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# Platelet-rich plasma therapy enhances endometrial receptivity in thin endometrium patients undergoing frozen embryo transfer cycles: results from a prospective cohort observational study

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#### ABSTRACT

*Objective:* To evaluate the impact of intrauterine instillation of autologous platelet-rich plasma (PRP) on women with thin endometrium undergoing frozen embryo transfer.

Methods: A prospective cohort observational study was carried out at Akanksha IVF Centre, New Delhi, from 1st August 2023 to 31st July 2024. The study included 100 patients under 40 years with thin endometrium (<7 mm on transvaginal sonography). Participants received hormone replacement therapy (sequential incremental dosage of estradiol valerate) from day 2 of the menstrual cycle. Among them, 70 patients received intrauterine PRP instillation on days 7, 9, and 11 of the cycle, while the remaining 30 patients did not undergo this treatment. Endometrial thickness was monitored, and progesterone was initiated on day 14 or once endometrial thickness surpassed 7 mm, followed by blastocyst transfer on day 6 of progesterone. Pregnancy outcomes were assessed using urine pregnancy tests or serum beta human chorionic gonadotropin levels followed by ultrasound to confirm fetal viability. The main outcomes assessed were improvement in endometrial thickness and clinical pregnancy rate.

Results: The administration of PRP through intrauterine instillation significantly increased mean endometrial thickness in the PRP group compared to the non-PRP group (p=0.032). The clinical pregnancy rate was 35.71 % in the PRP group versus 10 % in the non-PRP group (p=0.0251). No adverse reactions were observed

Conclusions: PRP therapy significantly enhances endometrial receptivity and improves pregnancy outcomes in patients with refractory thin endometrium. It offers a promising adjunctive treatment for patients facing repeated cycle cancellations in frozen embryo transfer.

# Introduction

Infertility affects a significant portion of the global population, with approximately 13 % experiencing challenges in conceiving [1]. Successful pregnancy relies heavily on the health and function of the uterus, particularly the endometrium [2]. In a natural menstrual cycle, the endometrium reaches its peak receptivity for embryo implantation about 5–7 days after ovulation, coinciding with the blastocyst stage of embryo development [3]. However, several other factors like structural defects in the uterus (polyps, adhesions, etc.) and endometrial thickness

(EMT) can influence endometrial receptivity [4]. Successful implantation requires optimal endometrial receptivity, embryo viability, and precise coordination between the day-5 embryo and the endometrial lining. Although advances in assisted reproductive technologies (ART) have significantly improved pregnancy rates, implantation failure continues to be a major challenge.

Approximately one-third of implantation failures are related to issues with the embryo itself, while insufficient endometrial receptivity and inadequate communication between embryo and endometrium contribute to the remaining two-thirds of failures [5]. Thin en-

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dometrium exhibits inadequate growth of glandular epithelium, increased uterine blood flow impedance, reduced vascular endothelial growth factor (VEGF) expression, and impaired neoangiogenesis [6]. Uterine blood flow plays a crucial role in promoting endometrial growth [7]. Various factors can contribute to a thin endometrium, with inflammation and iatrogenic causes being the most prevalent. In India, common inflammatory conditions, such as genital tuberculosis, can damage the stratum basalis, leading to fibrosis and hindering the repair and renewal of the endometrial lining [8]. Common iatrogenic causes include surgical procedures like repeated curettage, hysteroscopic or laparoscopic myomectomy [9], and imprudent use of medications like clomiphene citrate, which can lead to endometrial damage or intrauterine adhesions [10]. In some cases, reduced endometrial thickness could be idiopathic, and can be influenced by individual uterine structure or intrinsic endometrial factors [11].

Various approaches have been explored to enhance the receptivity of endometrium and EMT. These include hormonal supplementation like estradiol which is administered orally, vaginally or transdermally [12]. The benefits of vasoactive agents like low-dose aspirin [13] and the potential of tocopherol/vitamin E and pentoxifylline [14] have also been explored. Intra-vaginal sildenafil [15] and tamoxifen [16] have also been investigated as a therapeutic option. The role of intrauterine infusion of granulocyte colony stimulating factor (G-CSF) [17], and stem cell therapy [18] have also been evaluated in enhancing endometrial function. PRP is an autologous blood plasma mixture enriched with platelets at 4-5 times the concentration found in normal circulating blood. It is derived by centrifuging the patient's peripheral venous blood sample. When activated at the injury or inflammation site, platelets release growth factors that play a key role in activating fibroblasts, recruiting leukocytes, and promoting the proliferation and migration of various cell types involved in tissue repair [19].

