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Original Article

Efficacy of Subendometrial Platelet-Rich Plasma Infusion on Endometrial Thickness and Vascularity in Frozen Embryo Transfer

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ABSTRACT

Background: Although various groups have reported the effects of intrauterine infusion of platelet-rich plasma, studies evaluating the effectiveness of injecting it hysteroscopically at the endomyometrial junction are limited. The latter has more effects on the angiogenic growth of cells. Platelet-rich plasma contains a high concentration of vascular endometrial growth factors and cytokines which are essential for endometrial proliferation. These are inadequately expressed in a deficient endometrium and are enhanced after its administration. The objective of the study was to assess the effect of subendometrial injection of autologous platelet-rich plasma treatment on endometrial thickness and vascularity on refractive endometrium during frozen embryo transfer. **Materials and Methods:** Data was collected from 232 women with endometrial thicknesses less than or equal to 7mm. Pre, post endometrial thickness and vascularity were assessed before and after platelet rich plasma administration. **Results:** Among 232 women, 8 were lost in follow-up. Among 224 women, endometrial thickness increased for 152, was not changed for 35, and decreased for 37. The mean endometrial thickness prior to infusion was 5.9mm which was significantly improved to 6.6mm after platelet-rich plasma infusion. Endometrial vascularity significantly improved for 124 women and decreased for 11 with no improvement observed in 89 women after platelet-rich plasma administration. **Conclusion:** Subendometrial administration of platelet-rich plasma has effectively improved the thickness and vascularity of endometrium thereby helping in pregnancy outcomes. Further in-depth molecular studies are required to interpret this therapy's specific mechanism and beneficial role on the endometrium.

Keywords: Platelet-rich plasma, Frozen embryo transfer, Subendometrial injection, Endometrial thickness, Endometrial vascularity.

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INTRODUCTION

The advent of technology has brought significant advances in *in vitro* Fertilization (IVF) techniques and embryo transfer. Recent research findings have thrown new light on the importance of the assessment of Endometrial Thickness (EMT) and its effect on assisted reproductive technology outcomes.[1] With both fresh as well as frozen embryo transfers, a reduction in positive pregnancy outcomes was observed with a decrease in endometrial thickness.[2] EMT less than 7 mm is regarded inadequate for embryo transfer and is associated with reduced pregnancy outcome.[3,4] Thin endometrium can result from inflammatory and iatrogenic causes. Reduced vascularity and estradiol values can inhibit endometrial growth. Inherent endometrial thinness has also been noted as a causative factor.[5] Studies by I. Miwa *et al.*[6] have noted the distinguishing features of thin endometrium as having a drastic reduction in glandular epithelial growth, vascular endothelial growth factor expression, vascular development, and enhanced uterine blood flow impedance. Endometrial receptivity is widely regarded as a key factor in the success of IVF. Several sonographic parameters have shown promising application in the positive establishment of endometrial receptivity encompassing endometrial thickness, pattern, volume, as well as endometrial and subendometrial blood flow.[7,8] Among these, endometrial thickness and endometrial pattern have been widely accepted as prognostic indicators for endometrial receptivity.

To enhance the thickness and receptivity of the endometrium, several treatment options are available to patients with thin endometrium. These approaches comprise hormonal management by estradiol, tamoxifen, human chorionic gonadotropin and gonadotropin-releasing hormone agonists,

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vasoactive agents such as aspirin, vitamin E, pentoxifylline, and sildenafil, intra-uterine infusion of a growth factor such as Granulocyte Colony Stimulating Factor. Recent approaches include Platelet-Rich Plasma (PRP) therapy, electrical stimulation, regenerative medicine, and the presentation of endometrial receptivity array.[1-3,9,10] Out of these, autologous platelet-rich plasma transfusion was considered a safer method.

Platelet-rich plasma is blood plasma prepared from fresh whole blood that has been supplemented with platelets. It is collected from peripheral veins and contains several cytokines and growth-promoting factors.[11,12] Platelets play a major role in hemostasis. The secreted platelet proteins enhance cell migration, proliferation, and angiogenesis thereby helping in tissue regeneration.

