

Effect of Platelet-rich Plasma in Regeneration of Thin Endometrium and Its Implications in *in vitro* Fertilization Cycles: A Novel Approach

Kiran Pandey¹, Ruchika Garg², Pavika Lal³, Rashmi Upadhyay⁴, Gangadhar Sahoo⁵

ABSTRACT

The thin endometrium is an important cause of failure of cycle cancellations in *in vitro* fertilization (IVF). Several modalities like estrogen, low-dose aspirin, heparin, vaginal sildenafil, pentoxifylline, and granulocyte-colony stimulating factor (G-CSF) intrauterine perfusion have been tried and studied in patients with a thin endometrium. We discuss platelet-rich plasma (PRP) administration by intrauterine infusion as a novel approach in these patients. We reviewed and analyzed all important and relevant articles including case series, pilot studies, and case reports published from January 2000 to December 2020. Studies pertaining to other uses of PRP were not included. We found that intrauterine infusion of PRP can significantly increase the endometrial thickness and improve the pregnancy rates in infertile patients with thin endometrium <6 mm.

Keywords: ART, Endometrial thickness, Infertility, PRP.

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INTRODUCTION

Infertility affects 13% of couples worldwide¹ and despite extensive workup in many couples; etiology in around 10–25% of the couples remains unexplained which has brought implantation and endometrial receptivity into the light.² Endometrial tissues contain receptors for cytokines, growth factors, and lipids that are vital for endometrial proliferation as well as its receptivity for conceptus. Endometrial thickness (ET) >7 mm promotes successful implantation.³ High impedance blood flow in radial arteries of the uterine vasculature results in poor epithelial growth, reduced expression of vascular endothelial growth factor (VEGF) leading to implantation failure.

According to the European Society of Human Reproduction and Embryology (EHRE) consortium, recurrent implantation failure (RIF) is defined as the absence of gestational sac on ultrasound at 5 weeks or more after frozen embryo transfer (FET) following 3 FET with high-quality embryos or after the transfer of 10 or more embryos in multiple transfers.^{4,5} Recurrent implantation failure is a major challenge in reproductive medicine and despite several advances; still, no universal consensus exists. Many strategies such as estrogen, low-dose aspirin, heparin, vaginal sildenafil, pentoxifylline, and granulocyte-colony stimulating factor (G-CSF) intrauterine perfusion have been extensively used to increase the ET if not optimal.^{6,7} However, these methods were not found to be very impressive in all cases especially with a thin refractory endometrium. Platelet-rich plasma (PRP) may be effective in promoting endometrial growth, increasing ET and improving endometrial vascularity, and improving pregnancy outcomes in repeated implantation failure due to thin endometrium.

Platelet-rich plasma is a fraction of plasma prepared from autologous blood which is highly enriched with platelets and contain a variety of cytokines and growth factors like VEGF, transforming growth factor (TGF), platelet-derived growth factor (PDGF), and epidermal growth factor (EGF) that support cellular migration, proliferation, and growth.⁸

^{1,4}Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, Uttar Pradesh, India

²Department of Gynecology, SN Medical College, Agra, Uttar Pradesh, India

³Department of Obstetrics and Gynecology, Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, Uttar Pradesh, India

⁵Institute of Medical Sciences and SUM Hospital, SOA (Deemed to be University), Bhubaneswar, Odisha, India

Corresponding Author: Pavika Lal, Department of Obstetrics and Gynecology, Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, Uttar Pradesh, India, e-mail: lalpavika@gmail.com

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Platelet-rich plasma has been used in various fields of dermatology, dentistry, orthopedics, and sports medicine since platelets have the inherent property to induce healing by secreting various growth factors.⁹ Keeping this in mind a lot of research is going on in the field of reproductive medicine and gynecology. The objective of this review is to evaluate the effectiveness of PRP as a treatment of suboptimal endometrium in infertile women and its role in cases of assisted reproduction technology.

MATERIALS AND METHODS

A thorough review search was done using MEDLINE, Scopus, PubMed, and Google Scholar databases to investigate studies regarding PRP therapy in infertile women with refractory ET. We searched the databases from January 2000 to December 2019. We used "Platelet Rich Plasma", "PRP", "IVF", "thin endometrium", "infertility", and "Gynecology" as keywords for our search strategy.

The studies found for this review were mainly case reports, case series, and pilot studies. Studies with uses in other branches of medicine were excluded.

