

The Effect of Intrauterine Infusion of Plasma Enriched Platelet on Live Birth Rate in Patients with Implantation Failure: A Retrospective Uncontrolled Study

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ABSTRACT

Background & Objective: Autologous platelet-rich plasma consists of concentrated autologous plasma and several cytokines and growth factors released by activated platelets in injury and inflammation. There is an increasing trend towards the effectiveness of intrauterine PRP infusion in repeated implantation failure patients. The aim of the present study was to describe the impact of intrauterine platelet-rich plasma infusion on the live birth rate in patients with repeated implantation failure.

Materials & Methods: The present retrospective uncontrolled study was performed on 96 patients with more than two failed intracytoplasmic sperm injection cycles at Mehr medical institute between 2019 and 2021. Forty-eight hours before embryo transfer, patients received 1 mL lympho-platelet-rich plasma through an intrauterine insemination catheter. Patients were evaluated for pregnancy rate. Endometrial preparation for frozen-thawed embryo transfer was performed.

Results: Participants' basal and stimulation characteristics, including gonadotropin dosage, the total number of oocytes, metaphase II oocytes and embryos, endometrial thickness, embryo transfer, quality of transferred embryos, and blastocyst transfer rate were evaluated. A total of 33 and 27 chemical (34.3%) and clinical pregnancies (28.1%) were achieved. Twenty (20.8%) and nineteen (20%) cycles resulted in ongoing pregnancies or live births, respectively.

Conclusion: The current study suggests that platelet-rich plasma infusion 48 hours before frozen-thawed embryo transfer may be a good option for repeated implantation failure patients and results in 20% live birth.

Keywords: Embryo implantation, Intracytoplasmic sperm injection, Plasma enriched platelet, Pregnancy



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Introduction

Recurrent implantation failure (RIF) refers to the failure of implantation following the transfer of good-quality embryos through several cycles of in vitro fertilization (IVF). It became a common challenge among physicians and patients.

Implantation failure may result from an aberration in any stage of implantation, including apposition, adhesion, and invasion. Multiple factors contribute to implantation failure but can be classified into endometrial receptivity disturbances and embryonic

defects (1). When the quality of embryos is good, non-functioning and non-receptive endometrium remain challenging issues for physicians due to the lack of beneficial therapeutic options in these settings.

Different methods have been applied for overcoming implantation failure and increasing live birth chances in RIF patients, such as endometrial stimulation, hysteroscopic treatment of cavity abnormalities, blastocyst transfer, and immunotherapy (2).

In recent years, uterine instead of systemic immunomodulation was preferred for RIF with the continued development of reproductive immunology. Intrauterine infusion of autologous peripheral blood mononuclear cells and platelet-rich plasma (PRP), human chorionic gonadotropin (hCG), and granulocyte colony-stimulating factor (G-CSF) has been suggested. Still, there is not any consensus on the advantages of one modality over others (3).

PRP consists of concentrated autologous plasma and several cytokines and growth factors released by activated platelets in injury and inflammation (4-6). They exert proliferative, pro-regenerative, angiogenic, pro-inflammatory, antiapoptotic, and chemotactic effects (7). Chang *et al.* (8) first suggested that PRP can increase the endometrial thickness (ENT) in IVF patients with resistant thin endometrium. It has become a preferable choice for improving the pregnancy rate. Moreover, it has shown promise in improving implantation and pregnancy rates (9-11) in RIF, but there are not adequate results regarding the effect of PRP on the pregnancy rate. The aim of the present study was to describe the impact of intrauterine infusion PRP on the live birth rate in patients with RIF.

Methods

Ninety-six intracytoplasmic sperm injection cycles were included in the present retrospective uncontrolled descriptive study. All patients diagnosed with RIF related to the number of failed implantation cycles (more than 2 cycles) at Mehr medical institute were included in this study.

Age less than 42 years and follicle-stimulating hormone (FSH) < 10 ng/mL were considered inclusion criteria. The exclusion criteria were a severe male factor, hematological disorders, and severe endometriosis.

