RESEARCH ARTICLE

A Comparison of Platelet-rich Plasma and Human Chorionic Gonadotropin in Enhancing Reproductive Outcomes in Women Who Had Previously Failed Implantation: A Retrospective Cohort Study

Shrutika S Khapre[1], Deepti Shrivastava[2], Mangesh D Hivre[3]

Received on: 25 March 2024; *Accepted on:* 27 June 2024; *Published on:* 02 September 2024

Abstract

Introduction: A thin endometrium is a significant contributor to failed embryo implantation. A considerable percentage of women who have thin endometrium are resistant to conventional therapeutic approaches. Administering platelet-rich plasma (PRP) directly into the uterus can potentially augment the thickness and vascularity of the endometrium, thereby enhancing its receptivity and encouraging embryo implantation. Human chorionic gonadotropin (HCG) plays a crucial paracrine role during implantation of embryos. This research aimed to compare the efficacy of PRP and HCG in patients who had previously had unsuccessful implantation.

Materials and methods: A retrospective study was conducted at Wardha Test Tube Baby Centre, Sawangi (Meghe), Wardha, over 1 year. About 40 infertile women with previously failed implantation undergoing frozen-thawed embryo transfer who have a persistently thin endometrial lining (< 7 mm) despite standard hormone replacement therapy were given intrauterine PRP or intrauterine HCG injection and were analyzed and compared. An increment in endometrial thickness (ET) and obstetric outcomes were assessed.

Results: Among the cases assessed, group A exhibited a significantly higher mean ET (7.72 ± 0.33) after intrauterine PRP infusion than group B (7.35 ± 0.31) with intrauterine HCG infusion (*p*-value –0.001). The distribution of implantation rate, clinical pregnancy rate (CPR), and live birth rate was considerably more in the PRP cohort (75, 54.2, and 80%, respectively) than in the HCG group (40, 30.2, and 45%, respectively) (*p*-value < 0.05). Amidst the two groups, there were no appreciable variations in the distribution of the biochemical pregnancy rate (BPR) and miscarriage rate (*p*-value > 0.05).

Conclusion: With intrauterine PRP administration, ET significantly increased along with notable improvements in CPR, IR, and live birth rates (LBR). In our study, the cycle cancellation rate was zero.

Keywords: Clinical pregnancy rate, Endometrial thickness, Human chorionic gonadotropin, Implantation failure, Implantation rate, Live birth rate, Platelet-rich plasma.

Journal of South Asian Federation of Obstetrics and Gynaecology (2024): 10.5005/jp-journals-10006-2487

Introduction

For embryo implantation to be successful, there must be a healthy embryo, a receptive endometrium, a well-coordinated molecular interplay between the two, and immune protection from the recipient. Repeated good-quality embryo transfers culminating in unsuccessful pregnancies are defined as recurrent implantation failure (RIF). Addressing RIF is a challenging endeavor in assisted reproductive technology (ART).

An ideal endometrial thickness (ET) is a crucial element associated with fruitful embryo implantation. When analyzing the optimum ET necessary for implantation, Kasius et al.'s 2014 meta-analysis revealed that the likelihood of clinical pregnancy was substantially lower for an ET <7 mm than in instances with ET >7 mm (23.3 vs 48.1%).[1]

Numerous intrauterine therapies are being recommended to increase endometrial receptivity and aid in embryo implantation in females who have experienced IF. Higher doses or extended use of exogenous estrogen, aspirin at low doses, vaginal sildenafil, pentoxiphylline, endometrial scratching, intrauterine injections of G-CSF, platelet-rich plasma (PRP) and human chorionic gonadotropin (HCG), and are few therapeutic approaches being used to achieve an optimal endometrial lining. A considerable percentage of women who have thin endometrium are resistant to conventional therapeutic approaches.

