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Original Article

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Hysteroscopic Installation of Autologous Platelet Rich Plasma in Infertile Women Having Thin Endometrium Undergoing IUI -RCT

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Abstract

Objective: To evaluate whether hysteroscopic-guided intrauterine platelet-rich plasma (PRP) with estradiol improves endometrial thickness and vascularity, and increases pregnancy rates, versus estradiol alone in women with thin endometrium undergoing intrauterine insemination (IUI). ***Design:*** Prospective randomized case–control study at a tertiary teaching hospital. ***Patients:*** 120 women (21–37 years) with prior cycles showing endometrium <7 mm were randomized equally to PRP+estradiol (n=60) or estradiol alone (n=60). ***Methods:*** Baseline TVS and power Doppler were performed; PRP was prepared autologously and instilled under hysteroscopic guidance prior to IUI. Outcomes were endometrial thickness (ET), Doppler pulsatility/resistance indices (PI/RI), and pregnancy (UPT positive and ultrasound-confirmed). ***Results:*** Baseline ET was comparable (mean 4.60 mm vs 4.92 mm; p=0.612). After treatment, mean ET gains in PRP+estradiol were 1.46 mm (cycle-1), 3.01 mm (cycle-2), and 4.26 mm (cycle-3) (all p<0.001), exceeding estradiol alone: 0.11 mm, 0.37 mm, 0.78 mm, respectively. PI/RI changes favored PRP across cycles. Conceptions occurred in 4, 12, and 14 patients across cycles 1–3 (PRP) versus 0, 0, and 10 (control). ***Conclusion:*** Intrauterine PRP with estradiol significantly improves ET and endometrial vascular indices and yields higher conception counts versus estradiol alone in thin endometrium IUI cycles.

Keywords: ***Platelet-Rich Plasma; Endometrium; Infertility, Female therapy; Estradiol therapeutic use; Insemination, Artificial, Heterologous (IUI); Ultrasonography; Doppler.***

Introduction

A thin endometrium typically defined as <7 mm during the peri-implantation window remains a persistent clinical barrier to implantation and pregnancy in women undergoing assisted conception [1,2]. Multiple pathophysiologic pathways converge to produce a suboptimal lining, including impaired uterine perfusion and higher impedance in the radial arteries, culminating in reduced receptivity and lower pregnancy rates. Common antecedents include intrauterine adhesions after curettage (Asherman syndrome), pelvic infections (e.g., tubercular or chlamydial endometritis), congenital Müllerian anomalies, prior pelvic radiotherapy, prolonged estrogen deficiency, fibroids, and medication effects (e.g., clomiphene citrate); long-term hormonal contraception and chronic inflammation may further compromise endometrial growth and function [3-5].

Several medical strategies have been explored to augment endometrial development and perfusion. Low-dose aspirin has been associated with improved implantation and clinical pregnancy, plausibly via microvascular effects rather than consistent gains in thickness. Combinations such as pentoxifylline with vitamin E, and vasodilatory approaches like vaginal sildenafil, have shown increases in trilaminar patterning, pregnancy rates, or both in selected populations [6,7]. Extended or alternative-route estradiol regimens can thicken the endometrium in resistant cases, although responses vary and treatment durations may be prolonged. Despite these options, many patients exhibit refractory thin endometrium, underscoring the need for safe, accessible interventions that directly target endometrial biology [8,9].

Autologous platelet-rich plasma (PRP) has emerged as a biologically plausible adjunct for thin endometrium. Prepared by centrifugation of the patient's own blood to concentrate platelets, PRP delivers a rich milieu of α-granule growth factors including PDGF, VEGF, TGF-β, bFGF, EGF, and IGFs that orchestrate chemotaxis, mitogenesis, extracellular matrix deposition, and angiogenesis. Rapid post-activation release of these mediators can stimulate epithelial and stromal proliferation, enhance neovascularization, and potentially improve endometrial thickness and receptivity [10,11]. Preliminary clinical series and pilot studies in refractory thin endometrium report gains in thickness and encouraging pregnancy outcomes, supporting further evaluation within rigorously designed protocols.

