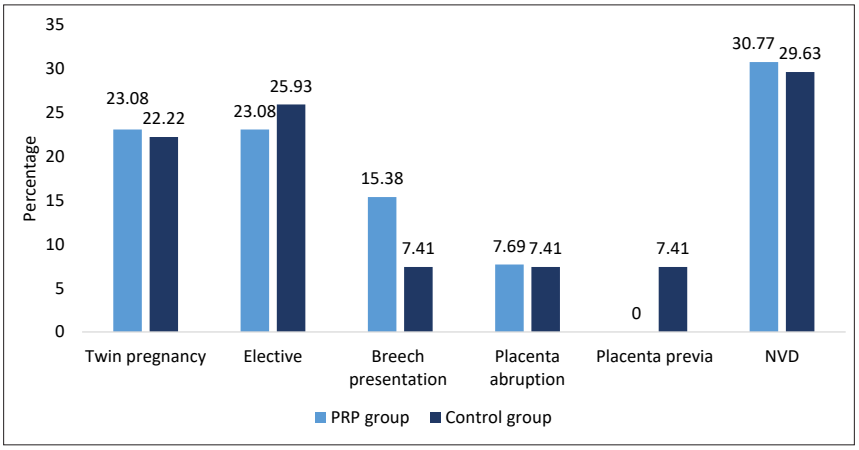

Figure 2. The Etiology of Cesarean Section in PRP and Control Groups. Note. PRP: Platelet-rich plasma.

pregnancy outcomes in RIF patients with normal growth endometrium. This study included 120 RIF patients who had experienced implantation failure after three or more ETs. The results of the present study indicated that the intrauterine infusion of PRP before ET can significantly improve the clinical pregnancy and live birth in RIF women, which is independent of the woman's age, the AMH level, endometrial thickness, and the number of good-quality transferred embryos.

The incidence of preterm delivery was higher in the PRP group compared to the control group independent of the cause of infertility and maternal age.

The positive effect of using PRP on implantation may be partly related to the mechanical stimulation of the endometrium induced by the insertion of the catheter into the uterine cavity although this is only a possibility and no definitive conclusion can be drawn in this regard.

Chronic endometritis is a persistent inflammation of the uterine gland and endometrial stroma and is usually asymptomatic. Various studies have recently reported that the prevalence of subclinical chronic endometritis is high in RIF patients. Chronic endometritis could have a deleterious effect on receptivity via altering the expression of some genes that encode cytokines and chemokines involved in the implantation process. The results of some animal studies showed that the intrauterine administration of autologous PRP is effective in the treatment of endometritis and can improve implantation via activating peripheral blood mononuclear cells (PBMCs) and modulating the excessive uterine inflammatory response (28-31).

A recent study indicated that dialogue between the platelet and PBMC can induce the activation of PBMC and the release of several cytokines and growth factors (32). The findings of another similar study showed that the intrauterine infusion of cultured PBMC before ET is effective in the improvement of pregnancy outcomes in RIF patients (33).

In addition to hemostasis, platelet release mediators induce human extravillous trophoblast migration and differentiation to modulate spiral artery in uterine and its consequence is regulation of the placentation process (34).

The balance between pro-inflammatory and anti-inflammatory cytokine response is essential for embryo implantation, and disturbance in each of these expressions could result in RIF (13,14).

Lédée et al demonstrated that 56.6% of RIF patients have up-regulated endometrial immune profile in comparison with fertile women, hence, PRP insemination may worsen this condition. Therefore, endometrial immune profiling and personalized treatment approaches are recommended in RIF patients (35). In addition, it is suggested that further studies compare PRP and endometrial scratching in a control group to obtain more accurate results.

According to some human studies, PRR can improve endometrial growth and uterine receptivity by its angiogenic factor or antimicrobial and anti-inflammatory properties (15,16).

According to the above-mentioned discussion, it seems that the intrauterine administration of PRP modulates the microenvironment of the uterus and improves endometrial growth and uterine receptivity by its angiogenic factor or antimicrobial and anti-inflammatory properties (36, 37).

Limitations of the Study

However, our study had some limitations. Due to the nature of this study, it was un-blinded and no placebo was used in the control group for ethical reasons. Considering that the clinical pregnancy rate is an objective outcome, these factors are unlikely to create any bias. Further, a large sample size is needed to have better comparison outcomes between the two groups.

Conclusions

PRP is effective in improving pregnancy outcomes in RIF patients and is prepared from the autologous blood sample, easily available inexpensive treatment without the risk of transmission of infection and immunological reaction. The exact mechanism of PRP in this field and which group of patients are most likely to benefit from this intervention should be clarified as well. It seemed that PRP can be used as a new promising method for the treatment of RIF patients.

Authors' Contribution

LS, AA, MA and PL developed the original idea and the protocol, abstracted, and prepared the manuscript. SHM, FS, PL and SK participated in the study design and analyzed the data. Except SK, all authors contributed to the data gathering. All authors read and approved the final manuscript.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

This study was approved by the Ethics committee of Tehran University of Medical Sciences, and informed consent was obtained from all participants. A demographic form of medical records was filled for each patient.

