International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Nayak SK et al. Int J Reprod Contracept Obstet Gynecol. 2025 Mar;14(3):736-740
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20250355

Original Research Article

Comparison of effect of autologous platelet rich plasma and estrogen replacement vs estrogen replacement alone on implantation and pregnancy outcome in IUI cycles in infertility patients

Suvendu Kumar Nayak[1], Baidyanath Pathak[2]*

[1]Department of Obstetrics and Gynecology, 166 Miliary Hospital, Satwari Cantt. Jammu, Jammu and Kashmir, India
[2]Department of Obstetrics & Gynaecology, Manipal Tata Medical College, Jamshedpur, Jharkhand, India

Received: 17 January 2025
Revised: 02 February 2025
Accepted: 03 February 2025

***Correspondence:**
Dr. Baidyanath Pathak,
E-mail: bpathak_go@yahoo.co.in

ABSTRACT

Background: Successful embryo implantation requires an appropriate embryonic development coincident with a receptive endometrium. Thin endometrium, non-responsive to standard treatments is still a challenge in assisted reproductive technique, which usually results either in cycle cancellation or failed ART cycle. The minimal endometrial thickness required for implantation is now considered about 7 mm at the end of natural or medically induced follicular phase. The aim of this study is to detect any significant effect of platelet rich plasma (PRP) intrauterine infusion on endometrial proliferation, implantation and pregnancy rates.
Methods: This study was carried out for a period of 12 months in a tertiary care post graduate teaching hospital. 50 patients fulfilling the inclusion criteria were divided into two groups based on randomisation. One group received PRP plus estradiol (Group P) and other group received only estradiol (Group E). All patients underwent ovulation induction with letrozole and serial monitoring of endometrial thickness was done by USG (TVS) and results were compared.
Results: The mean endometrial thickness on the day of IUI in Group P was 9.1 mm+0.67 mm and in Group E was 7.56 mm+0.62 mm. The mean increase in endometrial thickness after PRP instillation was 3.4 mm+0.60 mm which is significantly higher than the Group E with mean increase of 1.5 mm+0.9 mm, which was statistically significant. However, there was no statistically significant increase in positive pregnancy rate and pregnancy outcome.
Conclusions: Our study concluded that PRP instillation increased the endometrial thickness in the patients with thin endometrium. However, there was no effect on the positive pregnancy rates and outcome.

Keywords: Endometrial thickness, Estradiol, Infertility, Platelet rich plasma

INTRODUCTION

Optimum endometrial condition is essential for successful embryonic implantation and development.[1] Many times thin endometrium poses a challenge in ART and leads to cancellation of the cycle or failure of the cycle.[2] Approximately 7 mm of endometrial thickness at the end of follicular phase is considered to be adequate for successful implantation. This applies to both for natural cycles as well as medically induced cycles. However, various studies have suggested the cutoff values between 7 and 10 mm for successful implantation.[3-5] Platelet-rich plasma (PRP), prepared from fresh whole blood of the individual, contains various factors like vascular endothelial growth factor (VEGF), transforming growth factor (TGF), platelet-derived growth factor (PDGF) and epidermal growth factor (EGF).[8-10] They can regulate cell migration, attachment, proliferation, differentiation and promote extracellular matrix accumulation.[8-10] PRP leads to production of various cytokines and growth factors (GFs) which cause proliferation of endometrium.[6,7] Studies have suggested that intra uterine infusion of

autologous PRP increases endometrial thickness and increases chances of implantation and pregnancy rate. PRP intrauterine infusion might be a new alternative for patients with poor endometrial growth, although more evidence is required before it becomes a routine practice in cases of thin endometrium.[11,12]

The aim of this case control study is to detect any significant effect of PRP intrauterine infusion on endometrial proliferation, implantation and pregnancy rates.

METHODS

This case control study was carried out for a period of one year in the department of Obstetrics and Gynaecology at Command Hospital Air Force, a tertiary care PG teaching hospital in Bangalore, India, for a period of 12 months from November 2017 to October 2018.