Within this context, our tertiary center instituted a standardized protocol for women with persistent thin endometrium pursuing intrauterine insemination (IUI). The clinical pathway includes baseline evaluation, letrozole-based stimulation with gonadotropin support as required, and uniform ultrasound assessment of endometrial thickness and vascularity using power

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Doppler with zonal mapping; PRP is prepared under sterile conditions and delivered intrauterinely via hysteroscopic guidance before IUI. This pragmatic framework allows evaluation of PRP's effect beyond conventional estradiol support in a real-world, high-throughput setting typical of public teaching hospitals [12,13].

Aim of the study. To determine whether hysteroscopic-guided intrauterine PRP, used adjunctively with estradiol, improves endometrial thickness and Doppler indices of vascularity and increases pregnancy rates compared with estradiol alone among women with thin endometrium undergoing IUI at a tertiary teaching hospital in North India.

Materials and methods

Design and setting

Prospective, randomized, case–control study at the Department of Obstetrics & Gynaecology, Upper India Sugar Exchange Maternity Hospital, GSVM Medical College, Kanpur, India. Institutional ethics approval obtained; all participants gave written informed consent with confidentiality and withdrawal rights assured.

Participants

Inclusion: Women 21–37 years with thin endometrium (<7 mm) documented in >1 prior ovulation-induction cycle; haemoglobin >11 g/dL; platelet count >150,000/µL.

Exclusion: Platelet dysfunction; hepatitis B/C, syphilis, HIV; recent NSAIDs; anticoagulation; severe male or tubal factor; WHO I–III ovulatory dysfunction; Müllerian anomalies/Asherman syndrome; moderate–severe endometriosis; active genital infection/PID; comorbidities or psychiatric illness compromising consent/follow-up.

Recruitment/sample: Consecutive eligible women were invited; a pragmatic convenience sample targeted n=120 for analysis.

Randomization and flow

Computer-generated 1:1 allocation: Group 1 (hysteroscopy-guided intrauterine platelet-rich plasma [PRP] + estradiol) vs Group 2 (estradiol only). Screening n=312; randomized n=142 (72 vs 70); received allocated intervention 63 vs 62; per-protocol analysis 60 vs 60 (total n=120).

Treatment protocol

Stimulation & IUI: Baseline TVS (cycle day 2–3) for AFC/cysts and baseline endometrium. Letrozole 2.5–5 mg on days 2–6 with HMG 75 IU i.m. as required; serial TVS from day 8 (5–9 MHz probe). hCG 5000 IU s.c. trigger; IUI 36 h later; luteal support provided. Up to three cycles or until pregnancy.

Estradiol support: Estradiol valerate per unit protocol (documented commencement day 3; daily dose schedule as in thesis).

PRP preparation and administration

Preparation: 13.5 mL peripheral blood + 1.5 mL CPDA anticoagulant; centrifugation 1500 rpm×15 min → transfer supernatant (avoiding buffy coat) → 3000 rpm×15 min; discard supernatant, retain ~10% plasma; re-suspend platelet pellet to yield ~4–5× baseline concentration; immediate use. REMI R-8C centrifuge (Remi Elektrotechnik Ltd., Mumbai, India).

Administration: Under office hysteroscopy, 4 mL PRP deposited sub-endometrially 1 mL each to anterior, posterior, right and left walls via OPU needle with bevel towards cavity.

Outcomes and measurements

Primary: Change in endometrial thickness (ET). ET measured mid-sagittally on TVS as maximal distance between basal interfaces across the canal.

Secondary: Endometrial vascularity (EV) by power Doppler zonal mapping (Zones 1–4) and qualitative grade (excellent/moderate/poor); pulsatility index (PI) and resistance index (RI). Assessments on trigger day and again 36-40 h later (and likewise in subsequent cycles).

