

Effects of intrauterine autologous platelet-rich plasma infusions on outcomes in women with repetitive in vitro fertilization failures: a prospective randomized study

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Purpose: Evaluation of the effect of platelet-rich plasma (PRP) containing platelet-derived growth factor on in vitro fertilization (IVF) failure patients. **Methods:** In this clinical trial, 80 eligible patients (infertile women with at least two IVF failures) were randomly assigned into two groups, including patients who received an intrauterine infusion of PRP (n: 40) and controls (n: 40). Before PRP therapy, standard hormone replacement therapy was performed for all patients to endometrial thickness preparation. After sonographic assessment of endometrium, PRP was injected into all patients' endometrium whether they had an appropriate endometrial thickness or not. Then, the embryo transferring was done through IVF. Eventually, the consequences of fertility, embryo implantation, and pregnancy were evaluated. Data analysis was performed using SPSS version 22. **Results:** The rate of successful IVF [6 (15%)], pregnancy rate [5 (12.5%)], and live birth [5 (12.5%)] were relatively higher in patients undergoing PRP therapy compared with controls [2 (5%), 1 (2.5%) and 0, respectively]. However, their statistical difference was not significant between the two groups ($P > 0.05$). **Conclusion:** Our findings suggest that endometrial injection of platelet-rich plasma for IVF failure patients did not significantly improve the IVF process, pregnancy, and live birth rates.

Keywords

Platelet-rich plasma; Platelet-derived growth factor; In vitro fertilization; Pregnancy rate; Live birth; Women

1. Introduction

The successful fetus implantation requires the proper growth of the fetus simultaneously with an appropriate receptive endometrium. The thin endometrium is not responsive to standard treatments, and it's still a challenge for assisted reproductive techniques (ART) which usually leads to cycle cessation and unplanned embryo freezing [1, 2]. So far, various strategies have been developed for the treatment of thin endometrium, including the long-term exogenous estrogen therapy [3], use of low dose aspirin [4], vitamin E [5], sildenafil citrate (vaginal) [6], electroacupuncture [7], and use of granulocyte colony-stimulating factor (G-CSF) [8]. However, the mentioned treatments are not successful in a number of women with a thin endometrium.

Several studies in different countries have investigated

the therapeutic effect of platelet-rich plasma (PRP) containing platelet-derived growth factors (PDGF) on endometrial growth and provided significant results [9–12]. PRP is prepared from whole fresh blood containing several growth factors and cytokines that include PDGF, transforming growth factor-beta ($TGF\beta$), fibroblast growth factor (FGF), insulin-like growth factor 1 and 2, vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), keratinocyte growth factor (KGF), connective tissue growth factor (CTGF) [13, 14]. The endometrium of healthy women expresses PDGF ligand subunits and its receptors subunits [15]. In vitro studies have shown that stromal and epithelial endometrial cells replicate in response to PDGF [16, 17].

Previously, PRP has been studied as a treatment for several medical disorders, including nerve damages, eye epithelium defects, hair loss, myocardial damage, osteoarthritis, and tendinitis. Despite the widespread use of PRP in various medical fields, its effectiveness on obstetrics and gynecology diseases has been studied in rare studies [11, 12, 18]. Accordingly, the present study was designed to investigate the effect of PRP containing PDGF on the unsuccessful embryo implantation in women undergoing IVF, whether they had an appropriate endometrial thickness or not. The effects of PRP therapy on IVF failure patients were evaluated based on the rates of embryo implantation, successful pregnancy, and live birth. Our findings provide valuable information to improve pregnancy outcomes through the IVF process.

Statement of Significance

Problem: Most cases of female infertility are faced with in vitro fertilization-failure due to the thin endometrium or other unknown reasons.

What is Already Known: So far, the considerable therapeutic effect of PRP containing PDGF has been shown on endometrial growth.

What this Paper Adds: This study evaluated the therapeutic effect of PRP in the improvement of the IVF process, pregnancy, and live birth rates.

