



AUTOLOGOUS PLATELET-RICH PLASMA FOR INFERTILE WOMEN WITH THIN ENDOMETRIUM: A NON-RANDOMIZED CLINICAL TRIAL

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INTRODUCTION

Since the inception of Assisted Reproductive Techniques (ART) the management of infertility has evolved tremendously. Despite these advancements recurrent implantation failure (RIF) still remains a challenging problem for patients and clinicians. The success of an Embryo Transfer, considered by some as the bottleneck of ART, is heavily dependent on the Endometrial thickness and receptivity. Hence, cycle cancellation due to an inadequate endometrium is a well known occurrence.

Chronically thin endometrium resistant to standard treatments affects a small number of patients undergoing IVF but is of considerable importance because endometrium **below 7mm** in is widely considered sub-optimal for transfer and associated with reduced pregnancy chances.^[1] Various remedies have been proposed, including extended estrogen administration,^[2] low-dose aspirin^[3], treatment with pentoxifylline and tocopherol^[4] and with vaginal sildenafil citrate.^[5] However, even with these remedies, some women remain unresponsive.

Intrauterine infusion of autologous Platelet Rich Plasma (PRP) is a relatively new approach for the treatment and cytokines that stimulate tissue regeneration and growth. The aim of this study was to evaluate the effectiveness of intrauterine infusion of PRP in the treatment of thin endometrium in Frozen-thawed Embryo Transfer (FET) cycles.

MATERIALS AND METHODS

This was a prospective interventional study carried out in infertile women undergoing ART treatment at the Rajendra Nagar Hospital & IVF Centre, Lucknow, India between August 2018 and July 2019. We recruited 119 women with endometrial thickness below 7mm on the 12th to 13th day of the cycle. In 108 patients hysteroscopic examination was performed before the cycle, if it had not been done previously. 11 patients opted out of the study. Hormone replacement therapy (HRT) was performed for endometrial preparation in all participants: Estradiol Valerate 6 mg/day was started on the 2nd or 3rd day of the menstrual cycle and it was increased to 8 mg/d on day 9-10 because of inadequate endometrial growth (<7 mm).

Exclusion Criteria

- Age less than 25 years or more than 45 years
- BMI >30kg/m²
- Known history of endocrine or systemic disorders
- History of Bleeding Diathesis
- Thrombocytopenia
- Severe endometriosis
- Congenital uterine anomalies

PRP infusion was performed on day 11-12 in all the patients due to thin endometrium and it was repeated on day 13-14. During the cycle, whenever the endometrial thickness was more than 7 mm, suppository Progesterone 400 mg twice-a-day was started and embryo transfer (ET) was carried out per embryonic stage. Estradiol Valerate and progesterone supplementation were continued for 2 weeks after ET and if the serum β HCG was positive, hormone supplementations were continued until 12 weeks of gestation.

PRP was obtained from a fresh whole blood collected from a peripheral vein. The blood sample was centrifuged at 1500g (RCF) for 10 minutes and the repeated. Then 0.5-1ml of PRP was infused into the uterine cavity through a Tomcat catheter. The endometrial thickening was evaluated by ultrasonography 24-48h after the instillation and, if the endometrial lining reached 7mm, the Embryo-transfer was performed.

Primary Outcome Measures

- Endometrial Thickness > 7 mm** measured by means of transvaginal ultrasound [Time Frame: 48h after the intrauterine PRP infusion].

Secondary Outcome Measures

- Positive Pregnancy Test Rate** [Time Frame: Approximately 3 weeks after treatment]; by serum Beta-HCG done two weeks after Embryo-transfer.
- Implantation Rate** [Time Frame: Approximately 6 weeks after treatment]; defined by number of gestational sacs seen on early ultrasound divided by number of embryos transferred.
- Clinical Pregnancy Rate** [Time Frame: Approximately 8 weeks after treatment]. Defined by the number of foetal poles with heartbeat seen on 6-8 week ultrasound divided by the number of embryos transferred.