PRP can help in the proliferation of epithelial cells, fibroblasts, and mesenchymal stem cells in the endometrial lining by augmenting the adhesion molecule expression, attracting stem cells, and promoting the migration of endometrial cells [20]. Additionally, PRP therapy also has an anti-inflammatory effect. It suppresses key regulators of inflammation like nuclear-factor kappa-B (NF-kB) and modulates the expression of COX-2 and various other important inflammatory cytokines involved in the process of implantation [21]. Furthermore, PRP therapy reduces fibrosis by lowering the expression of factors associated with fibrotic development, resulting in enhanced chances of successful implantation and improved live birth rates [22].

It could be suggested that refractory thin endometrium may originate from endometrial injury. Therefore, PRP instillation might facilitate the regeneration of the endometrium, leading to increased thickness and improved receptivity [23]. However, the impact of PRP on pregnancy outcome including clinical pregnancy rates and live birth rates is still under investigation. Previous studies on PRP in endometrial pathology have indicated potential enhancements in the receptivity of the endometrium, but determining the optimal dosage and scheduling of intrauterine instillation requires careful planning and evaluation [22–26]. Therefore, this study was conducted with the aim of assessing the role of intrauterine instillation of PRP on endometrial thickness and pregnancy outcomes in patients with thin endometrium undergoing a frozen embryo transfer (FET) cycle.

#### Materials and methods

A prospective observational cohort study was carried out at Akanksha IVF Centre, New Delhi, from 1st August 2023 to 31st July 2024 involving 100 patients with thin endometrium undergoing FET cycles. Sample size was calculated at 95 % confidence level and taking the mean improvement in endometrial thickness after PRP infusion in patients undergoing frozen embryo transfer as 0.83 with standard deviation of 0.79 (Dogra Y et al, JBRA Assist Reprod 2022) and with an al-

lowable error of 0.25, the sample size estimated to be 39 using the formula.

$$n = (Z_{1-\alpha/2})^2 \sigma^2/E^2$$

where n = sample size

 $Z\alpha=1.96$  value of the standard normal variate corresponding to level of significance alpha 5 %.

 $\sigma$  – Standard deviation = 0.79.

E- allowable error = 0.25.

A total of 100 patients were enrolled in this observational study. They were divided into two groups: 70 patients received Platelet-Rich Plasma (PRP) treatment, while 30 patients did not receive PRP.

Ethical Committee approval was taken from the Independent Ethical Committee (IEC) – Indian Fertility Society, approval number F.1/IEC/IFS/2023/No.16. The study was conducted in accordance with the approved protocol after taking a written informed consent from all the participants. The study included women under 40 years of age with thin endometrium (less than 7 mm on the day of starting progesterone in the previous cycle, measured by transvaginal ultrasonography at the thickest part of the uterine longitudinal axis) who were planned for FET during the specified period. Exclusion criteria included adenomyosis, endometrial or uterine pathology (such as polyps or submucous fibroids), and patients with platelet dysfunction syndrome, thrombocytopenia, or blood coagulation defects.

In patients with persistently thin endometrial lining, a structured approach to endometrial preparation was undertaken using hormone replacement therapy (HRT). All participants in the study were administered estradiol valerate (Tab Progynova® 2 mg, Bayer Zydus Pharma Pvt Ltd, India) in a sequential incremental manner, starting from the second day of their periods at 6 mg/day and gradually increasing the dose up to 12 mg/day. Among them, 70 patients received additional treatment in the form of intrauterine instillation of PRP, which was extracted from an autologous peripheral blood sample under aseptic conditions via a two-step centrifugation method. Fifteen millilitres of peripheral venous blood was taken in a vial layered with an anticoagulant solution (ACD-A: Anticoagulant Citrate Dextrose Solution, Solution A) and immediately centrifuged at 175g for a duration of 12 min to separate the red blood cells (RBCs). The plasma and buffy coat layer were then transferred to another tube and subjected to centrifugation at a speed of 1300g for 7 min. The platelet-rich pellet obtained at the end of these two centrifugations was mixed with 1 ml of supernatant. The resultant 0.5-1 ml of PRP was instilled transcervically into the uterine cavity using an intrauterine insemination (IUI) catheter within an hour of its preparation. This PRP preparation technique was standardized to attain platelet counts of more than  $1,000,000/\mu l$  in the final sample. To monitor the endometrial response, the EMT and the endometrial pattern were evaluated every 48 h using transvaginal ultrasonography. The intrauterine instillation of PRP was scheduled thrice during the frozen embryo transfer cycle on days 7, 9, and 11 of the endometrial lining preparation phase. The remaining 30 patients did not receive intrauterine PRP instillation.

