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*Case Report*

# Subendometrial Autologous Platelet-Rich Plasma Injection to Optimize Thin Unresponsive Endometrium in a Patient with Recurrent Implantation Failure: A Case Report

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**Abstract: Objectives:** To evaluate the potential role of hysteroscopic subendometrial autologous platelet-rich plasma application in a patient with refractory thin endometrium after multiple high-quality embryo transfers. **Methods:** We report the case of a 45-year-old female with a 9-year history of infertility, 15 previous IVF cycles, 8 frozen embryo transfers with a persistently thin endometrium of <7mm. After the exclusion of intrauterine pathology via diagnostic hysteroscopy, leukocyte-poor PRP was activated with calcium gluconate and injected into the subendometrial region. A comparison of endometrial thickness, as well as uterine and subendometrial arterial blood flow before and after PRP application was made. **Results:** In the subsequent cycle, endometrial thickness increased to 8.2 mm, Doppler vascular parameters improved, and a euploid frozen embryo transfer resulted in a clinical pregnancy and live birth. This case supports further investigation of hysteroscopic subendometrial PRP in selected patients. **Conclusion:** The regenerative characteristics of PRP in optimizing blood flow should be considered crucial to improving the microcirculation of the endometrial basal layer and subsequent tissue remodeling.

**Keywords:** Thin Endometrium; Platelet-Rich Plasma; Hysteroscopy; Recurrent Implantation Failure; Frozen Embryo Transfer; Live Birth

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## 1. Introduction

Uterine factors contributing to implantation remain incompletely understood. A thin endometrium is associated with implantation failure and lower pregnancy rates in assisted reproduction [1] and a thickness of 7mm is commonly used as a cut off in determining whether to proceed with embryo transfer regardless of whether it is a fresh or frozen embryo [2,3]. According to a study conducted by Mahajan et al., 9.1% of patients with a thin endometrium are refractory to classical hormonal therapy [4]. A thin endometrium has been associated with chronic endometritis, impaired vascularization, increased vascular resistance, and reduced expression of vascular endothelial growth factor (VEGF) [5]. New studies using Doppler measurements of the high pulsatility index (PI) and resistance index (RI) of the spiral arteries confirm their association with endometrial growth and implantation rates [6]. Several adjuvant approaches such as aspirin, sildenafil citrate, L-arginine, and G-CSF (Granulocyte Colony-Stimulating Factor) have been investigated, but no protocol has demonstrated a clear superiority in order to be applied clinically [7].

Platelet-rich plasma (PRP) has emerged as a potential regenerative approach. Intrauterine PRP injection was first reported in 2015 [8], and hysteroscopic subendometrial PRP injection was described in 2020 [9]. PRP contains autologous platelet-derived bioactive molecules that may support angiogenesis, stromal proliferation, tissue remodeling, and endometrial regeneration which are all physiological processes essential to endometrial growth [10,11].

The clinical value of PRP remains insufficiently defined, and there is no accepted protocol regarding preparation, platelet concentration, leukocyte content, activation, dose, timing, or route. This case report describes hysteroscopic subendometrial leukocyte-poor autologous PRP in a patient with a refractory thin endometrium undergoing euploid frozen embryo transfer (FET).

## 2. Case Report

A 45-year-old woman presented with a 9-year history of infertility consisting of 15 previous IVF cycles, 8 FET cycles, and 2 unsuccessful pregnancies: one biochemical pregnancy and one missed abortion at eight weeks gestation managed surgically. During the preceding years, endometrial thickness consistently remained below 7 mm, and repeated hormone replacement therapy failed to achieve a thickness greater than 6.1 mm.

Before PRP application, diagnostic hysteroscopy excluded Asherman syndrome, intrauterine adhesions, and other pathology undetectable by ultrasound. Due to recurrent implantation failure (RIF), the Th1/Th2 cell ratio in peripheral blood was assessed and found to be within the reference range [12].

Endometrial thickness was measured by transvaginal ultrasound in the longitudinal plane as the maximum distance between the two endometrial-myometrial junctions. Endometrial and subendometrial blood flow was evaluated using two-dimensional transvaginal color Doppler ultrasound with a Voluson E22 machine. Resistance index (RI) and pulsatility index (PI) were measured in the uterine and spiral arteries before and after PRP treatment.