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References

1. Achache H, Revel A. Endometrial receptivity markers, the journey to successful embryo implantation. Hum Reprod Update. 2006;12(6):731-746. doi:10.1093/humupd/dml004
2. Coughlan C, Ledger W, Wang Q, et al. Recurrent implantation failure: definition and management. Reprod Biomed Online. 2014;28(1):14-38. doi:10.1016/j.rbmo.2013.08.011
3. Papanikolaou EG, Kolibianakis EM, Tournaye H, et al. Live birth rates after transfer of equal number of blastocysts or

cleavage-stage embryos in IVF. A systematic review and meta-analysis. Hum Reprod. 2008;23(1):91-99. doi:10.1093/humrep/dem339
4. Caglar GS, Asimakopoulos B, Nikolettos N, Diedrich K, Al-Hasani S. Preimplantation genetic diagnosis for aneuploidy screening in repeated implantation failure. Reprod Biomed Online. 2005;10(3):381-388. doi:10.1016/s1472-6483(10)61800-7
5. Martins WP, Rocha IA, Ferriani RA, Nastri CO. Assisted hatching of human embryos: a systematic review and meta-analysis of randomized controlled trials. Hum Reprod Update. 2011;17(4):438-453. doi:10.1093/humupd/dmr012
6. D'Arpe S, Franceschetti S, Caccetta J, Pietrangeli D, Muzii L, Panici PB. Management of hydrosalpinx before IVF: a literature review. J Obstet Gynaecol. 2015;35(6):547-550. doi:10.3109/01443615.2014.985768
7. Potdar N, Gelbaya T, Nardo LG. Endometrial injury to overcome recurrent embryo implantation failure: a systematic review and meta-analysis. Reprod Biomed Online. 2012;25(6):561-571. doi:10.1016/j.rbmo.2012.08.005
8. Agha Hosseini M, Ebrahimi N, Mahdavi A, et al. Hysteroscopy in patients with repeated implantation failure improves the outcome of assisted reproductive technology in fresh and frozen cycles. J Obstet Gynaecol Res. 2014;40(5):1324-1330. doi:10.1111/jog.12315
9. Simón C, Martín JC, Pellicer A. Paracrine regulators of implantation. Baillieres Best Pract Res Clin Obstet Gynaecol. 2000;14(5):815-826. doi:10.1053/beog.2000.0121
10. Simon A, Laufer N. Repeated implantation failure: clinical approach. Fertil Steril. 2012;97(5):1039-1043. doi:10.1016/j.fertnstert.2012.03.010
11. Sak ME, Gul T, Evsen MS, et al. Fibroblast growth factor-1 expression in the endometrium of patients with repeated implantation failure after in vitro fertilization. Eur Rev Med Pharmacol Sci. 2013;17(3):398-402.
12. Shim SH, Kim JO, Jeon YJ, et al. Association between vascular endothelial growth factor promoter polymorphisms and the risk of recurrent implantation failure. Exp Ther Med. 2018;15(2):2109-2119. doi:10.3892/etm.2017.5641
13. Liang PY, Diao LH, Huang CY, et al. The pro-inflammatory and anti-inflammatory cytokine profile in peripheral blood of women with recurrent implantation failure. Reprod Biomed Online. 2015;31(6):823-826. doi:10.1016/j.rbmo.2015.08.009
14. Subramani E, Madogwe E, Ray CD, et al. Dysregulated leukemia inhibitory factor and its receptor regulated signal transducers and activators of transcription 3 pathway: a possible cause for repeated implantation failure in women with dormant genital tuberculosis? Fertil Steril. 2016;105(4):1076-1084.e1075. doi:10.1016/j.fertnstert.2015.12.015
15. Amable PR, Carias RB, Teixeira MV, et al. Platelet-rich plasma preparation for regenerative medicine: optimization and quantification of cytokines and growth factors. Stem Cell Res Ther. 2013;4(3):67. doi:10.1186/scrt218
16. Masuki H, Okudera T, Watanebe T, et al. Growth factor and pro-inflammatory cytokine contents in platelet-rich plasma (PRP), plasma rich in growth factors (PRGF), advanced platelet-rich fibrin (A-PRF), and concentrated growth factors (CGF). Int J Implant Dent. 2016;2(1):19. doi:10.1186/s40729-016-0052-4
17. Chang Y, Li J, Chen 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(1):1286-1290.
18. Chang Y, Li J, Wei LN, Pang J, Chen J, Liang X. Autologous platelet-rich plasma infusion improves clinical pregnancy rate in frozen embryo transfer cycles for women with thin endometrium. Medicine (Baltimore). 2019;98(3):e14062. doi:10.1097/md.0000000000014062
19. Farimani M, Poorolajal J, Rabiee S, Bahmanzadeh M. Successful pregnancy and live birth after intrauterine administration of autologous platelet-rich plasma in a woman with recurrent implantation failure: a case report. Int J Reprod Biomed. 2017;15(12):803-806.
20. Kim H, Shin JE, Koo HS, Kwon H, Choi DH, Kim JH. Effect of autologous platelet-rich plasma treatment on refractory thin endometrium during the frozen embryo transfer cycle: a pilot study. Front Endocrinol (Lausanne). 2019;10:61. doi:10.3389/fendo.2019.00061
21. 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(10):625-628.
22. Nazari L, Salehpour S, Hoseini S, Zadehmodarres S, Azargashb E. Effects of autologous platelet-rich plasma on endometrial expansion in patients undergoing frozen-thawed embryo transfer: a double-blind RCT. Int J Reprod Biomed. 2019;17(6):443-448. doi:10.18502/ijrm.v17i6.4816
23. Tandulwadkar SR, Naralkar MV, Surana AD, Selvakarthick M, Kharat AH. Autologous intrauterine platelet-rich plasma instillation for suboptimal endometrium in frozen embryo transfer cycles: a pilot study. J Hum Reprod Sci. 2017;10(3):208-212. doi:10.4103/jhrs.JHRS_28_17
24. Tehranian A, Esfehani-Mehr B, Pirjani R, Rezaei N, Heidary SA, Sepidarkish M. Application of autologous platelet-rich plasma (PRP) on wound healing after caesarean section in high-risk patients. Iran Red Crescent Med J. 2016;18(7):e34449. doi:10.5812/ircmj.34449
25. Aghajanova L, Houshdaran S, Balayan S, et al. In vitro evidence that platelet-rich plasma stimulates cellular processes involved in endometrial regeneration. J Assist Reprod Genet. 2018;35(5):757-770. doi:10.1007/s10815-018-1130-8
26. Aghajanova L, Cedars MI, Huddleston HG. Platelet-rich plasma in the management of Asherman syndrome: case report. J Assist Reprod Genet. 2018;35(5):771-775. doi:10.1007/s10815-018-1135-3
27. Zhang S, Li P, Yuan Z, Tan J. Platelet-rich plasma improves therapeutic effects of menstrual blood-derived stromal cells in rat model of intrauterine adhesion. Stem Cell Res Ther. 2019;10(1):61. doi:10.1186/s13287-019-1155-7
28. Cicinelli E, Matteo M, Tinelli R, et al. Prevalence of chronic endometritis in repeated unexplained implantation failure and the IVF success rate after antibiotic therapy. Hum Reprod. 2015;30(2):323-330. doi:10.1093/humrep/deu292
29. Di Pietro C, Cicinelli E, Guglielmino MR, et al. Altered transcriptional regulation of cytokines, growth factors, and apoptotic proteins in the endometrium of infertile women with chronic endometritis. Am J Reprod Immunol. 2013;69(5):509-517. doi:10.1111/aji.12076
30. Marini MG, Perrini C, Esposti P, et al. Effects of platelet-rich plasma in a model of bovine endometrial inflammation in vitro. Reprod Biol Endocrinol. 2016;14(1):58. doi:10.1186/s12958-016-0195-4
31. Reghini MF, Ramires Neto C, Segabinazzi LG, et al. Inflammatory response in chronic degenerative endometritis mares treated with platelet-rich plasma. Theriogenology. 2016;86(2):516-522. doi:10.1016/j.theriogenology.2016.01.029
32. Yoshioka S, Fujiwara H, Nakayama T, Kosaka K, Mori T, Fujii S. Intrauterine administration of autologous peripheral blood mononuclear cells promotes implantation rates in patients