50 infertility cases with endometrial thickness<7 mm undergoing IUI were included in the study. Patients with congenital or acquired uterine anomaly and unruptured follicle despite HCG trigger were excluded from the study. These patients were divided into two groups with intrauterine infusion of PRP along with estradiol to one group (Group P) and only estradiol to another group (Group E).

Controlled ovarian stimulation was done with tab let Letrozole 5 mg OD from D2 to D6 of the cycle. Estradiol valerate 6 mg/day (2 mg TDS) was started with follicle size more than 14 mm but endometrial thickness less than 7 mm.

Serial monitoring of the follicle size and endometrial thickness were carried out. Ovulation trigger with Inj HCG 10, 000 IU was given with follicle size≥18. IUI done only once for all the cases 32-36 hours after the HCG trigger. Semen sample was prepared using double gradient centrifugation along with swim-up technique (DGC+SWIM-UP) and 0.5 ml of processed semen used for IUI. Estradiol valerate and progesterone supplementation were continued for 2 weeks after IUI and if the serum βHCG was positive, progesterone support was continued till 12 weeks of gestation.

For the study group with endometrial thickness of<7 mm on day of ovulation trigger, were administered 0.5 ml of PRP through intrauterine catheter by slow infusion. PRP was prepared from autologous blood using a two-step centrifuge process. 10 ml of peripheral venous blood was drawn in the syringe that contained 1.5 ml of Acid Citrate Dextrose-A Anticoagulant solution (ACD-A) and centrifuged immediately at 1200 rpm for 12 min (soft spin) to separate the red blood cells. The supernatant plasma was transferred into a sterile tube without anticoagulant, was centrifuged again at 3300 rpm for 7 min (hard spin) to obtain a platelet concentrate. The lower 1/3rd is PRP and upper 2/3rd is platelet poor plasma (PPP). PPP were removed and the platelet pellet suspended in minimum quantity (1 ml) of plasma by gently shaking the tube to obtain PRP. Then, 0.5 ml of PRP was infused into the uterine cavity with the IUI catheter. Endometrial thickness was then assessed by routine vaginal ultrasound before infusion and again at the time of IUI.

The primary outcome was the increase in the endometrial thickness on the day of IUI as compared to the day of HCG trigger and the secondary outcomes were pregnancies, determined by positive serum βHCG, 2 weeks after IUI and the presence of fetal heartbeat in the transvaginal ultrasound. These pregnancies were followed till delivery to know the pregnancy outcomes.

Statistical analysis was done using chi square test.

RESULTS

A total 50 patients were divided into two groups, Group P (PRP and Estrogen) and Group E (Estrogen only) with 25 patients in each group. The age of patients was comparable, ranging from 22 to 35 years. The mean age in Group P was 29.32 (SD+2.84) whereas in Group E was 29.42 (SD+3.01) with p=0.100 (Table 1).

The total number of primary infertility and secondary infertility in the PRP group were 17 (68%) and 08 (32 %) respectively. Whereas the number of primary and secondary infertility Estrogen only group were 20 (80%) and 5 (20%) respectively. Both the groups remained comparable with p value>0.05 (Table 2).

Table 3 shows various female factors contributing to infertility in both the groups without any statistically significant difference between the groups.

Table 4 shows various male factors contributing to infertility in the study populations without any statistically significant difference between the Group P and Group E.

Table 5 shows the number of IUI cycles for patients of both the groups. The number of IUI cycles in both the groups remained comparable.

Mean endometrial thickness (ET) on day 2 and on the day of ovulation trigger table 6. The mean ET on day 2 in group P and group E were 3.06±0.73 mm and 3.34±0.06 mm respectively which were comparable. The ET on the day of ovulation trigger were 5.70±0.44 mm and 6.06±0.53 mm respectively which also remained comparable.