[1]Department of Obstetrics and Gynaecology, Datta Meghe Institute of Higher Education and Research (DMIHER), Sawangi (Meghe), Wardha, Maharashtra, India

[2]Department of Obstetrics and Gynaecology, JNMC, Sawangi (Meghe), Wardha, Maharashtra, India

[3]Department of Surgery, Mahatma Gandhi Institute of Medical Sciences, Sevagram, Wardha, Maharashtra, India

Corresponding Author: Shrutika S Khapre, Department of Obstetrics and Gynaecology, Datta Meghe Institute of Higher Education and Research (DMIHER), Sawangi (Meghe), Wardha, Maharashtra, India, Phone: +91 9075671355, e-mail: shrutika.khapre.15@gmail.com

How to cite this article: Khapre SS, Shrivastava D, Hivre MD. A Comparison of Platelet-rich Plasma and Human Chorionic Gonadotropin in Enhancing Reproductive Outcomes in Women Who Had Previously Failed Implantation: A Retrospective Cohort Study. J South Asian Feder Obst Gynae 2024;16(Suppl 2):S57–S61.

Source of support: Nil

Conflict of interest: None

For more than 20 years, PRP has already been frequently used in regenerative medicine.[2] It has proregenerative qualities and a four to fivefold higher platelet concentration than the normal range.[2] Platelet-rich plasma contains cytokines, growth factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF), IGF 1, CCL 5, HGF, FGF, and CXCL 12, and cell adhesion molecules.[2] By influencing the production of cytokines like interleukin-6, IL-8, and IL-1b, intrauterine instillation of PRP may increase ET and vascularity, enhance endometrial receptivity, and encourage embryo implantation.[3]

During embryo implantation, HCG plays a crucial paracrine role.[4] Vascular endothelial growth factor, leukemia inhibitory factor (LIF), and matrix metalloproteinase (MMP-9), which are essential elements in the implantation process, are stimulated by intrauterine HCG administration, while macrophage colony-stimulating factor (M-CSF) and insulin-like growth factor binding protein 1 (IGFBP-1) are inhibited (Licht et al., 2007). Human chorionic gonadotropin may facilitate vascular interaction and trophoblast invasion in early pregnancy according to several lines of evidence.[4,5] Human chorionic gonadotropin has been shown to increase immunological tolerance after embryo implantation and can maintain the transformation of human endometrial stromal cells into decidua.[4,6] At least, 500 UI of intrauterine HCG is the dosage that works best.[4]

Information on PRP use in women who have experienced prior IF is scarce. The current study aimed to assess PRP's and HCG's role in women who had experienced prior IF.

Aims and Objectives

Aims

To assess and compare the potential of PRP and HCG intrauterine instillation in enhancing ET and boosting obstetric outcomes during frozen-thawed embryo transfer (FET) in infertile women who had previously failed implantation with suboptimal endometrium and also to compare the potential of HCG in patients who had previously had unsuccessful implantation.

Objectives

- The primary goal of the research project is to compare the efficacy of PRP and HCG intrauterine infusions on the ET during FET in women who have previously experienced implantation failure (IF) with an unfavorable endometrial pattern.
- The secondary objectives are to study the biochemical pregnancy, implantation, clinical pregnancy, and live birth rates (LBRs).

Materials and Methods

We utilized a retrospective cohort design to analyze and contrast the beneficial effects of PRP and HCG instillation into the uterine cavity in 40 infertile women with previously failed implantation undergoing FET conducted following intrauterine PRP or intrauterine HCG injection. The study was conducted at Wardha Test Tube Baby Centre, Sawangi (Meghe), Wardha, over 1 year between February 2022 and January 2023.

Inclusion Criteria

Women with prior IF who have ET persistently less than 7 mm despite standard hormone replacement therapy (HRT). Endometrial thickness was assessed in the uterus sagittal plane at its widest point. To rule out the influence of embryo quality, only blastocysts with Gardner's classification grade of 3BB or higher were transferred.