DISCUSSION

The thin endometrium is among the important causes of cycle cancellations in assisted reproductive technology (ART) cycles and many modalities have been tried in this regard but not all cases have benefitted from them.

Some approaches for thin endometrium are low-dose aspirin,¹⁰ pentoxifylline and vitamin E,¹¹ sildenafil citrate,¹² and estrogen.¹³

Platelet-rich Plasma for the Treatment of Refractory thin Endometrium

Thin endometrium poorly correlates with the pregnancy rate and may be due to high blood flow impedance of uterine radial arteries. Different strategies have been used for a time long to improve ET, especially in refractory cases. Platelet-rich plasma is a new modality in this aspect. Platelet concentrates vary based on the method of preparations, and the products obtained. Ehrenfest et al. proposed four types of preparation namely pure platelet-rich plasma (P-PRP)—or leukocyte-poor platelet-rich plasma, pure platelet-rich fibrin (P-PRF)—or leukocyte-poor platelet-rich fibrin and leukocyte- and platelet-rich fibrin (L-PRF) leukocyte- and platelet-rich fibrin (L-PRF) obtained from centrifugation of blood.¹⁴

Weissman et al. suggested a minimum ET of 7 mm to maximize pregnancy rates.¹⁵ Richter et al. evaluated the positive relationship between ET and clinical outcome of *in vitro* fertilization (IVF) in 1294 infertility patients undergoing fresh embryo transfer.¹⁶

Chang et al.¹⁷ for the first time in literature reported positive results of intrauterine infusion of autologous PRP in improving the ET. Endometrial thickness was significantly higher in the PRP group than in the control group (7.65 ± 0.22 vs 6.52 ± 0.31 mm, $P < 0.05$, respectively) with a lower cancellation rate for the PRP group ($p < 0.01$). Kim et al.¹⁸ proposed that higher implantation, pregnancy, and live birth rates with refractory thin endometrium with PRP administration. However, this result needs to be validated by large randomized and controlled studies. In a similar study by Nazari et al.¹⁹ in 20 patients with a history of RIF failing to conceive after three or more ET with high-quality embryos. Intrauterine infusion of 0.5 mL PRP was done followed by blastocyst transfers after 48

hours. Eighteen patients had biochemical pregnancy out of which 16 had clinical pregnancy.

Colombo et al.²⁰ concluded that ET increased with the endometrial three-layer pattern and suggested that PRP administration could improve the multiple implantation failures caused by the inefficient expression of adhesion molecules. Zadehmodarres et al.²¹ evaluated 10 patients with persistent ET < 7 mm and concluded that PRP was effective for endometrial growth in infertile women with a thin endometrium. These results were on par with the data of Molina et al.²² who did a prospective study on 19 patients undergoing IVF, aged between 33 years and 45 years with a history of refractory endometrium and at least one failed IVF attempt and with the exclusion of patients with no history of failed IVF or without refractory endometrium. Endometrial thickness > 7 mm was reported with the first use of PRP; and in all 19 cases, ETs > 9 mm were evident after the 2nd administration with 73.7% of positive pregnancy tests.

Eftekhari et al.²³ conducted a random control trial (RCT), including 83 women with a poor endometrial response to standard hormone replacement therapy (HRT) < 7 mm. Endometrial thickness increased significantly to 8.67 ± 0.64 in PRP group than in controls ($p = 0.001$). This increase was higher in women who conceived in the PRP group (p ++value: 0.031). The implantation rate and per-cycle clinical pregnancy rate were significantly higher in the PRP group ($p = 0.002$ and 0.044, respectively). A study by Coksuer et al.²⁴ to evaluate the effect of intrauterine PRP treatment on frozen-thawed embryo transfer (FET) cycles in patients suffering from unexplained infertility patients with a history of RIF. Endometrial thickness, clinical pregnancy rate, and live birth rate were also significantly higher in the PRP group than the control group.