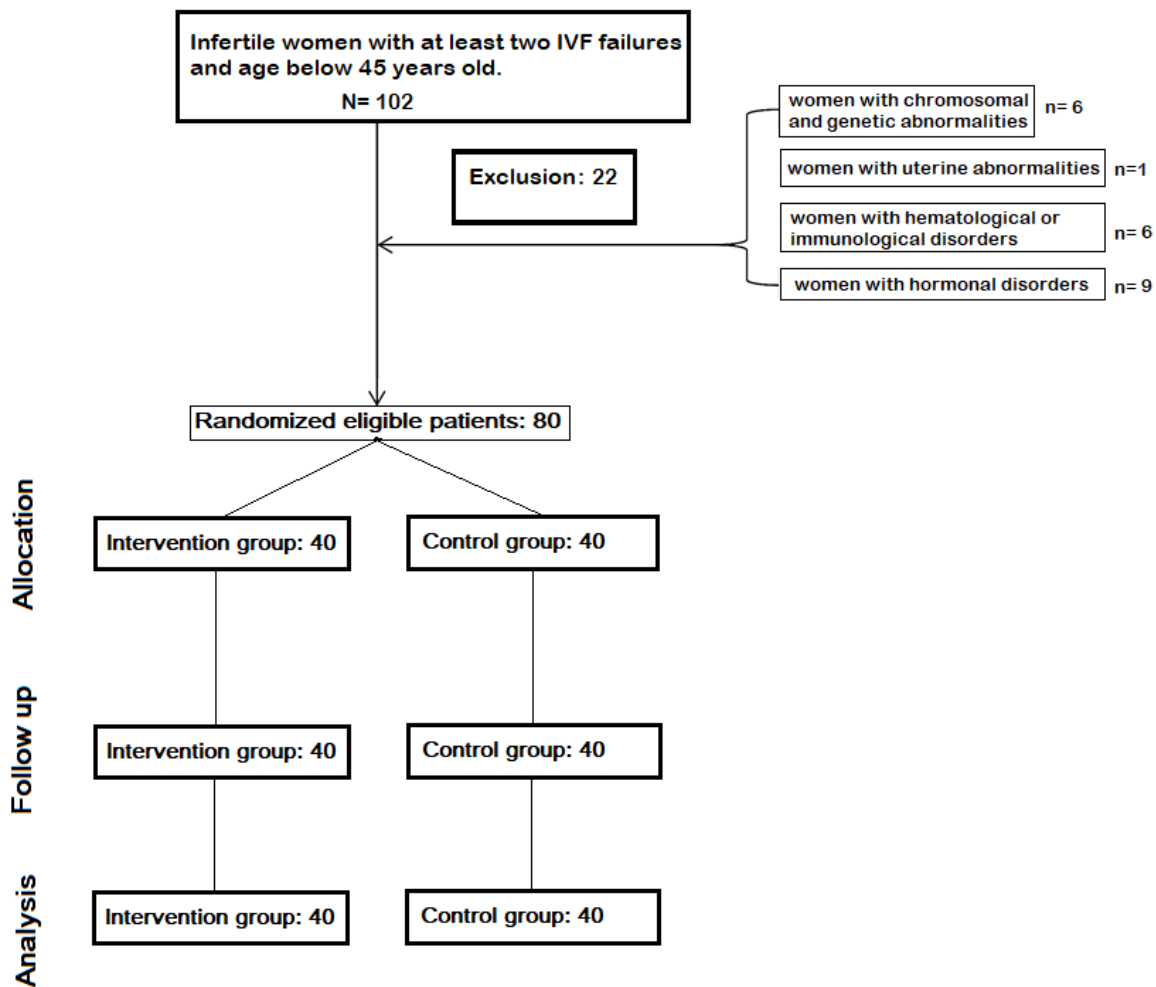


Fig. 1. Flowchart: The inclusion and exclusion criteria to select eligible infertile women.