Table 1: Comparison of age, body mass index, and infertility duration within the study cohorts

	Group A – PRP (n = 20)		*Group B – HCG (n = 20)*	
Parameters	*Mean*	*SD*	*Mean*	*SD*
Age (years)	35.75	6.88	36.55	5.36
BMI (kg/m^2)	27.15	6.43	26.96	3.95
Duration of infertility (years)	10.37	6.03	8.10	5.70

Values are mean and SD, and *p*-value by independent sample *t*-test. *p*-value < 0.05 is considered to be statistically significant. NS, statistically nonsignificant

Exclusion Criteria

Women with a distorted uterine cavity shape due to pathologies like endometrial polyps, submucous fibroids, adhesions, adenomyosis, endometriosis, uterine anomalies, and hydrosalpinx.

Before being enrolled, each participant gave her written consent after being fully informed. The research received approval from the Institutional Ethical Committee of DMIHER (Ref No. DMIHER(DU)/IEC/2023/612).

After ovarian suppression, FET was carried out during an HRT cycle. Patients were distributed into two groups, group A receiving PRP intrauterine injections and group B receiving 1500 IU of HCG intrauterine injections. There were 20 participants per group.

All patients received a dose of 6 mg of oral estradiol per day beginning on day 2 of their menstrual cycle for endometrial preparation. On day 10, a transvaginal ultrasound (TVS) was performed. If ET < 7 mm, PRP or HCG was instilled in the endometrial cavity guided by ultrasound (according to the assigned group). After 48 hours, ET was re-evaluated, and PRP infusion was repeated as necessary. Progesterone injections of 100 mg were administered intramuscularly daily when ET reached more than 7 mm, and blastocyst transfer was conducted on the 6th day.

Autologous PRP was made using blood under sterile circumstances. A syringe containing anticoagulant was used to draw 15 cm^3 of venous blood, which was then centrifuged at 175 gm for 12 minutes to isolate the RBCs. Another empty tube was used to collect the plasma and buffy coat, which was then centrifuged at 1300 gm for 7 minutes. Within an hour of preparation, a volume of 1 mL of PRP was instilled into the uterus.

One vial containing 5,000 IU HCG was dissolved in 5 ccs of distilled water to prepare HCG for intrauterine injection. And 1.5 ccs containing 1500 IU of HCG was instilled into the uterus using an IUI cannula. For 30 minutes, patients were instructed to stay in the lithotomy position. Adequate progesterone support was given. After 2 weeks of embryo transfer, serum β-HCG levels were checked; TVS was done two more weeks later to ensure clinical pregnancy.

An increment in the ET and obstetric outcomes were assessed.

Results

There was no substantial difference in the overall distribution of mean age, body mass index (BMI), and infertility duration among the patients examined in the two cohorts (*p*-value > 0.05) (Table 1).

Among 20 patients in the PRP group, 14 (70.0%) suffered from primary infertility, and 6 (30.0%) had secondary infertility. Of 20 cases in the HCG group, 12 (60.0%) had primary infertility, and

Table 2: Comparison within the study cohorts – median FSH, LH, AMH, and AFC

	Group A – PRP (n = 20)		*Group B – HCG (n = 20)*		
Parameters	*Median*	*Min–Max*	*Median*	*Min–Max*	*p-value*
FSH (mIU/mL)	7.59	1.38–11.12	7.55	1.52–19.20	0.598^{NS}
LH (mIU/mL)	5.77	2.18–10.15	6.61	2.80–12.80	0.588^{NS}
AMH (ng/mL)	0.51	0.06–5.04	0.57	0.03–4.40	0.626^{NS}
AFC	7.0	2–24	7.5	2–14	0.892^{NS}

Values are median and min–max, *p*-value by Mann–Whitney *U* test. *p*-value < 0.05 is considered to be statistically significant. AFC, antral follicle count; NS, statistically nonsignificant

Table 3: Comparison of baseline ET, ET after estrogen priming, and ET before and after PRP/HCG within two groups