PRP Preparation

According to the manufacturer's instruction (Rooyagen, Iran) for preparing 1.5 mL lympho-PRP with 2000 lymphocyte/ μ L. Platelet concentration was 4-5 times higher than basal, which 8.5 mL peripheral venous blood was drawn and centrifuged to separate red blood cells (12 min, 1200 rpm). Forty-eight hours

before embryo transfer, patients received 1 mL lympho-PRP through an intrauterine insemination catheter (Cook, USA).

Ovarian stimulation

Pituitary suppression was accomplished with GnRH analogues. In the GnRH agonist protocol, decapeptyl (1.875 mg, Ferring, Germany) was administered in cycle day 21 prior to ovarian stimulation. Ovarian stimulation was done with human menopausal gonadotropin and recombinant FSH according to personalized characteristics until the day of hCG administration. In the GnRH antagonist cycle, cetrotide (0.25 mg, Merck Serono, Germany) was administered daily, starting from the day that dominant follicles reached 11 mm in diameter. When at least 3 follicles reach 18 mm, triggering was performed with hCG in almost all patients, except those with increasing probabilities of ovarian hyperstimulation syndrome. Oocyte retrieval was performed 36 h after final triggering. Aspirated oocytes were fertilized with intracytoplasmic sperm injection, and day 3 embryos were graded according to the number, size, and amount of fragmentation of blastomeres. All embryos were vitrified.

Frozen Embryo Transfer

Endometrium was prepared with oral estradiol and followed with progesterone (for three to five days according to the developmental stage of the embryos) when approximately 7 mm endometrial thickness with a triple-line pattern was seen on ultrasound.

Results

A total of 69 participants with a history of RIF were entered into this study. Causes of infertility were: tubal factor (n=44 (16.8%)), ovulatory factor (n=43 (16.41%)), male factor (n=49 (18.7%)), combined (n=94 (35.88%)) and other (n=32 (12.21%)). [Table 1](#) provides a baseline characteristics summary of patients. All stimulation characteristics of participants, including gonadotropin dosage, the total number of oocytes, metaphase II oocytes and embryos, endometrial thickness (ENT), embryo transfer, quality of transferred embryos, and blastocyst transfer rate are expressed in [Table 2](#).

Table 1. Baseline characteristics of patients

Variables	
Age (years)	32±6.1
BMI (kg/m ²)	26.12±3.68
Primary infertility (years)	8.28±7.02
Secondary infertility (years)	4.01±3.75
Failed implantation	2.61±1.68
History of failed embryo transfer	2.61±1.68
FSH (mIU/ml)	5.1±2.3
AMH (ng/ml)	3.72±2.48

BMI: Body mass index
 FSH: follicle stimulating hormone
 AMH: Anti mullerian hormone

Table 2. Ovarian stimulation characteristics

Variables	
Gonadotropin dosage (IU)	2757.8±1174.8
Total number of oocytes	14.8±8.7
Total number of metaphase II oocytes	11.9±8
Total number of embryos	8.3±5.5
Endometrial thickness (mm)	8.5±1.1
Embryo transfer	2.6±0.8
Quality of transferred embryos (Top:1, Good:2, Poor:3)	1.8±0.6
Blastocyst transfer (%)	66 (68.8)

mean±SD

A total of 33 and 27 chemical (34.3%) and clinical pregnancies (28.1%) were achieved. Twenty (20.8%)

and nineteen (20%) cycles resulted in ongoing pregnancies or live births, respectively ([Table 3](#)).

Table 3. Pregnancy outcome

Variables	
Chemical pregnancy (%)	33 (34.3)
Clinical pregnancy (%)	27 (28.1)
Ongoing pregnancy (%)	20 (20.8)
Live birth (%)	19 (19.8)

Discussion

The present report described 96 IVF cycles in patients who underwent PRP due to RIF. Our results indicated a considerable effect of PRP in patients with different causes of infertility. Approximately 34% of the cycles resulted in chemical pregnancies, of which 28%, 21%, and 20% moved on to clinical, ongoing pregnancies, and live births, respectively.

