

Platelet Rich Plasma in Repeated Implantation Failure in Women with Thin Endometrium Thickness

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ABSTRACT

Background: repeated implantation failure (RIF) is a major challenge in reproductive medicine. Platelet rich plasma (PRP) was able to promote the endometrial growth and improve pregnancy outcome of patients with thin endometrium.

Aim of the study: it was to evaluate the effectiveness of intrauterine infusion of PRP in treatment of thin endometrium in frozen-thawed embryo (FTE) transfer.

Patients and Methods: the study included 10 infertile patients with thin endometrium (<7mm) in Frozen Embryo Transfer (FET) program. Estradiol valerate 12 mg/d was started on day 3 of menstrual cycle. PRP was prepared from autologous blood and infused into the uterine cavity. Endometrial thickness was re-assessed and if the endometrial thickness wasn't satisfactory infusion of PRP was repeated 2-4 times. Cleavage stage embryos were transferred on the 3rd day after progesterone administration, and blastocysts were transferred on the 5th day after progesterone administration.

Results: the endometrial thickness increased after PRP infusion in all the patients, and reached >7mm on the day of progesterone administration. Sixty percent of the patients became pregnant; 83.3% continued pregnancy and 16.7% experienced missed abortion.

Conclusion: intrauterine PRP may be effective in promoting endometrial growth, endometrial thickness, and improving pregnancy out come in repeated implantation failure.

Keywords: Platelet Rich Plasma, Repeated, Implantation Failure, Endometrial Thickness

INTRODUCTION

Repeated implantation failure (RIF) is a major challenge in reproductive medicine. Despite several methods that have been described for management, still no universal agreement about any of these methods. The endometrium is one of the main factors in pregnancy during Assisted Reproductive Technology (ART) treatment some cycle are cancelled due to inadequate endometrial growth. The pregnancy rate is increased with growing endometrial thickness. In several studies the minimum endometrium thickness for embryo transfer was reported to be 7mm⁽¹⁾.

Platelet rich plasma (PRP) was able to promote the endometrial growth and improve pregnancy outcome of patients with thin endometrium⁽²⁾.

Thin endometrium, non-responsive to treatment, is still a challenge in assisted reproductive technique (ART), which usually result in cycle cancellation and unplanned embryo cryopreservation⁽³⁾.

Various strategies have been developed to improve endometrial growth, uterine blood flow and increase endometrial thickness. These strategies include extended use exogenous estrogen, aspirin, vitamin E, vaginal sildenafil citrate, electroacupuncture, and application of granulocyte colony stimulation factor^(1,2,4-8).

However, a number of women with thin endometrium remain non responsive even with the use of these strategies⁽⁹⁾.

Intrauterine infusion of platelet rich plasma (PRP) is a new approach that had been suggested for the treatment of thin endometrium⁽¹⁰⁾.

PRP is blood plasma prepared from fresh whole blood that has been enriched with platelet. It is collected from peripheral veins and contains several growth factors such as vascular endothelial growth factors (VEGF), epidermal growth factors (EGF) and other cytokines that stimulate proliferation and growth⁽¹¹⁾.

Recently, PRP has been used in several medical condition in ophthalmology, surgery and wound healing⁽¹²⁾.

AIM

The aim of this study is to evaluate the effectiveness of intrauterine infusion of PRP in treatment of thin endometrium in FTE (frozen-thawed embryo) transfer.

PATIENTS AND METHODS

Study design:

This study is a non-randomized, non-controlled, clinical trial.

Study site and time:

The study was carried out in Obstetrics and Gynecology Department, Tanta University hospital, Tanta, Egypt from January 2018 to August 2019.

Study patients:

The study was conducted on 10 infertile female patients with repeated implantation failure. The patients had thin endometrium (endometrium <7mm) in Frozen Embryo Transfer (FET) program. The patients were selected in the previous fresh embryo transfer cycles when these cycles were cancelled because of thin endometrium thickness on the day of administration of human chorionic gonadotropin (HCG). The age of the selected patients ranged from 30 to 39 years.

Study procedure:

In this study the effects of PRP was investigated.