From day 16 of the menstrual cycle, the patient began with self-administration of 3.75 mg Leuprolide acetate intramuscularly and 7 days later, a hysteroscopy was scheduled.

Autologous PRP was prepared using the RegenKit BCT-3 system (FDA approved PRP Kit) according to the manufacturer instructions [13]. The blood was centrifuged using a one way centrifugation method. The system used is classified as leukocyte-poor PRP [12]. The final platelet count was 380 million platelets per milliliter. Immediately before application, PRP was activated with calcium gluconate to promote platelet degranulation and growth factor release [14].

A total of 8 mL of activated PRP was subendometrially injected over 1-2 minutes using a 17-gauge single-lumen ovum pick-up needle under direct hysteroscopic guidance. PRP was injected 2-3 mm deep into the subendometrial region and distributed across four uterine sites, with 2.0 mL applied at each site. Previous clinical experience shows that adding calcium gluconate to the sample thickens the consistency to a gelatinous texture and therefore injection must be performed rapidly following activation. No leakage of injected material was observed during the procedure.

On day 2 of the subsequent menstrual cycle, oral estradiol valerate was commenced at 6 mg daily and gradually increased to 12 mg daily. Endometrial thickness reached 7.0 mm on cycle day 11 and 8.2 mm on cycle day 14. Doppler assessment showed improved vascularization: spiral artery PI decreased from 1.47 to 0.95 and RI from 0.69 to 0.59; left uterine artery PI decreased from 2.97 to 1.85 and RI from 0.82 to 0.68 and right uterine artery PI decreased from 3.10 to 2.03 and RI from 0.89 to 0.78 (Table 1).

Vaginal progesterone 800 mg daily was commenced when a satisfactory endometrial thickness was achieved. Serum progesterone was 13 ng/mL on the day before FET. A single euploid blastocyst was transferred on the fifth day of progesterone exposure. A clinical pregnancy was confirmed by ultrasound at six weeks. The patient delivered a live female neonate by elective caesarean section at term. The newborn weighed 2,850 g, measured 50 cm, and had Apgar scores of 9/10. Abnormal placental adherence with uterine atony was observed during delivery and successfully managed. Both the patient and newborn were discharged home healthy and well.

**Table 1. Endometrial and Doppler parameters before and after PRP treatment**

| Parameter | Before PRP treatment | After PRP treatment |
|---|---|---|
| Maximum endometrial thickness previously achieved with HRT | 6.1 mm | — |
| Endometrial thickness, cycle day 11 after PRP | — | 7.0 mm |
| Endometrial thickness, cycle day 14 after PRP | — | 8.2 mm |
| Spiral artery PI | 1.47 | 0.95 |
| Spiral artery RI | 0.69 | 0.59 |
| Left uterine artery PI | 2.97 | 1.85 |
| Left uterine artery RI | 0.82 | 0.68 |
| Right uterine artery PI | 3.10 | 2.03 |
| Right uterine artery RI | 0.89 | 0.78 |
| Serum progesterone before FET | — | 13 ng/mL |
| Embryo transferred | — | Single euploid blastocyst |
| Outcome | — | Clinical pregnancy and live birth |

**Abbreviations:** FET, frozen embryo transfer; HRT, hormone replacement therapy; PI, pulsatility index; PRP, platelet-rich plasma; RI, resistance index.

## 3. Discussion

Successful implantation requires a synchronized interaction between an embryo, a receptive endometrium, and an efficient embryo transfer. Uterine factors such as intracavitary lesions, adhesions, basal endometrial damage, inadequate preparation, and transfer outside the implantation window may interfere with successful implantation [15].

In this case, hysteroscopic subendometrial PRP was followed by endometrial growth beyond the previously achieved maximum and by improved Doppler parameters. Because diagnostic hysteroscopy excluded structural pathology and Th1/Th2 assessment was normal, refractory thin endometrium remained the main clinical limitation before treatment. In addition to the importance of the endometrial thickness, a study has found a reduction to complete absence of molecules which are defined as markers of endometrial receptivity, such as VEGF, beta interleukin, LIF in the endometrial tissue samples from subfertility patients with endometrial growth problems [16].