For successful implantation, the endometrium needs to regenerate and proliferate properly following the physiologic cyclic shedding. Different cells, growth factors, pro-inflammatory cytokines, and local chemokines are involved in this complex process, including endothelial, epithelial, and stem cells and fibroblasts (2). They interact in terms of migration, proliferation, and trans-differentiation through mesenchymal to epithelial transition. Proper endometrial thickness (ENT) is considered an important indicator of endometrial growth and receptivity. For embryo transfer, ENT at the end of the follicular phase must be at least 7 mm (9).

Platelets possess chemokines with the ability to induce endothelial migration (10, 11). The study by

Tandulwadkar *et al.* showed that PRP could induce neo-angiogenesis in women undergoing frozen embryo transfer cycles with suboptimal endometrium. It increased vascularity that reaches 3 and 4 endometrial zones, which was detected by higher vascular signals on power Doppler (12). Literature on using PRP for enhancing endometrial thickness and receptivity has been encouraging (13).

In regards to leukocyte and fibrin levels, four types of PRP are available, including platelet-rich fibrin (L-PRF), pure platelet-rich fibrin (P-PRF), leukocyte, and platelet-rich plasma (L-PRP), and pure platelet-rich (P-PRP). It can be safely and easily applied because it carries no potential risk of disease transmission, immunologic reaction, or cross-contamination because it is an autologous product. Besides, it remains a non-invasive and easily accessible therapeutic option with low cost (14, 15).

Recently, more studies have been performed to evaluate the effects of intrauterine infusion of PRP on pregnancy outcomes in RIF patients, but the results are

conflicting. The heterogeneity between studies was related to dosage and type of intrauterine PRP infusion.

In a study of 85 RIF patients with a normal ENT (≥ 7 mm), 42 patients received 1 mL of PRP 2 days before ET, while 43 were included in the control group. The pregnancy outcomes, were similar between groups and they concluded that PRP is not an efficient adjuvant treatment (16).

This is constructed by Nazari *et al.* (17), who performed a pilot study on 20 women with a history of RIF and candidates for frozen-thawed embryo transfer (FET) and underwent intrauterine infusion of 0.5 mL PRP 48 hours before blastocyst transfer. The rate of pregnancy, early miscarriage, and molar pregnancy were 90, 5, and 5 percent, respectively. In this study, 16 had clinical pregnancies resulting in a live birth.

In 123 RIF patients, Mehrafza *et al.* found that intrauterine infusion of PRP 48 hours before FET can positively affect pregnancy outcomes compared with systemic GCSF administration (18). This is similar to Zamaniyan *et al.*, who, in 98 RIF women with FET, found that PRP infusion 48 hours before FET positively affects pregnancy outcome (19).

Also, in a prospective observational cohort study, Noushin *et al.* reported an improvement in FET outcome with an increase in the rate of ongoing pregnancy and live birth in RIF patients who underwent PRP infusion following observation of 7 mm ENT at ultrasound (20). Another study on 138 RIF patients who underwent PRP infusion 48 hours before ET has pointed out the effectiveness of PRP infusion on pregnancy rate (21).

The exact mechanism of action of PRP on endometrial receptivity is unknown. However, findings support the improvement of pregnancy outcomes by increasing ENT (22, 23). Also, it was indicated that PRP enhances endometrial receptivity via immune

interactions between embryo and endometrium at the time of implantation (24).

The advantage of the present study is the report on the live birth rate, which is the most important endpoint of ART. However, the absence of a control group was the present study's main limitation.

Conclusion

In conclusion, the current study suggests that intrauterine infusion of PRP 48 hours before FET results in 20% live birth. More research is needed to confirm the present result.

Author contributions

Dr. Marzieh Mehrafza: contributed to protocol writing, management of the study, and manuscript writing and editing, Azadeh Raoufi: contributed to data collection, data analysis, and manuscript writing and editing; Dr. Tahereh Zare Yousefi: performed experiments and data collection. Elmira Hosseinzadeh: contributed to data collection, Termeh Shakery: contributed to data collection, Gholam Reza Pourseify: supervised the research, and Dr. Amirhossein Tamimi: contributed to critical manuscript revision.

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Conflict of Interest

The authors declared no conflict of interest.

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