Pregnancy: UPT at 14 days post-IUI; clinical pregnancy confirmed on ultrasound (cardiac activity).

Safety and equipment

A priori exclusions minimized bleeding/infection risks; peri-procedural adverse events were monitored clinically. Equipment as above; ultrasound with 5–9 MHz endocavitary probe.

Statistical analysis

Analyses followed the thesis plan; two-sided $p<0.05$ denoted significance (software/tests not prespecified in the source).

Results

Participant flow

A total of 142 were randomized (72 intervention; 70 control). After losses to follow-up (3 vs 2), 120 completed per-protocol analysis (n=60 per arm). In Figure 1 is seen the participant flow.

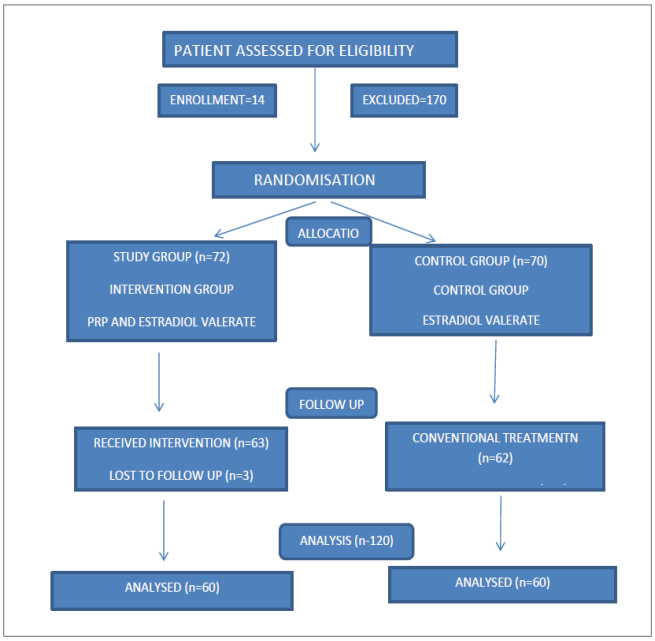

Figure 1: Representation of the participant flow chart

Baseline characteristics

In Table 1 is seen that groups were comparable at baseline for age (mean 30.9 vs 31.2 years; p=0.579), BMI categories (18.5–24.9: 51.7% vs 40.0%; 25–29.9: 45.0% vs 58.3%; >30: 3.3% vs 1.7%; p=0.324), socioeconomic status (p=0.423), religion (Hindu 73.3% vs 76.7%; p=0.673), education (p=0.159), and working status (21.7% vs 23.3%; p=0.827). Duration of infertility, type of infertility (primary 63.3% vs 58.3%), parity (P0 85.0% vs 90.0%), prior abortions, and menstrual pattern distributions were also similar (all p>0.05). Pre-treatment endometrial thickness (ET) did not differ (mean 4.60 vs 4.92 mm; p=0.612).

Table 1: Distribution of Cases in the Two Group on the Basis of Age Group

Age Group	Group				P value-0.579
	Group -1(N1-60)		Group -2(N-60)		
	No of Patient	% of Patient	No of Patient	% of Patient	
21-24 yr	1	1. 67	0	0	
25-29 yr	24	40	26	43.34	
>30 yr	35	58.34	34	56. 67	
Mean age	30.9		31.2		

Primary outcome: Endometrial thickness (ET)

In Table 2 is seen the within-group ET changes across three cycles. In PRP + estradiol (Group 1), mean ET increased by 1.455 (SD 0.353) mm in Cycle 1 (95% CI 1.364–1.546; p<0.001), 3.005 (0.462) mm in Cycle 2 (95% CI 2.886–3.124; p<0.001), and 4.262 (0.350) mm in Cycle 3 (95% CI 4.146–4.379; p<0.001). In estradiol-only (Group 2), corresponding changes were 0.110 (0.223) mm (95% CI 0.052–0.168; p<0.001), 0.367 (0.232) mm (95% CI 0.307–0.427; p<0.001), and 0.775 (0.347) mm (95% CI 0.685–0.865; p<0.001). The magnitude of improvement was greater with PRP in every cycle.