Increase in ET

The mean ET and increase of mean ET on the day of IUI has been shown in table 7. The mean ET on the day of IUI were 9.1±0.67 mm and 7.56±0.62 mm in group P and in group E respectively. The mean increase in ET were 3.4±0.67 mm and 1.5±0.9 mm in group P and group E respectively. The 95% Of CI is 1.465 to 2.335 and the p

value is<0.0001 which indicate that the increase in ET in group P is statistically significant. This implies that PRP instillation increases the endometrial thickness significantly.

Positive pregnancy

Out of the 25 patients in each group, 03 (12%) and 02 (08%) patients had positive pregnancy in group P and group E respectively. However, this was not statistically significant. 02 (08%) in group P and 01 (04%) in group E had progressed to term gestation and 01 (04%) had abortion in each group. This finding is also not statistically significant.

Table 1: Age distribution of patients studied.

Age (in years)	Group P		Group E		
	No	%	No	%	
21-25	8	32.0	06	24.0	P=0.100
26-30	10	40.0	11	44.0	
31-35	7	28.0	8	32.0	
Total	25	100.0	25	100.0	
Mean±SD	29.32±2.84		29.42±3.01		

Table 2: Distribution of type of infertility in each group.

Infertility	Group P		Group E		P value
	No	%	No	%	
Primary	17	68.0	20	80.0	0.3334
Secondary	08	32.0	05	20.0	
Total	25	100.0	25	100.0	

Table 3: Distribution of patients according to female factors in each group.

Female factors	Group P (n=25)		Group E (n=25)		P value
	No	%	No	%	
Normal	22	88	21	84	0.5273
Ovarian	3	12	3	12	
Tubal	-	-	1	4	
Total	25	100	25	100	

Table 4: Distribution of patients according to male factors in each group.

Factors	Group P (n=25)		Group E (n=25)		P value
	No	%	No	%	
Normal	20	80	22	88	0.7782
Oligozoospermia	3	12	1	4	
Asthenozoospermia	1	4	2	8	
Azoospermia	1	4	0	0	
Total	25	100	25	100	

Table 5: Distribution of patients according to IUI cycle in each group.

Intra-uterine insemination cycle number	Group P (n=25)	Group E (n=25)	P value
First	3 (12%)	7 (28%)	0.3730
Second	9 (36%)	10 (40%)	
Third	11 (44%)	6 (24%)	
Fourth	2 (8%)	2 (8%)	
Total	25 (100%)	25 (100%)	

Table 6: Mean endometrial thickness on day 2 of cycle in each group.

	Mean ET day 2	Mean ET on the day of ovulation trigger
Group P	3.06±0.73 mm	5.70±0.44 mm
Group E	3.34±0.6 mm	6.06±0.53 mm

Table 7: Mean ET and increase in ET on the day of IUI in each group.

	Mean ET on the of ovulation trigger	Mean ET on the day of IUI	Mean Increase in ET
Group P	5.70±0.44 mm	9.1±0.67 mm	3.4±0.60 mm
Group E	6.06±0.53 mm	7.56±0.62 mm	1.5±0.9 mm

95% of CI–1.465 to 2.335, P<0.0001

DISCUSSION

The minimal endometrial thickness required for implantation, has been considered to be about 7 mm. Intrauterine infusion of platelet-rich plasma (PRP) can increase endometrial thickness by virtue of containing various growth factors in higher concentration. This could be ap option for treatment of thin endometrium, specifically in cases where thin endometrium is the only detectable factors hampering success of infertility treatment.