2. Materials and method

Eligible patients were randomly assigned into two groups, including patients who have received an intrauterine infusion of PRP and patients without PRP injection (controls). The inclusion criteria were infertile women with at least two IVF failures and age below 41 years old. The exclusion criteria were women with chromosomal, genetic, and uterine abnormalities, hematological or immunological disorders, and hormonal disorders. Also, the embryos that arise from such maternal and paternal abnormalities were excluded (Fig. 1).

Before PRP therapy and embryo transfer process, standard hormone replacement therapy (HRT) with Estradiol valerate (Transdermal dosage: 0.2_0.4 mg/day; Aburaihan, Iran) was performed for all patients to endometrial thickness preparation. This dose causes blood levels of 200 to 400 pg/mL which is equivalent to the normal level in the late follicular phase [19]. Eventually, the endometrial thickness reached the appropriate size (7-10 mm) in 38 patients while 2 women did not reach the appropriate size (7 mm). Endometrial thickness is measured by ultrasound from the echogenic border to the echogenic border across the endometrial cavity on a sagittal midline image.

For luteal phase support in IVF women, we used Crinone

8% Progesterone Vaginal Gel containing 90 mg of progesterone (Merck KGaA, Darmstadt, Germany) on a daily dosage of 1.125 g 8% gel, starting on the 18th - 21st day of the cycle.

After sonographic assessment of endometrial thickness, PRP (1.5 mL) was injected into all patients' endometrium whether they had an appropriate endometrial thickness (7-10 mm) or not (< 7 mm). Intrauterine infusion of PRP was performed 48 h before embryo transfer in those who had an appropriate endometrial thickness; however, PRP (1.5 mL) was re-injected for two patients who did not have an appropriate endometrial size 48 h after the first injection [11]. After sonographic reassessment, the embryo transfer process was done by Frydman catheter (Eurosurgical; Prodimed). Eventually, the consequences of fertility, embryo implantation, and pregnancy maintenance were evaluated.

PRP is prepared from autologous blood by "Fertilize Lympho-PRP kit". Firstly, 8.5 mL of venous blood was drawn from the syringe pre-filled with 1.5 mL of anticoagulant solution (ACD; Terumo; at a ratio of 10 : 1.5) and centrifuged immediately at 12,000X 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 was collected to another tube and re-centrifuged at 12,000X g for 10 min. White sediment of platelet pellets was formed at the bottom of the tube that was PRP. According to the PRP kit's instructions (PRP centrifuge kit; Prodizen, Korea), the white sediment dissolved in 1.5 mL plasma [the 1.5-line indicated on the tube for infertility cases] was used as PRP containing platelet growth factor. The IVF process is organized into four main steps as follows:

1. Stimulation/superovulation
2. Egg retrieval
3. Insemination and Fertilization
4. Embryo culture

The successful IVF and IVF failure were respectively defined as successful embryo implantation and the failure of implantation.

The "pregnancy live birth" was defined as the delivery of a live born child after 24 weeks of gestational age.

Considering the main purpose of the research, the researcher's idea, previous studies [20], and $\beta = 0.8$, $\alpha = 0.05$, $p_1 = 50\%$ and $p_2 = 80$, the sample size was calculated using the following formula (With considering 10% statistical outputs):

$$n = \frac{(z_{1-\alpha/2} + z_{\beta})^2 [p_1(1 - p_1) + p_2(1 - P_2)]}{(p_1 - P_2)^2} \quad (1)$$

N: 40

Totally: 80 N

2.1 Randomization, blinding, and allocation

This parallel-group, single-blind, and randomized controlled trial was randomized by designing a table of the randomized block size of 6. To maintain single-blinding, the responsible investigator was unaware of the grouping of each patient. But, the main physician and patients were aware. However, the physician did not consciously interfere in the selection of patients for each group. In fact, she started the treatment process on the advice of a second researcher, who had designed a table of the randomized block without knowing the patients' medical conditions.