The biological rationale for PRP is based on growth factors being released after platelet activation, including VEGF, EGF (Epidermal Growth Factor), TGF (Transforming Growth Factor), PDGF (Platelet-derived Growth Factor), FGF (Fibroblast Growth Factor), IGF-1 (Insulin-like Growth Factor 1), and cytokines. These molecules may promote stromal cell proliferation, angiogenesis, tissue remodeling, and local immune modulation [17,18]. VEGF is particularly relevant because insufficient angiogenesis has been implicated in abnormal endometrial development [14,15].

The route of administration may be important. Intrauterine infusion is simple, but hysteroscopic subendometrial application allows targeted delivery into the subendometrial/endomyometrial region involved in vascular remodeling and cyclic regeneration. Agarwal et al. reported favorable outcomes after hysteroscopic PRP instillation into the endomyometrial junction. Hysteroscopic application of PRP is done in a cycle preceding the FET cycle. Here, a clinical pregnancy rate of 52% and a live birth rate of 38% have been achieved [9]. Yu et al. also reported improved outcomes after hysteroscopic PRP injection compared with intrauterine infusion in persistent thin endometrium before euploid FET. An important fact is that in this study the same PRP application and embryo transfer are in the same cycle [19].

PRP enables an integrated multi-level process in the development of the endometrium. Remodeling of vascularization and new angiogenesis leads to optimal circulation, especially through the spiral arteries, which is important for increasing the receptivity of the endometrium [20]. Growth factors promote tissue regeneration by

activating endogenous stem cells and modulating the immune response [21]. It is believed that hysteroscopic subendometrial trauma itself has mechanical stimulation triggering a weak inflammatory response and subsequent initiation of self-reparative regeneration. The functionality of the process itself is in initiating the activity of stem/progenitor cells from the basal layer of endometrium. Observations from the study of Huniadi A. et al. show a positive effect on promoting endometrial proliferation, improving implantation rates and clinical pregnancy in women with a thin endometrium [22]. Nazari L et al. also describe improving pregnancy outcomes after PRP administration through significantly higher clinical pregnancy rate and live birth rate in the group with PRP [23].

Preparations differ in platelet concentration and leukocyte content, and leukocyte-poor PRP has been suggested as a favorable option in recurrent implantation failure [24]. In this case, leukocyte-poor PRP was used, which may preserve angiogenic and regenerative effects while limiting excessive inflammatory activation. Hysteroscopic application allows significantly higher volumes of PRP to be injected to the subendometrial area compared to intrauterine infusion. On the other hand, analyzing the studies where PRP did not achieve its effect, a new idea arises that the volume used may impact overall outcome [25].

However, caution must be taken. New insights into the pathogenesis of endometriosis and adenomyosis described in the study by Ibrahim et al. describe pale cells which are located in the basal glands of the endomyometrial-junctional-zone level. These cells can migrate to the myometrium, and they have also been found in peritoneal endometrial foci [26]. The increase in cytokine concentration and activated macrophages following PRP may increase the risk of adenomyosis development. Microtrauma in the endomyometrial zone secondary to PRP injection may also contribute to the pathogenesis of adenomyosis [9].

Differences in preparation, activation, volume, route, timing, and patient selection limit comparison across studies. Therefore, this case should be interpreted as hypothesis-generating rather than proof of efficacy.

## 4. Conclusion

Hysteroscopic subendometrial leukocyte-poor autologous PRP was associated with improved endometrial thickness, improved Doppler vascular parameters, successful implantation, and live birth rate in a patient with refractory thin endometrium and recurrent implantation failure. PRP should not be routinely recommended for all patients but may be considered in carefully selected cases after hysteroscopic evaluation. Further studies are required to standardize preparation, platelet concentration, leukocyte content, activation, injection volume, timing, frequency, and route.

### Ethics Statement

The procedure was performed in accordance with the ethical standards of our institution and was reviewed by the Institutional Ethics Committee. Written informed consent was obtained from the patient for PRP use and for publication of this case report. This case report was prepared in accordance with the principles of the Declaration of Helsinki.

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