FERTISERA™, A SUPER ACTIVATED AUTOLOGOUS PLATELET-RICH PLASMA THERAPY OPTIMIZES THE ENDOMETRIAL THICKNESS AND PREGNANCY OUTCOMES

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Abstract

Background: Pregnancy rate is increased with growing endometrial thickness. Intrauterine infusion of platelet-rich plasma is a new approach that has been suggested for the treatment of thin endometrium and Repeated implantation failure

Objective: The aim of the study was to evaluate the effect of FERTISERA™, Patented a super activated autologous platelet-rich plasma therapy in the endometrial thickness and pregnancy outcomes in south Indian women.

Methods: A prospective interventional trial was conducted in 698 patients were enrolled in this study based on the predetermined inclusion criteria from the year 2017 to 2020. FERTISERA™, Patented super activated autologous platelet rich plasma (PRP) was prepared by centrifugation of the patient's peripheral blood that has been enriched with platelets. A total of 2.5 mL of FERTISERA™, solution was divided into three equal portions where 5th day of menstrual cycles0.85ml,After 3 days gap the second dose (0.85ml)&3rd dose 0.85ml 48 hrs before embryo transfer infused into the uterine cavity .

Results: The positive pregnancy rate was 53% and achieved endometrial thickness above 7mm was 73% after FERTISERA™ PRP procedure. 8.6% of patients were cancelled cycle and remaining were negative pregnancy. There was a significant increase in the endometrium line thickness after the 2nd dose follow up when compared with baseline ($p<0.001$).

Conclusion: The present study concluded that FERTISERA™ PRP procedure can increase the endometrial thickening and receptivity and thus improve chances of conception.

Keywords: Platelet rich plasma; pregnancy rate; endometrial thickness; conception; intrauterine infusion

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1. Introduction

Despite advancements in the field of assisted reproductive technology (ART), data reveal that approximately 70% to 80% of implanted embryos fail to adhere. Immunological processes generated by decidual cells, such as growth factors, hormones, and cytokines, play a vital and critical part in endometrial implantation [1]. A healthy endometrial thickness is essential for a successful conception. According to Chen et al., 2006, endometrial thickness of less than 8 mm culminated in considerably lower implantation and pregnancy rates [2]. Due to the sheer thin endometrium, several frozen-thawed embryo transfer (FTET) cycles are cancelled, and there is no standard treatment for this condition

Many researchers have taken several steps in this regard. For women with thin endometrium, doctors have traditionally used substantial ovarian stimulation in an attempt to establish a desirable endometrial thickness through high levels of estrogen, but the results have indeed been limited [4]. Meanwhile, following extensive ovarianstimulation, the risk of ovarian hyperstimulationincreased, and the ideal timeframe for egg retrieval was sometimes missed [5]. The use of low dose aspirin for improved endometrial pattern and enhanced pregnancy rate in women with thin endometrium [6]. The use of Pentoxifylline and vitamin E, Sildenafil, and innovative technologies such as Granulocyte colony-stimulating factor (G- CSF) was also brought in light [7]. However, there are still unanswered questions about safety. To overcome such problems, Platelet rich plasma (PRP) therapy has been introduced (Figure 1). PRP is blood plasma that has been enhanced with platelets from fresh whole blood. It is generated from peripheral veins and contains various growth factors that encourage proliferation and growth, including vascular endothelial growth factor(VEGF), epidermal growth factor (EGF), and platelet derived growth factor (PDGF), transforming growth factor (TGF) and other cytokines [1]. The present study aimed to evaluate theeffectiveness of FERTISERA™ in the endometrial thickness and pregnancy outcomes in women.

Patients and methods

A prospective, interventional study was conducted based on the preliminary screen and pre-determined inclusion criteria patients. Patients included if they are free from anaemic conditions and not reported with any chronic complications. Patients excluded if repeated with conditions like bacterial vaginosis, anatomical uterus anomalies, uncontrolled diabetes, patient on anticoagulant therapy, anti-cancer medications and grade 3/4 endometriosis.

Study procedure

After the thorough screening, 30-40ml of blood samples were collected from every patient and the blood samples were centrifuged for 12 mins at 2000-3000 RPM based on patients Hemoglobin and platelet count conditions .After certain separation protocol again it is centrifuges for 10 mins at 2000-2500RPM and the supernatant layer is separated in order to isolate the platelets and inflammatory mediators. After that, a single dose of FERTISERA™ (0.85ml) was administered into the uterine cavity on the 5th day of cycle.2nd&3rd dose to be stored in Liquid nitrogen. Palm thaw the vial with sterile gloves right before infusions. Then 3 days after 1st dose on 8th day the 2nddose was administered and the 3rd dose was administered 48 hours before embryo transfers .Patients should stay in supine posture for 45 minutes after each dose infusions, Ultrasonography will be performed prior to 1st dose followed by 2nd dose to assess the improvement of endometrium thickness and 2 days before embryo transfer to assess endometrium thickness & vascularity final reports were compared with base line values.

Statistical analysis

Data are expressed as mean ± S.D. Statistical analysis was made by comparison of means of the unpaired t-test. P value less than 0.05 was considered as statistically significant. Statistical analyses were performed with Prism software (V8, GraphPad, and San Diego, CA).