Recently, PRP has been commonly applied in different clinical situations. For the first time Chang *et al.*, introduced the administration of platelet-rich plasma within the uterus as a new and effective treatment approach for thin endometrium.[12] Animal studies have shown regrowth of damaged endometrium and reduction in fibrosis as a result of autologous PRP therapy.[13] Further studies showed the occurrence of endometrial growth as well as successful pregnancy after PRP infusion.[14]

While there are many studies on the effect of intrauterine infusion of platelet-rich plasma, few studies exist on evaluating the effectiveness of injecting PRP hysteroscopically at the endomyometrial junction. Later has more effect on angiogenic growth cells. Further, the existing studies were characterized by a small study sample. So this study was carried out in a larger sample to assess whether subendometrial injection of autologous platelet-rich plasma enhances endometrial receptivity by improving endometrial thickness and vascularity in frozen embryo transfers.

MATERIALS AND METHODS

Study population

This clinical study assessed the efficacy of platelet-rich plasma therapy on refractive endometrium in 232 patients who were scheduled for frozen embryo transfers from December 2019 to August 2022. After getting the IEC approval patients fulfilling the inclusion and exclusion criteria were selected for the study and an informed written consent form was obtained from all the participants. 224 patients' data were included in the study out of 232 patients. The inclusion criteria encompassed patients diagnosed with a thin endometrium (less than or equal to 7mm), female partner age between 21-45 years, own oocyte and husband sperm, frozen thaw cycle for embryo transfer, good quality embryos, vascularity zone 1 and 2 as per Applebaum's criteria, normal parental karyotype, previous failed embryo transfer, body mass index less than 30 kg/m^2 and good quality oocyte and sperm. Patients with congenital uterine abnormalities, donor oocyte/donor sperm, acquired uterine abnormalities (Asherman's syndrome, Genital tuberculosis), female partner age more than 46 years, poor quality embryos, gross hydrosalpinges, body mass index equal to or more than 30kg/m^2, uncontrolled endocrine disorders (diabetes mellitus, hypothyroidism), autoimmune disorders, hematological disorders, chromosomal abnormality for the male or female partner, severe male infertility and male partner age more than 55 yrs were excluded.

Study Procedure

On the day of administration of PRP 18mL of venous blood was collected from the patients using 30mL syringes coated with 2cc of acid citrate. The blood sample was centrifuged at 1017G for 3 min. The buffy coat and the plasma above the buffy coat were collected and 0.7-1.0 mL of PRP was injected into the uterine cavity. Patients had subendometrial injections of PRP under hysteroscopic guidance from day 6 to day 10 of the menstrual cycle. A total of 4 mL of PRP was injected into the subendometrial region of the uterine cavity with an ovum pickup needle under hysteroscopic guidance- in all four walls of the cavity 1.0 mL in each wall. Optimum instillation was ensured by keeping the beveled edge of the needle up in a slanting position, marking the needle helps to determine the depth of the penetration of the needle. No leakage of injected fluid was seen on the withdrawal of the needle. PRP was injected within 30 min of preparation and estradiol valerate 2mg was given thrice daily post-PRP for the next 15 days. Endometrial preparation and embryo transfer followed.[15,16]

Statistical Analysis

The comparison of endometrial thickness and vascularity before and after PRP was carried out by using Paired *t*-test at a 5% level of significance. FET was done for 137 women and the outcome was analyzed.

RESULTS

A total of 232 women were given PRP and 8 women were lost to follow-up. Endometrial thickness was found to be increased in 152, not changed in 35, and decreased in 37 women. Mean endometrial thickness was 5.8 mm before PRP and 6.7 mm after PRP. There is a statistically significant difference observed in endometrial thickness after PRP at 0.05 significance level and confidence interval (-0.663+0.11). T statistic = 1.653813 *p* value = 0.000282 (Figure 1 and Table 1).

Endometrial vascularity improved in 124 and decreased in 11 whereas no improvement was noted in 89 women. There is a statistically significant difference observed in endometrial vascularity after PRP at 0.05 significance level and confidence interval (-0.33+0.092). T statistic = 1.653813, the *p*-value is 0.000254 (Figure 2 and Table 2).