The total number of patients included in the study were more compared to a study by Zadehmodarres et al, which included only 10 cases and like the study by Kim et al, where 24 women were recruited in each group.[11,13]

The age of the patients in this study ranged from 22 to 35 years. The mean age in Group P was 29.32 (SD+2.84) whereas in Group E it was 29.42 (SD+3.01), which is

comparable with Zadehmodarres et al, where the mean age was 31.3 years.[11] Primary infertility was the most common type in both the groups. The number of primary infertility and secondary infertility in the study were 17 (68%) and 08 (32 %) in the Group P respectively. The number of primary and secondary infertility in group E were 20 (80%) and 5 (20%) respectively. These numbers are more as compared to the study by Zadehmodarres et al where three patients had primary infertility and seven cases were secondary infertility.[11]

A total 03 (12%) had ovarian factor of infertility in group P, 01 (04%) tubal factors of infertility in group E. PCOS was the most common cause in both the groups. In comparison with our study, the study conducted by Shahrzad Zadehmodarres et al, had four cases of PCOS and Endometriosis in one patient and tubal factor in one patient. Similar study conducted by Yajie Chang et al, in their study had one case of Asherman syndrome and 3 cases of PCOS and 2 cases of Salpingitis. These two studies had similar female factor profile in comparison to our study.[14] Oligozoospermia was the most common cause in both the groups. Overall, 4 cases had oligozoospermia, 3 cases had Asthenozoospermia and one case of Azoospermia which is in comparison to Hounyoung Kim et al, where male factor contributing to the infertility was seen in 6 cases of the 24 cases.[13]

The mean increase in endometrial thickness after PRP instillation was 3.4 mm+0.60 mm which is significantly higher than the group E with estrogen alone which has shown increase in endometrial thickness by 1.5 mm±0.9 mm. These results are similar as compared to study conducted by Zadehmodarres et al, where the endometrial thickness was 4 mm, 6.1 mm, 7.2 mm in before PRP, 48 hr after first PRP instillation and 48 hr after second PRP instillation respectively.[11] Similar study conducted by Tandulwadkar et al, found that the mean pre-PRP endometrial thickness (ET) was 5 mm which significantly increased to 7.22 mm post-PRP.[15]

There was statistically significant difference in the endometrial thickness from day of trigger / PRP instillation to the endometrial thickness on the day of IUI. The study conducted by Obidniak et al, also found that the endometrial thickness was significantly higher in the study group (OR=2.91, 95% CI 1.37-7.21, p<0.05). The endometrium increased from 6.52 mm to 6.76 mm in control group and 7.56 mm to 9.18 mm in test group who received PRP.[16]

In our study 3 (12%) pregnancies were confirmed in the test group who received PRP. Out of three cases who conceived, one case had spontaneous abortion at 6 weeks POG and other two cases delivered at term. The calculated p value is 0.7378 which indicates no significant association of PRP instillation with pregnancy outcome (term gestation and abortion). The above findings were compared with the study conducted by Sunita R Tandulwadkar et al, where positive beta hCG rate was 60.93% and the clinical pregnancy rate was 45.31%.[15] We had 2 deliveries, both the deliveries were term deliveries. Both the cases who delivered had an uneventful delivery with normal birth weight.

These results were different from the results noted by Tandulwadkar et al and Obidniak et al, who stated that the clinical pregnancy rate was higher in the study group (53.3% vs 24.4%) (OR=3.63, 95% CI 1.48-8.90, p<0.01) in whom intrauterine perfusion with autologous PRP was administered.[15,16] The implantation rate differed significantly; in the study group it revealed 40.5% and in the control group - 20.9% (OR=2.43, 95% CI 1.13-5.21, p<0.05).[16]

However, our study had the similar results to the study conducted by A Madhavan et al, who found that the intrauterine PRP does not increase the implantation rates / clinical pregnancy rates.[17]

Kumbak et al, found that the pregnancy rate (PR) and implantation rate (IR) did not show a statistically significant difference though an increasing trend in increased endometrial thickness was observed.[18] A contrary view was given by Kasius et al, in 2014 based on a systemic review and meta-analysis which found no statistically significant improvement in the pregnancy rates.[19]

Small number of cases (25 in each arm) and short duration of the study remained the main limitations of the study. More studies with larger number of cases spanning over longer duration should be conducted to have clearer picture of beneficial role of PRP in this field.