	Group A – PRP (n = 20)		*Group B – HCG (n = 20)*		
ET (mm)	*Mean*	*SD*	*Mean*	*SD*	*p-value*
Baseline	4.36	0.62	4.30	0.49	0.735^{NS}
Post-estrogen priming	6.41	0.48	6.34	0.45	0.613^{NS}
Before intervention	6.41	0.48	6.34	0.45	0.613^{NS}
After intervention	7.72	0.33	7.35	0.31	0.001***

Values are mean and SD, and *p*-value by independent sample *t*-test. *p*-value < 0.05 is considered to be statistically significant. ***p*-value < 0.001; NS, statistically nonsignificant

8 (40.0%) had secondary infertility. No obvious distinction between the two study groups could be established in the distribution of infertility types among the cases examined (*p*-value > 0.05, *p*-value by Chi-square test).

Among the 20 cases in the PRP group, 12 (60.0%) had 1–2 IFs, and 8 (40.0%) had more than two failures. Of 20 cases in the HCG group, 14 (70.0%) had 1–2 failures, and 6 (30.0%) had more than two failures. No obvious distinction could be established between the two study groups in the distribution of no. of previous IFs among the cases examined (*p*-value > 0.05, *p*-value by Chi-square test).

The median follicle-stimulating hormone (FSH), luteinizing hormone (LH), anti-mullerian hormone (AMH), and antral follicle count (AFC) distributions of the studied cases did not significantly vary among the two research groups (Table 2).

The mean ET at baseline, mean ET after estrogen priming and before PRP in group A, and mean ET before HCG in group B did not vary substantially among the two research groups.

In the cases assessed, group A exhibited a significantly higher mean ET after intrauterine PRP infusion than group B with intrauterine HCG infusion (Tables 3 and 4).

The PRP cohort exhibited a significantly more notable increase in clinical pregnancy rate (CPR), implantation rate (IR), and LBR as opposed to the HCG cohort (*p*-value < 0.05). Amidst the two groups, there were no appreciable variations in the distribution of BPR and miscarriage rate (MR) (*p*-value > 0.05) (Fig. 1).

None of the cycles were canceled. Platelet-rich plasma or HCG administration did not cause any deleterious effects (Fig. 2).

Discussion

This study is notable for being one of the first to weigh intrauterine instillation of PRP and HCG on ET and assess the reproductive outcomes in women with previous IF with suboptimal endometrium.

Table 4: Analysis of obstetric outcomes within the study cohorts

	Group A – PRP (n = 20)		*Group B – HCG (n = 20)*		
Obstetric outcomes	*N*	*%*	*N*	*%*	*p-value*
Biochemical pregnancy rate	0	0.0	0	0.0	0.999^{NS}
Clinical pregnancy rate	15	75.0	8	40.0	0.025*
Implantation rate (IR)	26	54.2	13	30.2	0.021*
Live birth rate	16	80.0	9	45.0	0.048*
Miscarriage rate	3	15.0	2	10.0	0.999^{NS}

Values are *n* (% of cases), *p*-value by Chi-square test. *p*-value < 0.05 is considered to be statistically significant. NS, statistically nonsignificant

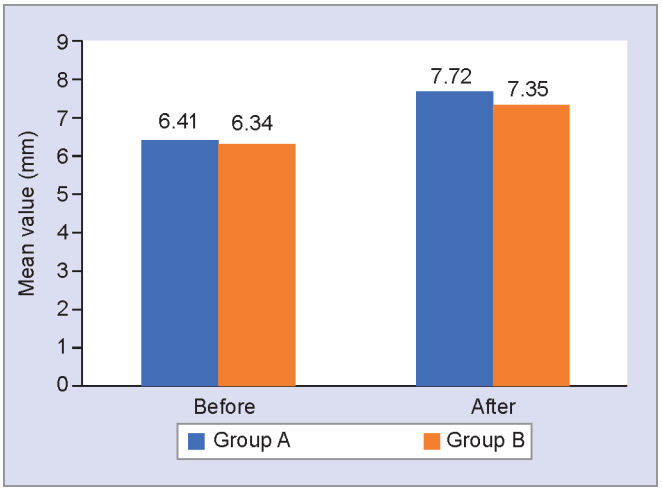

Fig. 1: Comparison of mean ET before and after PRP (Group A)/HCG (Group B) within two groups