Estrogen priming was continued till day 14 or till EMT exceeded 7 mm, followed by the addition of intramuscular Progesterone (Injection Uterone 100 mg, Jagsonpal Pharmaceuticals Ltd, India) once daily in preparation for blastocyst transfer. The embryo transfer was performed on the 6th day of Progesterone administration. After embryo transfer, intramuscular Progesterone (Injection Uterone 100 mg, Jagsonpal Pharmaceuticals Ltd, India) once daily and estradiol valerate (Tab Progynova® 2 mg, Bayer Zydus Pharma Pvt Ltd, India) 6 mg/day was given for luteal phase support.

Pregnancy outcomes were assessed through a urine pregnancy test and subsequent serum beta human chorionic gonadotropin (hCG) measurement, both conducted 14 days post-embryo transfer. If the pregnancy test was positive, participants underwent a transvaginal ultrasound after two weeks for localization of an intrauterine gestational sac

with or without cardiac activity (clinical pregnancy). The data was analyzed to evaluate the impact of PRP intrauterine instillation as a supplement to HRT in increasing EMT and enhancing the outcome of pregnancy in women with thin endometrium. Data was entered into a Microsoft Excel spreadsheet, and the final analysis was performed using the Statistical Package for Social Sciences (SPSS) software, version 25.0. Continuous variables were reported as mean values with standard deviations, while categorical variables were presented as frequencies and percentages across the PRP and non-PRP groups. Differences in mean values were assessed using the *t*-test, and the Chi-square test was applied for categorical data. A p-value of less than 0.05 was considered statistically significant.

### Results

A total of 100 patients were recruited for the study after meeting the designated inclusion and exclusion criteria. The baseline characteristics of the PRP and non PRP group were comparable (Table 1). There was no significant difference between the two groups regarding the type of infertility (Table 2). In terms of the expansion of endometrium, the average EMT on the final day of estrogen priming in the previous cycle was 5.72  $\pm$  0.84 mm, which significantly rose to 7.305  $\pm$  0.746 mm after PRP therapy in the current cycle. In the case of the non-PRP group, the average EMT did not show significant expansion, 5.68  $\pm$  0.53 mm in the previous cycle to 5.94  $\pm$  0.451 mm in the current cycle. The inter-group comparison showed a significant difference in endometrial expansion between Group 1 and Group 2 (P = 0.032) (Table 3). The clinical pregnancy rate (CPR) was significantly greater in the PRPtreated group (Group 1), with 35.71 % of patients achieving clinical pregnancy, compared to just 10 % in the non-PRP-treated group (Group 2). This difference was statistically significant (P = 0.0251) (Table 4).

Table 1 Baseline characteristics of study subjects (n = 100).

Parameter	Group 1(PRP Group) (n = 70)	Group 2 (non-PRP Group) (n = 30)
Mean Age	35.23 ± 4.62 years (range: 26–43 years)	36.31 ± 5.23 years (range: 24–45 years)
Mean BMI*	25.11 ± 3.57 kg/m <sup>2</sup> (range: 18.4–33.6 kg/m <sup>2</sup> )	$25.87 \pm 4.11 \text{ kg/m}^2$ (range: $18.9-35.1 \text{ kg/m}^2$ )
Mean Duration of Infertility	$5.81 \pm 2.99$ years (range: 2–13 years)	5.08 ± 2.22 years (range: 2–14 years)
Mean Basal FSH <sup>†</sup>	7.59 ± 2.34 mIU/ml (range: 4.12–14.30 mIU/ml)	6.84 ± 2.91 mIU/ml (range: 4.95–15.23 mIU/ml)
Mean Basal LH <sup>‡</sup>	5.8 ± 2.57 mIU/ml (range: 1.65–12 mIU/ml)	5.12 ± 3.31 mIU/ml (range: 2.83–11.46 mIU/ml)
Mean Basal AMH <sup>§</sup>	3.29 ± 2.79 ng/ml (range: 0.86–10.25 ng/ml)	2.97 ± 1.31 ng/ml (range: 0.71–8.20 ng/ml)
Mean Basal AFC	7.9 ± 5.49 (range: 0-25)	7.11 ± 4.68 (range: 0–21)
Average Baseline EMT**	5.72 ± 1.44 mm	5.96 ± 2.22 mm

- \* Body mass index.
- † Follicle stimulating hormone.
- ‡ Luteinizing hormone.
- § Anti Mullerian hormone.
- || Antral follicle count.
- \* Endometrial thickness.