CONCLUSION

Intrauterine instillation of PRP along with estrogen increases endometrial thickness. However, no significant increase in the pregnancy rates have been observed in our study. The lower pregnancy rate could be because of other factors related to infertility like poor semen quality, undetermined endometrial receptivity and other unexplained factors.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Teh WT, McBain J, Rogers P. What is the contribution of embryo-endometrial asynchrony to implantation failure. J Assis Reprod Gen. 2016;33(11):1419-3140.
2. Eftekhar M, Tabibnejad N, Tabatabaie AA. The thin endometrium in assisted reproductive technology: An ongoing challenge. Middle East Fert Soc J. 2018;23(1):1-7.

3. Cruz F, Bellver J. Live birth after embryo transfer in an unresponsive thin endometrium. Gynecological Endocrinol. 2014;30(7):481-4.
4. Mahajan N, Sharma S. The endometrium in assisted reproductive technology: How thin is thin. J of Human Reprod Sciences. 2016;9(1):3.
5. Papanikolaou EG, Kyrou D, Zervakakou G, Paggou E, Humaidan P. Follicular HCG endometrium priming for IVF patients experiencing resisting thin endometrium. A proof of concept study. J Assi Reprod Gen. 2013;30(10):1341-5.
6. Pietrzak WS, Eppley BL. Platelet rich plasma: biology and new technology. J Craniofac Surg. 2005;16(6):1043-54.
7. Eppley BL, Woodell JE, Higgins J. Platelet quantification and growth factor analysis from platelet-rich plasma: implications for wound healing. Plastic and reconstructive surgery. 2004;114(6):1502-8.
8. Weibrich G, Kleis WK, Hafner G, Hitzler WE. Growth factor levels in platelet-rich plasma and correlations with donor age, sex and platelet count. J Cranio-Maxillofac Surg. 2002;30(2):97-102.
9. Marx RE. Platelet-rich plasma: evidence to support its use. J Oral and Maxillofac Surg. 2004;62(4):489-96.
10. Eppley BL, Pietrzak WS, Blanton M. Platelet-rich plasma: a review of biology and applications in plastic surgery. Plastic Reconst Surg. 2006;118(6):147-59.
11. Zadehmodarres S, Salehpour S, Saharkhiz N, Nazari L. Treatment of thin endometrium with autologous platelet-rich plasma: a pilot study. JBRA. 2017;21(1):54.
12. Bos-Mikich A, de Oliveira R, Frantz N. Platelet-rich plasma therapy and reproductive medicine. J Ass Reprod and Gen. 2018;35(5):753-6.
13. 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. 2019;10:12-9.
14. 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 Experimen Med. 2015;8(1):1286.
15. 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 Human Reprod Sci. 2017;10(3):208.
16. Obidniak D, Gzgzyan A, Feoktistov A, Niauri D. Randomized controlled trial evaluating efficacy of autologous platelet-rich plasma therapy for patients with recurrent implantation failure. Fertility and Ster. 2017;108(3):370.
17. Madhavan A, Naidu P, Rani KK, Kaur J, Mahajan N. Intrauterine autologous platelet-rich plasma therapy to improve implantation rates in patients undergoing frozen embryo transfer: A pilot study. The Onco Fertility J. 2018;1;1(2):81.
18. Kumbak B, Erden HF, Tosun S, Akbas H, Ulug U, Bahçeci M. Outcome of assisted reproduction treatment in patients with endometrial thickness less than 7 mm. Reprod Biomed. 2009;18:79–84.
19. Kasius A, Smit JG, Torrance HL, Eijkemans MN, Mol BW, Opmeer BC. Endometrial thickness and pregnancy rates after IVF. A systematic review and analysis. Hum Reprod Update. 2014;20:530-41.

Cite this article as: Nayak SK, Pathak B. Comparison of effect of autologous platelet rich plasma and estrogen replacement vs estrogen replacement alone on implantation and pregnancy outcome in IUI cycles in infertility patients. Int J Reprod Contracept Obstet Gynecol 2025;14:736-40.