There have only been two studies that have reported LBR in unresponsive thin endometrium after PRP administration. Platelet-rich plasma is simple to prepare, inexpensive, and minimally invasive. Platelet-rich plasma has little chance of infection because it is made from autologous blood.

In the present study, the mean ET prior to PRP administration was 6.41 ± 0.48 mm, and after PRP administration, was 7.72 ± 0.33 mm, and the mean ET before HCG administration was 6.34 ± 0.45 mm and after HCG was 7.35 ± 0.31 mm. The mean ET after PRP administration was significantly higher in the cases investigated than the mean ET after HCG.

Dogra Y et al. carried out research in 2022, in which the mean ET prior to PRP administration was 5.83 ± 0.81 mm and after PRP was 7.14 ± 0.54 mm (*p*-value < 0.001) in Fresh IVF cycles. The mean ET prior to PRP administration was 5.52 ± 0.89 mm, and after PRP was 7.14 ± 0.68 mm (*p*-value < 0.001) in FET cycles.[7] Since the mean ET increased significantly following PRP instillation, the conclusions of this study are similar.

In the research conducted by Tandulwadkar SR et al., findings synchronous to our study were noted. The mean ET before PRP administration was 5 mm, and the mean ET following PRP administration was 7.22 mm ($p < 0.00001$).[1]

Our study's results correspond with the 2018 study by Molina A et al., in which ET > 7 mm was observed with the first use, and ET > 9 mm was apparent in all 19 cases following the second PRP administration.[8]

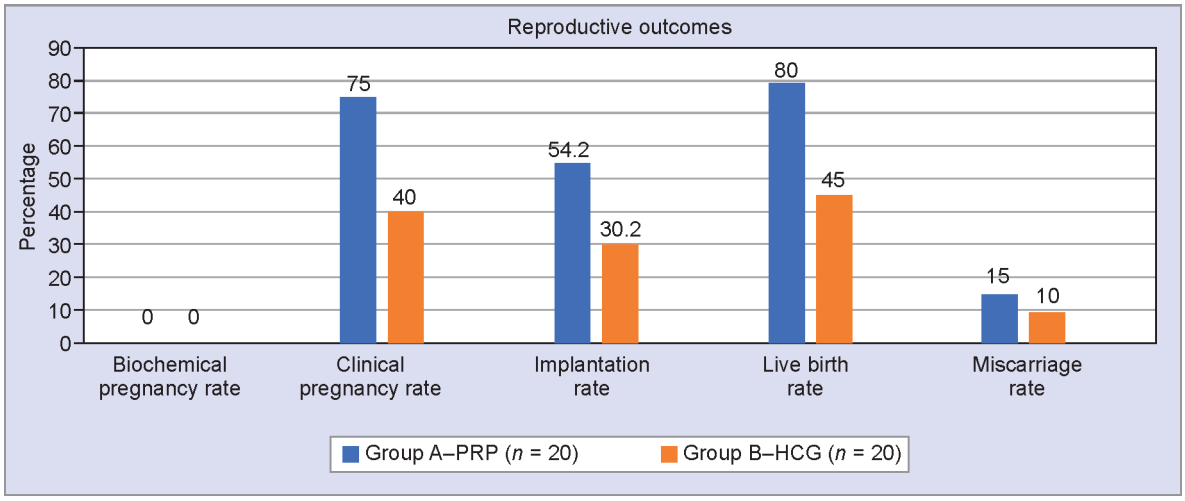

Fig. 2: Analysis of obstetric outcomes within the study cohorts

The mean increase was 0.6 mm in the Kim H et al. study from 2019, and the mean ET after PRP treatment was 6.0 mm. This distinction failed to be statistically significant, in contrast with our research.[9]

In the present study, CPR was 75%, IR was 54.2%, and LBR was 80% in the PRP group, and CPR was 40%, IR was 30.2%, and LBR was 45% among the patients in the HCG cohort. Relative to the HCG cohort, the PRP group's CPR, IR, and LBR were all substantially greater (p-value < 0.05).