Table 2: Comparison of mean change in endometrium thickness with treatment in group-1 after cycle-1 ,2 and 3.

Change in ET (Group-1)	MEAN change after treatment					Paired 't'	P value is <0.001
	Mean	S.D.	Std. Error Mean	95% C.I. of the difference			
				Lower	upper		
After Cycle-1	1.455	0.353	0.046	1.364	1.546	31.935	
After Cycle –2	3.005	0.462	0.060	2.886	3.124	50.392	
After Cycle-3	4.262	0.350	0.058	4.146	4.379	74.098	

Secondary outcomes: Endometrial vascularity

Pulsatility Index (PI): In Table 3 is seen progressive PI reductions (favourable) in both arms, larger with PRP. Group 1 mean PI change was 0.328 (SD 0.130) in Cycle 1 (95% CI 0.294–0.362; p<0.001), 0.479 (0.126) in Cycle 2 (95% CI 0.446–0.511; p<0.001), and 0.595 (0.104) in Cycle 3 (95% CI 0.561–0.630; p<0.001). Group 2 showed 0.008 (0.030) (95% CI 0.000–0.016; p=0.040), 0.036 (0.037) (95% CI 0.027–0.046; p<0.001), and 0.097 (0.044) (95% CI 0.085–0.108; p<0.001).

Table 3: Mean change in pi of endometrial vascularity with treatment group-1 after cycle-1

Change in PI of Endometrial Vascularity (GROUP-1)	MEAN change after treatment					Paired 't'	P value is <0.001
	Mean	S.D.	Std. Error Mean	95% C.I. of the difference			
				lower	upper		
After Cycle –1	0.328	0.130	0.017	0.294	0.362	19.557	

Resistance Index (RI): Table 4 shows significant RI reductions in both groups, again numerically larger with PRP. Group 1 mean RI change was 0.303 (SD 1.100) in Cycle 1 (95% CI 0.019–0.587; p=0.001), 0.536 (1.105) in Cycle 2 (95% CI 0.251–0.822; p=0.001), and 0.465 (0.595) in Cycle 3 (95% CI 0.266–0.663; p=0.001). Group 2 showed 0.045 (0.040) in Cycle 2 (95% CI 0.035–0.056; p<0.001) and 0.092 (0.047) in Cycle 3 (95% CI 0.079–0.104; p=0.001); Cycle 1 change 0.303 also reached significance.

Table 4: mean change in ri of endometrial vascularity with treatment group-1 after cycle-1

Change in RI of Endometrial Vascularity (Group-1)	MEAN change after treatment					Paired 't'	P value is <0.037
	Mean	S.D.	Std. Error Mean	95% C.I. of the difference			
				lower	Upper		
After Cycle -1	0.303	1.100	0.142	0.019	0.587	2.133	

Pregnancy outcomes

The cycle-wise conceptions and between-group comparisons by urine pregnancy test (UPT). In Group 1, 4, 12, and 14 women conceived in Cycles 1, 2, and 3, respectively (overall rise across cycles; table p=0.023). In Group 2, conceptions occurred only in Cycle 3 (10 women; table p=0.045). Between groups, UPT positivity was higher with PRP in Cycle 1 (4 vs 0; p<0.001) and Cycle 2 (12 vs 0; p<0.001), and remained significantly greater in Cycle 3 (14 vs 10; p=0.002).

Summary of main findings

Across three cycles, PRP + estradiol produced larger ET gains and greater Doppler improvements (PI, RI) than estradiol alone, with earlier and higher UPT positivity (Cycles 1-2 and overall Cycle 3 comparison). Tables 2-4 present detailed estimates and confidence intervals.