Mehrafza et al.²⁵ did a retrospective cohort study including 123 patients with a history of more than 2 repeated failed embryo transfers. Cycles were divided into two groups of intrauterine infusion of PRP ($n = 67$) and systemic administration of G-CSF ($n = 56$).²⁶ The clinical pregnancy rate was significantly higher in the PRP group than the G-CSF group (40.3 vs 21.4%, $p = 0.025$). Agarwal et al.²⁷ conducted a cross-sectional study in 32 infertility patients whose embryo transfer had been canceled in previous cycles due to thin endometrium. Platelet-rich plasma was injected hysteroscopically in them after which ET increased in 24 out of 32

Author, year	Study design	Study population	Sample size	Outcomes
Agarwal et al. (2020)	Cross-sectional	Women with primary and secondary infertility in whom previous cycles due to thin endometrium (< 7 mm) despite conventional therapy	32	ET increased in 24 patients: 12 out of 24 patients underwent embryo transfer out of which 10 had a clinical pregnancy and 2 had biochemical pregnancy
Mehrafza et al. (2019)	Retrospective cohort study	Women with > 2 repeated failed embryo transfers due to poor endometrial lining. 2 groups were divided which were administered intrauterine infusion of PRP ($n = 67$) and systemic administration of G-CSF ($n = 56$), respectively	123	ET and vascularity increased post-PRP. Clinical pregnancy was detected in 45.1%
Coksuer et al. (2019)	Retrospective cohort study	Women with history of RIF and unexplained infertility were divided into 2 groups, with suboptimal endometrial lining ($n = 34$) and optimal endometrial lining ($n = 36$)	34 in PRP group 36 in control group	ET increased. Clinical pregnancy rate and live birth also increased

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Author, year	Study design	Study population	Sample size	Outcomes
Kim et al. (2019)	Prospective interventional study	Patients with history of ≥ 2 failed IVF cycles and refractory thin endometrium (< 7 mm)	24 patients were compared against their previous cycles	PRP improved implantation, pregnancy and live birth rates in comparison to their previous cycles
Chang et al. (2019)	Prospective interventional study	Patients with thin endometrium < 7 mm and prior canceled FET	34 in PRP group and 30 in control	PRP had higher ET and lower cancellation rate. Higher implantation and clinical pregnancy rate in favor of PRP (27.94 vs 11.67%, $p < 0.05$; 44.12 vs 20%, $p < 0.05$, respectively)
Eftekhari et al. (2018)	Randomized clinical trial	Women with poor endometrial response to standard hormonal preparation (ET < 7 mm in the 13th day of FET cycle)	40 in PRP and 43 in control	PRP higher ET (0.001), implantation ($p = 0.002$) and pregnancy rate ($p = 0.044$)
Molina et al. (2018)	Prospective cohort study	Patients with a history of refractory endometrium	19	ET ≥ 7 mm was detected after the first PRP use and all cases experienced ET ≥ 9 mm after the second use. Embryo transfer was conducted in the entire study group. Positive pregnancy in 73.7% with live birth in 26.3%
Zadehmodarres et al. (2017)	Prospective cohort study	Patients with a history of canceled FET due to inadequate endometrium	10	ET increased in all patients with five of them were pregnant
Tandulwadkar et al. (2017) ²⁶	Prospective cohort study	Women experienced suboptimal growth or vascularity despite standard dose of hormonal preparation. Women with > 2 canceled cycles or recurrent implantation failure due to poor endometrial lining	68	ET and vascularity increased post-PRP. Clinical pregnancy was detected in 45.1%
Colombo et al. (2017)	Prospective interventional study	Patients with more than cryotransfers because of thin endometrium, i.e., ET < 6 mm	8	7 out of 8 patients had increase in ET and improved vascularity. 6 out of 7 patients who underwent embryo transfer beta-hCG was positive
Chang et al. (2015)	Prospective cohort study	Women who have a poor endometrial response (< 7 mm) to the standard hormonal preparation of FET and had to cancel their embryo transfer	5	Successful endometrial expansion and transfer for all patients with pregnancy detected in 4 cases

patients. Twelve of 24 patients who underwent embryo transfer conceived.

It is also important to mention that in a study by Kiran Pandey et al., PRP was found to be significantly better in improving the ET and vascularity in patients with unexplained infertility than conventional estradiol valerate and sildenafil citrate in non-IVF cycles.

CONCLUSION

In view of the previous studies, autologous PRP is a novel approach for improving the ET and increasing pregnancy rates of infertile women with thin refractory endometrium. Since PRP is obtained from the patient's own blood it is devoid of any side effects. Moreover, since it is easily available, inexpensive, and involves local administration, it can prove to be a boon for the infertile patients. Further research in the form of large scale randomized controlled trials is needed, to use PRP.

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