2.2 Statistical analysis

A chi-square test was used to detect a relationship between quality variables. Also, the Mann-Whitney U test or *t*-test was used for quantitative variables. Generalized Estimating Equations (GEE) were used to determine the relationship between variables measured over a number of times during the study [Considering *P*-value < 0.05 for all tests]. Data analysis was done using SPSS version 22.

2.3 Ethical approval

This clinical trial was approved by the ethics committee of Ahvaz Jundishapur University of Medical Sciences with **Ethical Code: IR.AJUMS.REC.1396.634**.

All subjects gave their informed consent before participating in the study. All procedures performed in this study involving human participants were in accordance with the ethi-

cal standards of the national research committee and with the 2008 Helsinki declaration and its later amendments or comparable ethical standards. This clinical trial has been registered in the Iranian Registry of Clinical Trials (**IRCT registration number: IRCT20180102038182N1**).

3. Results

All the demographic and clinical data of patients are presented in Table 1. Also, Table 1 presents the results of the statistical comparison of all variables in both the PRP⁺ group and controls (PRP⁻ group).

The successful IVF process was observed in 6 (15%) and 2 (5%) patients among the PRP⁺ and PRP⁻ groups, respectively. However, based on Fisher's exact test, there was not any statistically significant difference in terms of the successful IVF frequency between both groups (*P*-value = 0.2751). During the follow-up of patients, other IVF-related variables, including pregnancy rate, abortion, and live birth rate were investigated in both groups (Fig. 2). Although the rate of successful pregnancy and live birth rate were respectively higher in the PRP⁺ group compared with controls, there was not any statistically significant difference between both groups (*P*-Value > 0.05).

From a total of 8 women with successful IVF, 5 women were undergoing 2 embryos transfer and 3 women received single embryos. Also, from a total of 72 Unsuccessful IVF, 47 women have received 2 embryos and 25 were received single embryos. So, there was not any statistically significant correlation between successful IVF and the number of transferred embryos (*P*-Value: 0.223).

There was no azoospermia case or testicular sperm extraction (TESE) case.

The mean (SD) time elapsed since the first IVF was 1.66 ± 1.05 (1-5) years. From a total of 80 cases, 40 and 34 cases were respectively under standard HRT in the PRP⁺ group and control group. In the PRP⁺ group, 38 cases reached the appropriate thickness (7-10 mm) while 2 women did not reach an appropriate size (< 7 mm); after patient tracking, one of these two women eventually reached the successful pregnancy and live birth.

In the control group, 39 cases reached the appropriate thickness, but one case did not reach the appropriate thickness as well as the successful pregnancy and live birth.

4. Discussion

Receptive endometrium is one of several crucial factors for successful implantation and pregnancy [21]. The thin endometrium is not responsive to standard treatments, and it's still a challenge for ART [1, 2]. However, immunological, hormonal, anatomical, and infectious factors along with known genetic factors are involved in 50% of Pregnancy loss cases; in this regard, about 9.8% of infertile couples have chromosomal balanced rearrangement [22].

Several studies have investigated the therapeutic effect of PRP on endometrial growth and provided significant results [9-12]. In this regard, Munson *et al.*'s study evaluated the effects of PDGF on the proliferation of endometrial epithe-

Table 1. Statistical comparison of all variables in both PRP⁺ group and controls (PRP-group).