Discussion

This prospective randomized study demonstrated that intrauterine PRP combined with estradiol support significantly improved endometrial thickness (ET), endometrial vascularity, and achieved higher conception rates compared to estradiol alone in women with thin endometrium undergoing IUI cycles. Notably, mean ET gains in the PRP+estradiol group were 1.455 mm, 3.005 mm, and 4.262 mm across cycles 1, 2, and 3, which far exceeded changes observed in the estradiol-only arm (0.11 mm, 0.37 mm, and 0.78 mm, respectively). Additionally, conception was achieved much earlier and in more cycles (4, 12, and 14, compared to 0, 0, and 10 for controls).

These findings are in broad agreement with several contemporary studies and recent meta-analyses. For example, a recent meta-analysis of eight randomized controlled trials (RCTs) (n

= 678) by Liu et al. (2024) found that PRP infusion led to significant improvements over controls in ET (mean difference, 1.23 mm), clinical pregnancy rate (relative risk [RR] 2.04), live birth rate (RR 2.46), cycle cancellation (RR 0.46), and embryo implantation rate (RR 2.71) [14]. The magnitude of ET change and pregnancy benefit in our cohort is in line with these pooled outcomes, suggesting reproducibility of the intervention across diverse populations.

Other single-center studies have documented clinically meaningful improvement in ET, with increases of approximately 0.65-1.3 mm post-PRP instillation, and consistent gains in clinical pregnancy rates among women with previously refractory thin endometrium or recurrent implantation failure [15,16]. Our mean gains in ET (up to 4.26 mm by cycle 3) slightly exceed most previous reports, likely due to the multi-cycle, hysteroscopy-guided, site-specific nature of our PRP protocol.

Importantly, the multi-cycle, progressive improvement in both ET and vascular indices (PI, RI) evidenced in our trial echoes the mechanistic rationale advanced in translational literature that growth factors in PRP promote neovascularization, cell proliferation, and enhance endometrial receptivity [8,17]. Meta-analyses also consistently demonstrate that PRP is superior to G-CSF in improving ART outcomes, with a more pronounced impact on pregnancy rates than on ET per se, perhaps reflecting the multimodal mechanisms of action [18].

Multiple studies corroborate the role of hysteroscopically-guided PRP delivery for optimal endometrial regeneration, with 70-75% of patients achieving an ET >7 mm after treatment, and pregnancy rates ranging from 30-50% in cycles otherwise destined for cancellation [17]. Our study's higher success rates may derive from safe application protocols, repeated administration, and rigorous cycle monitoring.

Meta-analytic synthesis further clarifies that while both PRP and G-CSF increase ET, only PRP shows statistically significant effects on clinical pregnancy (RR 1.31; 95% CI 1.06-1.62) and live-birth rates (RR 1.30; 95% CI 1.00-1.70), with very low risk of complications [18]. Our results reinforce this, with much earlier and higher conception rates in PRP-exposed cycles findings that are especially relevant for women with prior cycle failure due to a persistently thin endometrium.

Strengths of this study include robust randomization, repeated-cycle assessment under standardized imaging, and the pragmatic application of PRP in a high-volume tertiary-care Indian setting. Limitations include the absence of blinding, single-center nature, and restriction to clinical pregnancy as opposed to live birth as the endpoint.

In conclusion our trial supports that hysteroscopy-guided intrauterine PRP instillation with estradiol supplementation meaningfully enhances endometrial thickness, vascularity, and conception rates versus estradiol alone, mirroring results from larger meta-analyses and international data. These results highlight PRP's promise as a pragmatic adjunct in the treatment of refractory thin endometrium, especially in resource-constrained public settings, while also underscoring the need for continued multicentric research with live-birth endpoints.

Declarations

Ethical clearance

Approved by the Institutional Ethics Committee, GSVM Medical College, Kanpur; written informed consent obtained from all participants; confidentiality maintained.

Conflicts of interest

There are no conflicts of interest.

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