**Table 2** Type of Infertility amongst study subjects (n = 100).

Infertility Type	Group 1 (PRP Group) (n = 70)	Group 2 (non-PRP Group) (n = 30)	p- value
Primary Infertility	48 (68.57 %)	22 (73.33 %)	0.871
Secondary Infertility	22 (31.42 %)	8 (26.66 %)	0.749

**Table 3** Endometrial expansion in study subjects (n = 100).

Group	Previous cycle EMT* (mm) (on the final day of estrogen priming)	Current cycle EMT* (mm) (on the final day of estrogen priming)	Difference in EMT* (mm)	p- value
Group 1 (PRP)	5.72 ± 0.84	$7.305 \pm 0.746$	$1.585 \pm 0.094$	0.032
Group 2 (non- PRP)	5.68 ± 0.53	5.94 ± 0.451	$0.26 \pm 0.079$	

<sup>\*</sup> Endometrial thickness.

**Table 4** Clinical pregnancy rate amongst study subjects (n = 100).

Group	Clinical Pregnancy Rate	p-value
Group 1 (PRP)	35.71 %	0.0251
Group 2 (non-PRP)	10 %	

#### Discussion

An optimal endometrial thickness is crucial for successful embryo implantation, making endometrial preparation an essential part of the embryo transfer process. Extensive research has been conducted on the physiological and pathological aspects of thin endometrium, along with various treatments aimed at enhancing its thickness. These treatments include extended estradiol therapy, vasoactive agents such as low-dose aspirin and sildenafil citrate, combinations like pentoxifylline and tocopherol, and intrauterine infusions of G-CSF. Despite these treatments, some patients continue to show inadequate response, leading to repeated cancellations of embryo transfer cycles or failure due to insufficient endometrial development. Effective treatment for thin endometrium continues to be a challenge, creating a need for innovative therapeutic approaches to improve endometrial thickness.

Platelets are usually the first responders to tissue damage. These anucleated cell fragments originate from megakaryocyte cells in the bone marrow and consist of cytoplasm divided into two parts: granules containing chromomeres and an agranular hyalomere rich in cytoskeletal proteins. These granules are composed of various growth factors like VEGF, in particular, which plays a critical role in neovascularization. Upon activation, platelets release these growth factors, which are crucial for initiating tissue repair processes. These factors activate fibroblasts, recruit leukocytes, and encourage the proliferation and migration of cells like smooth muscle cells and mesenchymal stem cells [19].

A key finding of this study was the statistically significant increase in mean EMT in the PRP-treated group compared to the other group, which did not receive PRP intervention (p = 0.0251). This finding indicates that PRP enhances the growth of the endometrium and creates a more favorable environment for embryo implantation. Moreover, the CPR in Group 1, the PRP-treated group, was significantly higher at 35.71 %, compared to only 10 % in Group 2, the non-PRP group (p = 0.0251). This dramatic difference in clinical pregnancy outcomes underscores PRP's potential as an effective treatment for enhancing pregnancy rates in patients with previously thin or inadequate endometrial lining.

Several studies have documented similar effects of PRP on endometrial function as well as pregnancy outcomes [22–26]. A study by Aghajanova et al., 2018 [20] explored PRP's impact on endometrial cells in vitro, observing increased cell migration and proliferation of stromal and mesenchymal cells. Chang et al., 2015 [24] demonstrated that intra-uterine PRP increased growth factor expression in the endometrium and thus led to successful pregnancies in 4 out of 5 patients with previous infertility. Zadehmodarres et al., 2017 [26] reported increased EMT (>7 mm) in patients with thin endometrium after PRP infusion, with 5 out of 10 patients achieving successful pregnancy. Colombo et al., 2017

[27] also found that 7 of 8 patients achieved trilaminar endometrium and 6 out of 8 had positive beta-hCG after PRP treatment. Molina et al., 2018 [28] observed a 73.7 % CPR and 26.3 % live birth rate in study subjects with low EMT treated with PRP. Eftekhar et al., 2018 [29] showed significant improvements in EMT and pregnancy rates in women receiving PRP in addition to HRT compared to the control group who received HRT alone.