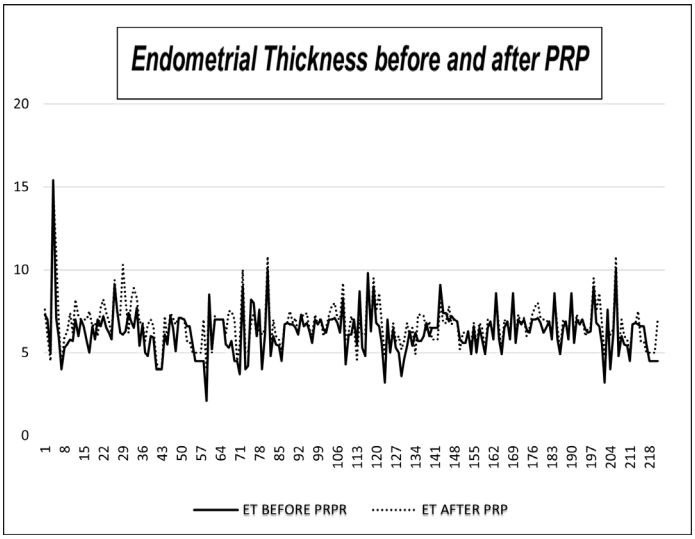

Figure 1: Trend on Endometrial Thickness before and after PRP.

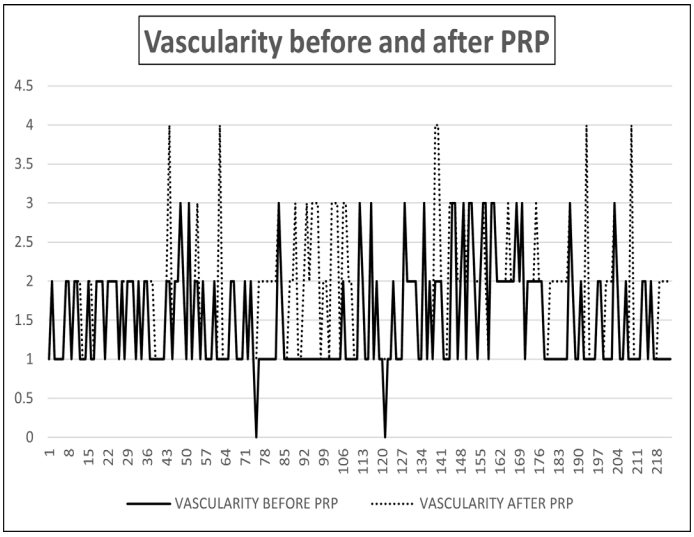

Figure 2: Trend on Vascularity before and after PRP.

Table 1: Endometrial thickness before and after PRP.

T-Test: Paired Two Sample for Means		
	ET before PRP	*ET after PRP*
Mean	5.874884	6.747674419
Variance	0.779419	0.900286958
Observations	224	224
Pearson Correlation	0.613044	
Hypothesized Mean Difference	0	
Df	171	
t Stat	-10.7598	
P(T<=t) one-tail	0.000282	
t Critical one-tail	1.653813	
P(T<=t) two-tail	6.02E-21	
t Critical two-tail	1.973934	

*ET-Endometrial thickness, PRP- Plasma Rich Protein.

Table 2: Vascularity before and after PRP.

T-Test: Paired Two Sample for Means		
	Vascularity befire PRP	*Vascularity after PRP*
Mean	1.582213	1.921230
Variance	0.540562	0.518802
Observations	224	224
Pearson Correlation	0.556058	
Hypothesized Mean Difference	0	
Df	171	
t Stat	-6.44794	
P(T<=t) one-tail	0.000254	
t Critical one-tail	1.653813	
P(T<=t) two-tail	1.12E-09	
t Critical two-tail	1.973934	

*PRP- Plasma Rich Protein.

Out of 224 women treated with PRP, FET was done for 147. 69 had Beta-Human Chorionic Gonadotropin (BHCG) of more than 25mIU/mL which was considered as positive that is 46.9% and 62 exhibited Clinical Pregnancy Rate (CPR) which corresponds to 42.1%. Six had blighted ovum, and cardiac activity did not establish for three. Out of 7 women, who had BHCG levels less than 100mIu/mL, 4 had biochemical pregnancy, and cardiac activity was established for 3. CPR was 41.08% in the group with an increase, 38.01% with a decrease, and 36.6% in the group with no change in endometrial thickness. Similarly, the CPR was 43.01% in women with increased, 42.4% in those with decreased, and 39.7% in the group with no change in vascularity.