RESULTS

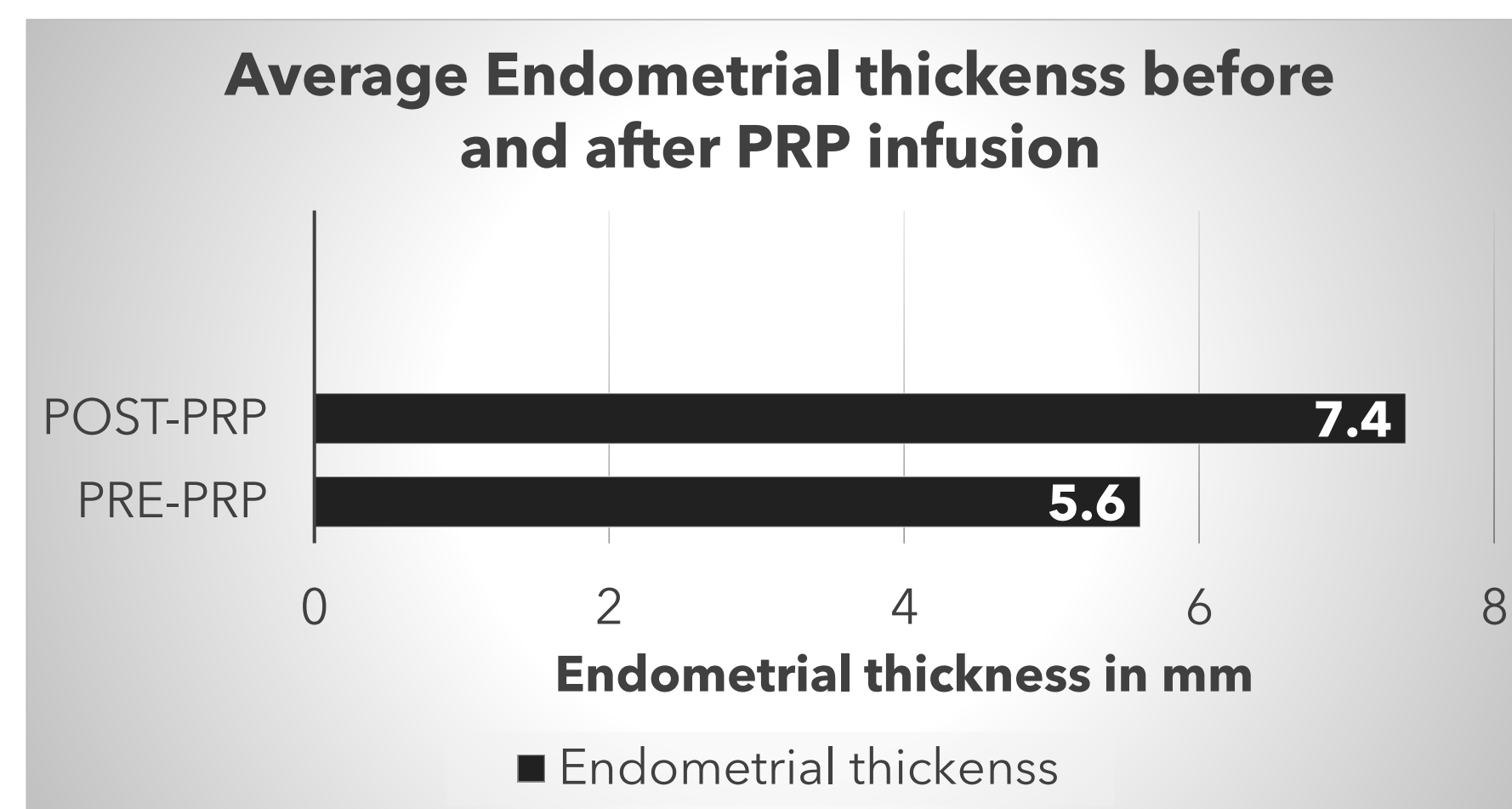
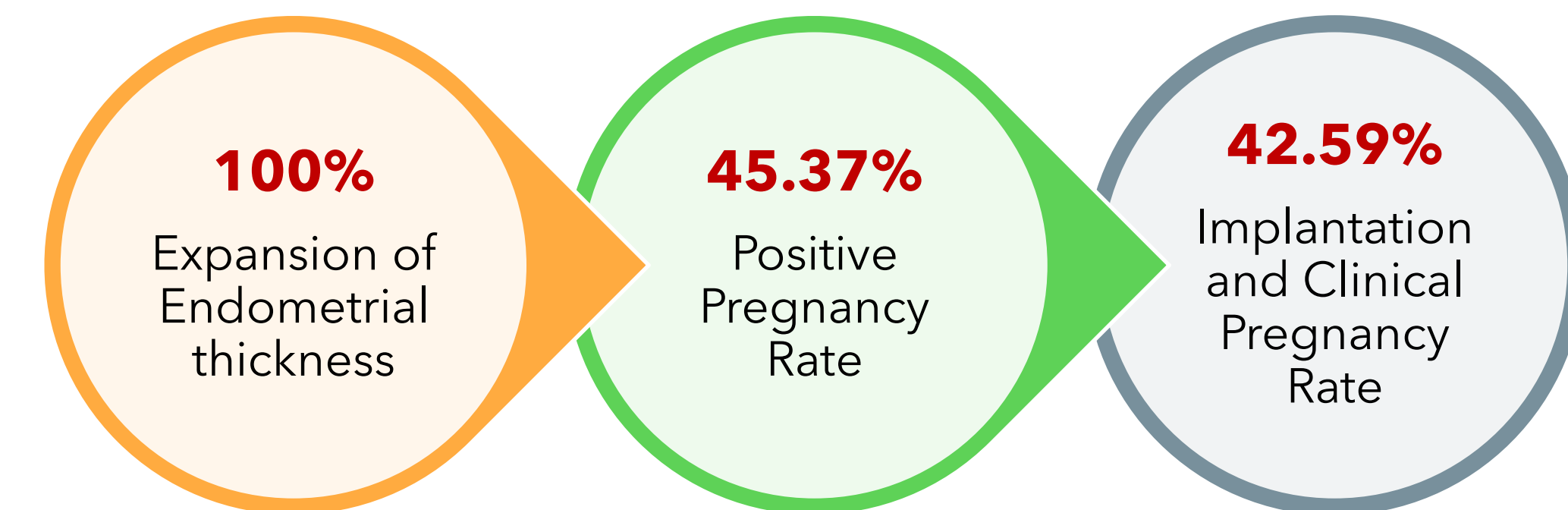