Variables	All women Mean ± SD [min-max], frequency	PRP ⁺ (n = 40)	PRP ⁻ (n = 40)	P-value
Age (years)	31.9 ± 4.46 (23-40)	34.15 ± 5.14	32.82 ± 5.18	0.33
Marriage duration	8.52 ± 4.22 (2-25)	8.82 ± 4.83	8.22 ± 3.54	0.9
Infertility duration	7.22 ± 3.36 (2-25)	7.5 ± 4.73	6.95 ± 3.04	0.85
Time elapsed since the first IVF*	1.66 ± 1.05 (1-5)	1.96 ± 1.51	1.36 ± 0.9	0.06
Educational status:				
Degree level under high school diploma	49 (61.3%)	24 (60%)	25 (62.5%)	
High school diploma or upper levels	31 (38.7%)	16 (40%)	15 (37.5%)	> 0.9
BMI				
< 30	59 (73.75%)	28 (70%)	31 (77.50%)	0.612
≥ 30	21 (26.25 %)	12 (30%)	9 (22.50%)	
Type of infertility				
Primary	66 (82.55%)	34 (85%)	32 (80%)	0.7695
Secondary	14 (17.5%)	6 (15%)	8 (20%)	
Cause of infertility:				
Male related causes	25 (31.3%)	12 (30%)	13 (32.5%)	0.901
Female related causes	23 (28.8%)	11 (27.5%)	12 (30%)	
Both causes	32 (40%)	17 (42.5%)	15 (37.5%)	
The number of IVF full cycles				
2	58 (72.5%)	34 (85%)	24 (60%)	0.0429 *
3	14 (17.5%)	4 (10%)	10 (25%)	
> 3	8 (10%)	2 (5%)	6 (15%)	
Number of embryos				
1	44 (55%)	20 (50%)	24 (60%)	0.1806
2	34 (42.5%)	20 (50%)	14 (60%)	
3	2 (2.5%)	0	2 (5%)	
Grade 4: high quality	42 (52.50%)	22 (55%)	18 (45%)	0.5026
Grade 3: good quality	38 (47.50%)	18 (45%)	22 (55%)	
Fresh Embryo	14 (17.5)	10 (25%)	4 (10%)	0.1395
Frozen Embryo	66 (82.5)	30 (75%)	36 (90%)	
IVF result:				
Successful	8 (10%)	6 (15%)	2 (5%)	0.2751
Unsuccessful	72 (90%)	34 (85%)	38 (80%)	
Successful pregnancy rate	8 (10%)	5 (12.5%)	1 (2.5%)	0.4643
Abortion	72 (90%)	1 (2.5%)	1 (2.5%)	
live birth rate	5 (12.5%)	5 (12.5%)	0	0.0547

BMI: Body mass index.

* Data presented as mean ± SD.

* Time interval from the first IVF.

Grade 4: high quality = 8 cell, day 3 embryo, no embryo fragmentation ,cells are very even, regular, and similarly sized.

Grade 3: good quality = 8 cell, day 3 embryo, minimal fragmentation, fairly regular in sized.

lial cells. Their results showed the existence of functional PDGF receptors on the endometrial epithelial cells that signal cell replication [23]. Previously, Surrey and Halme (1991) demonstrated that PDGF secreted from macrophages may have a significant role in endometrial cell proliferation [24]. The present study has investigated the effect of PRP containing PDGF on IVF outcomes, whether the endometrial thickness is appropriate (7-10 mm) or not (< 7 mm). Given that some infertility causes are unknown and not merely related to the endometrial thickness, we also assessed the effect of PRP therapy on two women with a thin endometrium (< 7 mm).

Based on our findings, the frequency of IVF success in the PRP⁺ group was partially more than PRP⁻ group. Although, this frequency difference was not statistically significant in-

dicating that PRP therapy showed not any significant effect on the IVF success rate. In this regard, Chang *et al.*'s study showed that PRP promotes endometrial growth and improve pregnancy outcome in patients with thin endometrium [12]. Recently, Zadehmodarres *et al.* (2017) evaluated the effectiveness of PRP in the treatment of thin endometrium on ten patients with a history of inadequate endometrial growth. They showed the considerable effectiveness of PRP on endometrial growth [19]. Jang *et al.* (2017) showed that intrauterine administration of autologous PRP stimulated and accelerated the regeneration of the endometrium as well as decreased fibrosis in female rats [25].