2. Results and discussion

In the four consecutive years (2017-2020), 698 patients were enrolled in this study based on the predetermined inclusion criteria. After therapy, in 2017, 29 patients were reported positive pregnancy, 13 reported cancelled cycle and 18 reported negative pregnancy. In 2018, 164 patients were reported positive pregnancy report, 20 with negative report and 06 patient ectopic pregnancy. In 2019, 268 patients were reported positive, 17 reported cancelled cycle, 10 reported with ectopic pregnancy. In 2019, 81 patients were reported positive, 10 reported cancelled cycle, 04 reported with ectopic pregnancy and 07 with negative report. After treatment, endometrium thickness in 2017 group at base line was 2±0.5 mm, in 2018 group 2±1.1mm, in 2019 group 2±1.5mm and in 2020 group 2±0.9mm. After the 1st dose, there was a significant improvement in the endometrium size in 2019 group 3±0.1* ($p<0.05$). However, there was a significant increase in the endometrium line thickness in all the groups after the 2nd dose follow up when compared with baseline ($p<0.001$). [Figure 2, 3 & Table 1]. Endometrial thickness is a key criterion for determining an embryo's uterine

receptivity. Clinical pregnancy rates rise in direct proportion to endometrial thickness over time. Persistent cycle cancellations or repetitive implantation failure may lead to poorer endometrialdevelopment or vascularity, imposing not only a psychological but also a financial burden on the patient [8]. PRP therapy has been introduced in the year in 2015 by Chang et al., 2015. The trials reported significant success rate with normal pregnancy in 4 out of 5 women. One patient had a

Missed abortion at the 9th week due to genetic issues. Onsite administration of PRP including multiple growth factors and cytokines may promote endometrial development and receptivity, according to this notion. PRP is made from an autologous blood sample, making it more accessible and inexpensive than other available methods including G-CSF. In the present study, FERTISERA™ PRP therapy was studied to determine the effect on refractory thin endometrium. On an average, rate of clinical pregnancy has increased gradually through the years (Figure 2) and has reached as high as 77.65% on the whole. Compared to the baseline, endometrium thickness was significantly increased in the 2nd dose when compared to baseline.

3. Conclusion

The present study concluded that FERTISERA™ procedure can increase the endometrial thickening and receptivity and thus improve chances of conception. These findings should set the foundation for a longer and larger randomized controlled trials that directly addressed the impact of FERTISERA™ on endometrial thickness in women with repeated implantation failure.

Ethical Statement

This study was conducted according to the standards of the International Committee on Harmonization on Good Clinical Practice (GCP) and the revised version of the Declaration of Helsinki. The Institutional Human Ethics Committee (IHEC) approved this study protocol.

Conflict of Interest

Conflict of interest exists with the company (MMC Pharmaceuticals Ltd) that may benefit from the results of the study.

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Table 1. Over all description of study population after treatment

Year	No of cases	Positive Pregnancy report	Cycle cancelled	Negative Pregnancy report	Thickness of endometrium at base line (mm)	Thickness of endometrium after 1st dose (mm)	Thickness of endometrium after 2nd dose (mm)
2017	60	29	13	18	2±0.5	2±0.9	8±1.1¶¶¶
2018	209	164	20	25	2±1.1	2±1.2	7.5±1.3¶¶¶
2019	327	268	17	42	2±1.5	3±0.1*	7±1.4¶¶¶
2020	102	81	10	11	2±0.9	2±1.7	8±1.5¶¶¶

Values are expressed in mean± SD; *(*) P<0.001;* Size of endometrium at base line (mm) *Vs* Size of endometrium after 1st dose

Values are expressed in mean± SD; *(¶¶¶) P<0.001;* Size of endometrium at base line (mm)*Vs* Size of endometrium after 2nd dose.

Figure 1. Platelet rich plasma

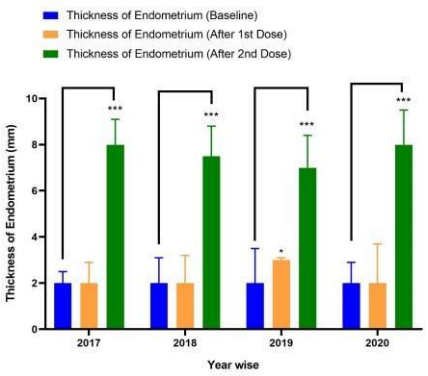

Figure 2. Changes in the thickness of the endometrium from baseline to second dose

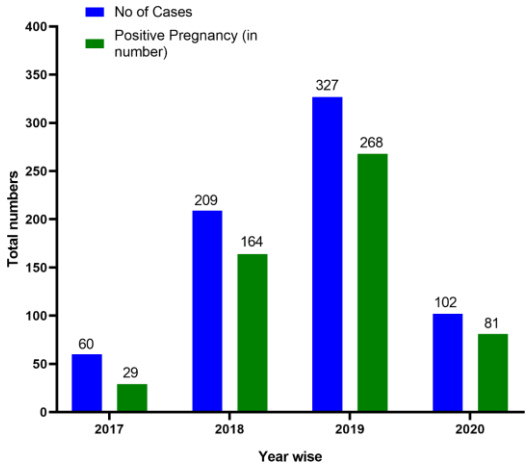

Figure 3. Year wise positive pregnancy reports