Hormone replacement therapy (HRT) protocol and PRP preparation:

Estradiol valerate (Progynova; Bayer Schering Pharma, France) at 12 mg/d was started on day 3 of menstrual cycle. PRP was prepared from autologous blood by a modified method according to **Yamaguchi et al.**⁽¹³⁾. On the 10th day of FTE cycle, 15 ml of venous blood was drawn in a syringe pre-filled with 5 ml of anticoagulant solution (ACD-A), and centrifuged immediately at 200° g for 10 min. The blood was divided into three layers: red blood cells at the bottom, cellular plasma in the supernatant and a buffy coat layer between them. The plasma layer and buffy coat were collected to another tube and re-centrifuged at 500° g for 10 min. The resulting pellet of platelets was mixed with 1 ml of supernatant, and then 0.5-1 ml of PRP was obtained. It was infused into the uterine cavity immediately with Tomcat catheter (0.5-4 ml). Endometrial thickness was re-assessed 72 hr later. If the endometrial thickness was not satisfactory infusion of PRP was repeated 2-4 times.

Cleavage stage embryos were transferred on the 3rd day after progesterone administration, and blastocysts were transferred on the 5th day after progesterone administration.

Treatment assessment:

Endometrial thickness was measured at the thickest part at the longitudinal axis of the uterus by an experienced ultra-sonographer. The thickness was measured thrice to confirm the endometrium thickness, and the average from the three measurements was recorded. The primary end-point was endometrial thickness measured in transvaginal sonography, the second endpoint was clinical pregnancy after embryo

transfer. Clinical pregnancy was confirmed when an intrauterine gestational sac was identified by transvaginal ultrasonography and a comparable increase in serum B-HCG was present.

Ethical considerations:

Protocol of the study was approved by the local Ethical Committee of Tanta Faculty of Medicine. The participant patients were fully informed about protocol of the treatment and accordingly they signed consents to participate in the study.

RESULTS

The endometrial thickness increased at 48-72 h after PRP infusion in all the patients, and reached >7 mm on the day of progesterone administration.

Six (60%) of the patients became pregnant; five (83.3%) continued pregnancy and one (16.7%) experienced missed abortion at 8 weeks.

DISCUSSION

The main objective of this study was to improve endometrial quality and implantation rates after the administration of platelet rich plasma in patients with refractory endometrium undergoing in vitro fertilization-embryo transfer treatment.

The study proves that platelet rich plasma is beneficial in promoting endometrial growth, increasing endometrial blood flow and endometrial thickness. This helped to increase the pregnancy rate and live birth rate in patients with repeated implantation failure due to poor endometrial growth and thin endometrial thickness.

Other studies pointed to the same conclusion, **Chang et al.**⁽¹⁰⁾ in their trial reported the efficacy of intrauterine infusion of PRP for endometrial growth in women with thin endometrium. They infused PRP in 5 women with inadequate endometrium who had poor response to conventional therapy during the FET cycle. The proper response to treatment was reported in all of them, and normal pregnancy was reported in 4 women.

The main advantage of this technique would be the availability of an autologous resource of low cost, which offers obvious benefits regarding the development of a receptive endometrium that favors embryo implantation.

Garcia-Velasco et al.⁽¹⁴⁾ performed an extensive literature review on the management of refractory endometrium. The review included studies with conventional hormone preparations (estradiol Valerate), as well as various drugs including acetylsalicylic acid (aspirin), sildenafil, vitamin E, GnRH agonists, HCG, I-arginine, pentoxifylline among others: as well as autologous preparations as growth factors, mainly G-SF,

stem cells, PRP and bone marrow. Finally, they concluded that despite the vast array of resources available today, it is still not easy to provide a pragmatic evidence-based approach that guides the clinician on how to improve refractory endometrium. In this sense and regarding the results of this study, it is considered important to complement them with the formal design of test protocols, as well as, comparative studies to establish the efficacy between different drugs and preparation, besides the inclusion of several years of data collection.

CONCLUSION

Intrauterine PRP may be effective in promoting endometrial growth, increasing endometrial thickness, and improving pregnancy outcome in repeated implantation failure due to thin endometrium.

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