Dogra Y et al. carried out research in 2022 in which CPR, IR, and LBR were 25, 13.8, and 33.3%, respectively, in Fresh IVF cycles and 9.1, 3.8 and 9.1% in FET cycles. No particularly noteworthy variation in the CPR, IR, and LBR in FET and fresh IVF cycles was observed. In this study, PRP improved the reproductive outcomes significantly in low-prognosis patients with tuberculosis, diminished ovarian reserve, and polycystic ovarian syndrome (PCOS).[7]

In Tandulwadkar SR et al.'s study (2017), 60.93% of patients had positive beta-hCG values, there were two biochemical pregnancies, and CPR was 45.31%.[1] The findings were in concordance with that of our research.

In the 2018 publication by Molina A et al., findings synchronous to our study were noted. And 73.7% of patients who received two PRP infusions as an adjunctive therapy became pregnant, while 26.3% did not. BPR was 10.5%, OPR was 26.3%, and LBR was 26.3%.[8]

Similar to our study, Kim H et al. in 2019 reported CPR of 30%, IR was 12.7%, and LBR of 20%. The treatment cycle yielded significantly better reproductive outcomes compared with the control cycle.[9]

In the study by Laokirkkiat P et al. in 2018, CPR and LBR were comparable in the hCG and control group (CPR – 42 vs 30%, $p = 0.077$ and LBR – 29 vs 23%, $p = 0.33$). As opposed to the control cohort, the hCG cohort's IR was substantially higher (28.8 vs 18.2%, $p = 0.030$).[10]

The research done by Liu X et al. (2018) observed that the CPR, IR, and LBR in the HCG study group were substantially greater relative to the control cohort (37.5 vs 25.17%, $p = 0.02$; 29.19 vs 19.4%, $p = 0.02$*; and 26.97 vs 17.22%, $p = 0.04$*, respectively). The study had no statistical variance in MR (22.81 vs 26.32%, $p = 0.69$).[11]

In the study done by Torky H et al. in 2022, the BPR, CPR, and IR were substantially more remarkable in the HCG cohort relative to the control cohort using a saline solution as placebo (49 vs 27.1%, $p = 0.007$*; 46.9 vs 22.9%, $p = 0.003$*; and 23.3 vs 13.6%, $p = < 0.001$*, respectively). The study had no statistical variance in MR (2.04 vs 4.2%, $p = 0.755$).[12]

In the Jin XH et al. meta-analysis comparing different intrauterine interventions for women with unexplained IFs, PRP significantly increased CPR (OR 3.78) and HCG (OR 1.80). Platelet-rich plasma also significantly increased the LBR (OR 5.960), but HCG did not. Platelet-rich plasma ranked the highest in improving reproductive outcomes.[2]

Conclusion

With intrauterine PRP administration, ET significantly increased, with notable improvements in CPR, IR, and LBR. In our study, the cycle cancellation rate was zero.

Clinical Significance

A thin endometrium significantly contributes to failed embryo implantation. Patients may be financially and emotionally burdened by RIF or the cancellation of cycles repeatedly due to inadequate endometrial growth or vascularity. Intrauterine PRP administration provides a suitable alternative, enabling these patients with a poor prognosis to have the opportunity to become pregnant by facilitating embryo transfer, which could not have been feasible with only conventional therapy.