DISCUSSION

PRP has been noted as a successful regenerative therapy for various gynaecological disorders and a promising strategy for treating endometrial receptivity.[17,18] It was known to have a beneficial effect on the growth of both endometrium as well as follicles, especially in elderly women with unresponsive endometrium. Because of its autologous nature, there were fewer occurrences of adverse reactions.[19]

The objective of the current study was to assess whether the subendometrial intrauterine administration of PRP enhances the endometrial thickness and vascularity thereby enhancing

its receptivity. A total of 224 women were assessed and frozen embryo transfer was done for 147. The endometrial thickness and vascularity were found to be improved post-PRP infusion. Although various groups have reported the efficacy of intrauterine PRP transfusion, studies evaluating the effectiveness of injecting PRP hysteroscopically at the endometrial junction were limited. The latter has more effect on the angiogenic growth of cells. PRP contains high concentrations of vascular endothelial growth factor, epidermal growth factor, platelet-derived growth factor, leukemia inhibiting factor, beta 3 integrin, transforming growth factor, and cytokines which are indispensable for endometrial proliferation. Studies have shown that these factors are insufficiently present in a defective endometrium and their levels are augmented after PRP administration.[12,20]

The receptivity of the uterine endometrium is extensively regulated by several cytokines, transcription factors, and genes at the molecular level.[21] Out of many cytokines, Leukemia Inhibitory Factor (LIF) was proven to have a major role in preparing the uterine lining for the implantation of the embryo.[22,23] Mice with deficient LIF exhibited poor implantation which was significantly enhanced with LIF administration.[24,25] PRP administration increased the expression of LIF in the stromal cells of uterine endometrium which might have improved the receptivity of endometrium and may improve the placentation of trophoblasts.[26]

In patients having a previous occurrence of poor endometrial growth in FET cycles, intrauterine administration of platelet-rich plasma increased endometrial thickness and 50% of patients achieved pregnancy. Similarly, a significant improvement in endometrial thickness was observed in our study though it did not correlate with a significant increase in pregnancy outcomes.[27,28] Nevertheless, an improvement was observed which was reflected in the results of the systematic review, and meta-analysis study on endometrial thickness where it was highlighted that ET was not necessarily associated with better pregnancy outcomes.[29] Studies have shown that an effective combination of growth factors like PDGF-AA, PDGF-AB, PDGF-BB, TGF-β1, TGF-β2, EGF, and anti-inflammatory cytokines IL-4, IL-13, IFN-α along with pro-inflammatory cytokines IL-8, IL-17 TNF-α which is present in platelet-rich plasma could enhance the endometrial receptivity.[30] Autologous PRP is a new and alternate mode of therapy for managing infertility issues specifically in women who do not respond to standard therapy. Several studies have highlighted the fact that it has helped regenerate the endometrium, restore the menstrual cycle, and enhance the receptivity of the endometrium.[31] Therefore, it can be presumed that administration of platelet-rich plasma enhances endometrial receptivity of the patients having refractory endometrium though in ways that cannot be assessed by endometrial thickness.

Autologous infusion of platelet-rich plasma assessed by power doppler increased the vascularity of uterine endometrium in the pregnancy-induced group.[32] Although, these findings are in agreement with our study, this improvement was not observed in all the patients. In this regard, embryo quality and synchrony could have a major influence on the pregnancy rate. Further, the clinical benefits of PRP vary with the type of PRP preparation that is used. In our study, the leukocytes in the leukocyte-rich PRP which was administrated could have increased the inflammatory process thereby enhancing the healing and might have helped in improving the implantation rate.[33] The live birth rate observed in previous studies after PRP treatment differed from our findings which could be due to the variation in the patient characteristics.[11,34]

As this was not a randomized control trial, the efficacy of platelet-rich plasma administration could be assessed only by comparing it with the latest cycle of each patient. The limitations of the study are that it involves invasive procedures and higher costs. Nevertheless, it can be surmised that subendometrial administration of platelet-rich plasma has been productive in augmenting the thickness and vascularity of endometrium thereby helping in improving the pregnancy outcome. Further detailed studies evaluating the molecular basis of PRP treatment are needed to identify the specific mechanism and the specific group of patients who would benefit maximally from the subendometrial PRP administration.

CONCLUSION

Subendometrial injection of platelet-rich plasma was effective in improving the thickness and vascularity of endometrium thereby improving the pregnancy outcome. The presence of leukocytes in PRP further enhanced endometrial healing. Further in-depth studies at the molecular level and well-defined randomized control trials are required to elucidate the specific mechanism of PRP treatment and its beneficial role on the endometrium.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

IVF: *In vitro* fertilization; **EMT:** Endometrial Thickness; **PRP:** Platelet Rich Plasma.

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