with repeated failure of IVF-embryo transfer. Hum Reprod. 2006;21(12):3290-3294. doi:10.1093/humrep/del312
33. Nobijari FF, Arefi SS, Moini A, et al. Endometrium immunomodulation by intrauterine insemination administration of treated peripheral blood mononuclear cell prior frozen/thawed embryos in patients with repeated implantation failure. Zygote. 2019;27(4):214-218. doi:10.1017/s0967199419000145
34. Sato Y, Fujiwara H, Zeng BX, Higuchi T, Yoshioka S, Fujii S. Platelet-derived soluble factors induce human extravillous trophoblast migration and differentiation: platelets are a possible regulator of trophoblast infiltration into maternal spiral arteries. Blood. 2005;106(2):428-435. doi:10.1182/blood-2005-02-0491
35. Lédée N, Petitbarat M, Chevrier L, et al. The uterine immune profile may help women with repeated unexplained embryo implantation failure after in vitro fertilization. Am J Reprod Immunol. 2016;75(3):388-401. doi:10.1111/aji.12483
36. Anitua E, de la Fuente M, Ferrando M, et al. Biological effects of plasma rich in growth factors (PRGF) on human endometrial fibroblasts. Eur J Obstet Gynecol Reprod Biol. 2016;206:125-130. doi:10.1016/j.ejogrb.2016.09.024
37. Bendinelli P, Matteucci E, Dogliotti G, et al. Molecular basis of anti-inflammatory action of platelet-rich plasma on human chondrocytes: mechanisms of NF-κB inhibition via HGF. J Cell Physiol. 2010;225(3):757-766. doi:10.1002/jcp.22274