Limitations

One of the research study's limitations is that it did not try to pinpoint precisely when intrauterine administration of PRP and HCG would have produced the best results. The research was executed in a retrospective manner. The sample size is small relatively. Selection bias was probable as patient recruitment was discretionary on the part of the clinician. High pregnancy rates in donor IVF cycles have been documented, which may cause prejudice. Our study did not evaluate sub-endometrial vascularity, endometrial pattern, and endometrial volume.

Acknowledgments

All authors contributed significantly to the project, including conceptualization, data analysis, manuscript drafting, and approval of the final version for publication. They are committed to ensuring the accuracy and integrity of the work.

Orcid

Shrutika S Khapre https://orcid.org/0000-0003-2227-8612
Deepti Shrivastava https://orcid.org/0000-0003-2058-9476
Mangesh D Hivre https://orcid.org/0000-0002-7694-7108

References

1. Tandulwadkar SR, Naralkar MV, Surana AD, et al. 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.
2. Jin XH, Li Y, Li D. Intrauterine interventions for women with two or more implantation failures: A systematic review and network meta-analysis. Front Endocrinol 2022;13:959121. DOI: 10.3389/fendo.2022.959121.
3. Mouanness M, Ali-Bynom S, Jackman J, et al. Use of intra-uterine injection of platelet-rich plasma (PRP) for endometrial receptivity and thickness: A literature review of the mechanisms of action. Rep Sci 2021;28:1659–1670. DOI: 10.1007/s43032-021-00579-2.
4. Conforti A, Longobardi S, Carbone L, et al. Does intrauterine injection of hCG improve IVF outcome? A systematic review and a meta-analysis. Int J Mol Sci 2022;23(20):12193. DOI: 10.3390/ijms232012193.
5. d'Hauterive SP, Close R, Gridelet V, et al. Human chorionic gonadotropin and early embryogenesis. Int J Mol Sci 2022;23(3):1380. DOI: 10.3390/ijms23031380.
6. Sha J, Liu F, Zhai J, et al. Alteration of Th17 and Foxp3+ regulatory T cells in patients with unexplained recurrent spontaneous abortion before and after the therapy of hCG combined with immunoglobulin. Exp Ther Med 2017;14(2):1114–1118. DOI: 10.3892/etm.2017.4574.
7. Dogra Y, Singh N, Vanamail P. Autologous platelet-rich plasma optimizes endometrial thickness and pregnancy outcomes in women with refractory thin endometrium of varied aetiology during fresh and frozen-thawed embryo transfer cycles. JBRA Assist Reprod 2022;26(1):13–21. DOI: 10.5935/1518-0557.20210037.
8. Molina A, Sánchez J, Sánchez W, et al. Platelet-rich plasma as an adjuvant in the endometrial preparation of patients with refractory endometrium. JBRA Assist Reprod 2018;22(1):42–48. DOI: 10.5935/1518-0557.20180009.
9. Kim H, Shin JE, Koo HS, et al. 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.
10. Laokirkkiat P, Thanaboonyawat I, Boonsuk S, et al. Increased implantation rate after intrauterine infusion of a small volume of human chorionic gonadotropin at the time of embryo transfer: A randomized, double-blind controlled study. Arch Gynecol Obstet 2019;299(1):267–275. DOI: 10.1007/s00404-018-4962-7.
11. Liu X, Ma D, Wang W, et al. Intrauterine administration of human chorionic gonadotropin improves the live birth rates of patients with repeated implantation failure in frozen-thawed blastocyst transfer cycles by increasing the percentage of peripheral regulatory T cells. Arch Gynecol Obstet 2019;299(4):1165–1172. DOI: 10.1007/s00404-019-05047-6.
12. Torky H, El-Desouky ES, El-Baz A, et al. Effect of intra uterine granulocyte colony stimulating factor vs human chorionic gonadotropin at ovum pick up day on pregnancy rate in IVF/ICSI cases with recurrent implantation failure. JBRA Assist Reprod 2022;26(2):274–279. DOI: 10.5935/1518-0557.20210056.