Figure 1. Endometrial Thickness before and after intrauterine PRP infusion

A total of 108 patients with a history of FET cancellation due to thin endometrium were recruited into the study. Uterine cavity abnormalities were ruled out before starting the cycle. All the participants underwent intra-uterine PRP infusion in the treatment cycles due to inadequate endometrium growth. We found that endometrial thickness increased at 48 h after the first PRP and reached more than 7 mm after the second PRP in all patients.

Embryo transfer was then carried out for all of them. 49 patients had a positive pregnancy test and in 46 of them the pregnancy progressed normally, with appearance of cardiac activity by 8 weeks.



DISCUSSION

Adequate endometrial thickness is a major factor for implantation and pregnancy. Women with persistent thin endometrium often do not undergo embryo transfer. Several methods have been described for endometrial preparation but there is dearth of a definitive guideline. In recent years, intrauterine infusion of G-CSF has been studied but inconsistent results have been reported. Besides, the safety profile of G-CSF remains questionable. Local infusion of PRP that contains several growth factors and cytokines may improve endometrial growth and receptivity, similar to G-CSF. PRP is collected from autologous blood sample, so in comparison to G-CSF, PRP is more accessible and affordable^[6].

This study revealed the efficacy of PRP on endometrial growth. Adequate endometrial growth was found in all the participants after two PRP infusions in all patients who had a history of cycle cancellation due to thin endometrium. At the present, however, there is limited evidence in literature in this regard. PRP is a safe procedure, with minimal risks of transmission of infectious disease and immunological reactions since it is made from autologous blood samples.

CONCLUSION

Our study demonstrates that PRP can expand endometrial thickness by recruiting growth factors to the endometrium and has the potential to improve chemical and clinical pregnancy rates in women with thin endometrium undergoing FET cycles. PRP is an innovative therapeutic modality. It is affordable, simple, easily performed, and effective. It is also a non-invasive modality with promising results and no known side effects. The risks of infectious disease transmission and immunological reactions are negligible since it is made from autologous blood samples. In our opinion, large randomized controlled studies are required to confirm its efficacy and safety in various gynaecological disorders.

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