In fact, the mentioned studies have merely focused on the effect of PRP therapy on the repairment of endometrial

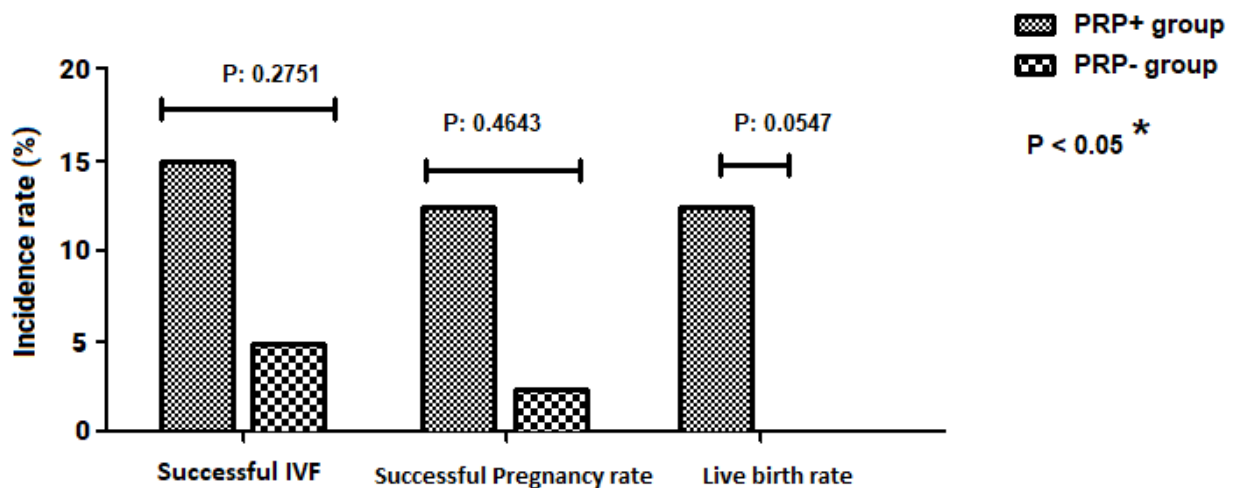


Fig. 2. Comparison of IVF-related variables (%) between PRP+ group and controls (PRP-group). Successful IVF: successful embryo implantation.

thickness while some infertility causes aren't merely related to the endometrial thickness. In this sense, although our results showed that PRP therapy can improve the IVF success rate whether the endometrial thickness is appropriate or not, its improvement effect was not statistically significant. So, our findings were inconsistent with the mentioned studies [12, 19]. Moreover, our study more comprehensively explored the effect of PRP therapy on the improvement of the IVF process, pregnancy rate as well as live birth rate following patient tracking. Although the successful pregnancy and live birth rates were found to be higher in the PRP⁺ group, this difference was not statistically significant between both groups. Also, the number of embryos (1 and/or 2) has not affected the success of the IVF process.

Considering the relative similarity of the method between our study with other studies [12, 20], the low sample size seems to be a disruptive factor in achieving accurate results. Hence, it's suggested to conduct more studies on a higher sample size to obtain more accurate results. However, our sample size was more than the sample size of previous studies.

In this clinical trial, the age range of 23-40 years old was considered; from a total of 8 women with successful IVF, 5 and 3 cases were under 35 and over 35 years old, respectively. Subsequently, from a total of 6 cases with a successful pregnancy, 3 cases were under 35 years old. Such a wide range of age may affect the patient's prognosis and could be a selection bias.

5. Conclusions

The injection of PRP into the endometrium of IVF-failure patients may usefully affect the outcomes of the IVF process, pregnancy rate, and live birth rate, but not significantly so. Nevertheless, more researches are needed into a higher sample size to reach more accurate findings.

6. Weaknesses of this study

Considering a higher sample size for this study may give us more accurate findings.

Author contributions

Z. M designed the research study. Z. M and P. R performed the research. N. M provided help on the clinical step of the research. M.C. P provided help and advice on the PRP Preparation. Z. M and P. R analyzed the data and M.C. P helped in interpreting the results. Z. M wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and with the 2008 Helsinki declaration and its later amendments or comparable ethical standards [Ethical Code: IR.AJUMS.REC.1396.634].

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Conflict of interest

The authors declare no conflict of interest.

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