A study conducted by Agarwal et al., 2020 [30] documented a 75 % success rate in attaining an EMT greater than 7 mm after hysteroscopic PRP infusion, resulting in conception and clinical pregnancy for many patients. Frantz et al., 2020 [31] found PRP treatment led to a 60 % CPR in study subjects with endometrium lining < 5 mm. Kim et al., 2019 [32] observed that PRP infusion significantly improved implantation rate (IR) and CPR in patients with refractory thin endometrium. An Indian study by Tandulwadkar et al., 2017 [33] concluded that PRP enhanced endometrial thickness and vascularity, resulting in a 45.31 % CPR. Another Indian study by Dogra et al., 2022 [23] found that PRP increased EMT and pregnancy outcomes in patients with Tuberculosis, diminished ovarian reserve, and polycystic ovarian syndrome (PCOS), with no adverse effects.

None of our study subjects experienced any adverse effects during the study. PRP preparation was undertaken by the same laboratory technician for all cases in our study, ensuring the elimination of technical bias. The same clinician performed all the ultrasounds and PRP intrauterine instillation throughout the study, ensuring consistent cycle management and enhancing the clinical robustness of the study. Our results aligned with those of most previous studies, indicating that this protocol may be suitable for future applications [22–26].

One major limitation of our study was the small sample size, which limited its generalizability and precluded the use of multivariate analysis. However, we included all cases that met our strict inclusion and exclusion criteria. Another limitation is that we did not record live birth rates, which was due to the relatively short duration of our study. Individual platelet counts were not estimated for each patient during PRP preparation prior to infusion. However, the PRP preparation protocol was standardized to achieve a platelet concentration exceeding 1,000,000/ $\mu$ l in the final sample, corresponding to a 4–5-fold increase over baseline blood levels.

Blinding of clinicians and patients was not feasible due to the observational design of the study. Since patients were enrolled on a first-come, first-served basis and treatments were given as part of routine clinical care, blinding was not feasible. Both patients and clinicians were necessarily aware of the procedures or interventions being performed, which makes blinding practically impossible in such real-world settings. Concealing the type of treatment from patients or clinicians could have posed ethical challenges and interfered with informed decision-making.

PRP intrauterine instillation offers several advantages: it is relatively simple to prepare, affordable, minimally invasive, and rich in growth factors and cytokines. Because it utilizes the patient's own blood, the risk of infection transmission is minimal. When performed with appropriate sterile technique, adverse effects are rare. Integrating this procedure into standard clinical practice could lessen the physical, financial, and emotional stress experienced by patients who frequently face cancelled cycles or repeated implantation failures.

#### Conclusion

The results of our study strongly endorse the use of autologous PRP therapy as an effective adjunctive treatment for women with refractory thin endometrium, especially those facing repeated cycle cancellations due to insufficient endometrial development. By enhancing endometrial growth and fostering a more receptive environment for embryo transfer, PRP therapy offers a promising alternative for women who have not responded well to traditional treatments like HRT.

### Work Attributed to

Akanksha IVF Centre, Mata Chanan Devi Hospital, Janakpuri, New Delhi – 110058. India.

### CRediT authorship contribution statement

Kanad Dev Nayar: Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization. Shweta Arora: Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Data curation. Sabina Sanan: Writing – review & editing, Writing – original draft, Investigation, Formal analysis. Manika Sachdeva: Writing – review & editing, Validation, Formal analysis. Ankita Sethi: Writing – review & editing, Visualization, Investigation. Gaurav Kant: Writing – review & editing, Validation, Project administration. Kapil Naya: Writing – review & editing, Validation, Investigation.

## **Declaration of competing interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Author's Declarations and Statements (Disclosure of Interest)

Ethics approval and consent to participate.

The study protocol, along with all relevant documents, were reviewed and approved by the Independent Ethical Committee – Indian Fertility Society (IEC-IFS) (Approval No. F.1/IEC/IFS/2023/No.16). The study was conducted in accordance with the approved protocol after taking a written informed consent from all the participants.

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# **Consent to Participate**

The authors certify that they have obtained all appropriate patient consent forms.

# Consent for publication

Consent for publication was obtained from all authors, the participants or legally authorized representatives involved in this study.

### Availability of data and materials (Data Sharing Statement)

The data that supports the findings of this research are not publicly available due to institutional restrictions. However, the datasets generated during study are available from corresponding author upon reasonable request.

### **Code Availability**

We confirm that EndNote Version 9, a freely available software application, was utilized for reference management.

### Declaration for Use of Generative AI or AI-assisted technologies

We, all the authors, declare that no generative AI or AI-assisted technologies have been utilized during drafting this manuscript.

#### **Previous presentation**

None.

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