Intrauterine infusion of autologous Platelet-rich plasma before frozen embryo transfer in patients with prior implantation failure: A randomized controlled study

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Abstract

Objectives: To evaluate whether intrauterine infusion of autologous platelet rich plasma (PRP) in patients with prior implantation failure (RIF) improves pregnancy rate or not.

Materials and methods: This randomized controlled study was conducted at 4 fertility centers in the period from December 1, 2018 to October, 2021. Patients with repeated implantation failure were recruited and randomly allocated into either study group who received PRP intrauterine infusion or control group who received intrauterine saline infusion. The primary outcome was occurrence of pregnancy. Secondary outcome was increase in endometrial thickness.

Results: Basal demographic data of enrolled patients were comparable. The endometrial thickness on the 11th day did not differ between control and treatment group, 8.5± 1.34mm and 8.18± 1.35mm respectively, P=0.23, while the thickness was significantly increased in the study group at FET P=0.04. Clinical pregnancy rate was 10.92% in the control group versus 16.81% in the study group (P= 0.22). Implantation rate was 15.97% in the control group versus 21.24% in the study group (P= 0.36). Endometrial thickness at FET was correlated to high pregnancy rate.

Conclusion: Although PRP infusion increased endometrial thickness and pregnancy rates in the treatment and control group, but the difference didn't reach to clinical significance.

Keywords: Repeated implantation failure, PRP, Frozen embryo transfer, implantation rate, Clinical pregnancy rate.

Introduction

Repeated implantation failure (RIF) is one of the frustrating conditions in assisted reproductive technologies. RIF means failed conception following at least 3 transfers of good quality embryos (≥4 embryos) in women aged ≤40 years.(1) Implantation requires optimally receptive endometrium, good thickness of endometrium ≥ 7 mm at start of progesterone supplementation, tolerance of maternal immune system to implanted embryo and finally implantation of euploid embryos.(2)

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Endometrial receptivity and success of implantation represent an obstacle in reproductive medicine and until now are unsolved secrets. Hostile environment interferes with implantation. The hostile environment includes submucosal myomas, endometrial polyps, chronic endometritis (CE), and intrauterine adhesions. Research on RIF is running and focusing on improvement of implantation environment. Many drugs and procedures will examined including Antibiotics, Sildenafil, Granulocyte colony stimulating factor, endometrial scratching (3)

PRP is recently studied in enhancing endometrial receptivity. The rationale for PRP administration is that PRP contains high concentrations of platelet-derived growth factors and cytokines that improve endometrial thickness and receptivity. These growth factors include platelet-derived growth factor (PDGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and transforming growth factor beta (TGF β). (4)

Zadehmodarres et al studied the effect of PRP intrauterine infusion in frozen embryo transfer in combination with hormonal therapy. PRP injections were done twice, starting on days 11-12 and repeated on days 13-14). Patients had endometrial thickness ≤7. Their results will improvement of endometrial thickness ≥7 mm and 50% of patients became pregnant. (5)

Recent studies showed that PRP not only improved endometrial thickness but also increased implantation rates when applied in patients with RIF. These studies recommended the use of PRP as a potential therapy in endometrial preparation for successful implantation. (6-,8)

The main objective of this study was assessment of PRP efficacy when infused inside uterine cavity prior to frozen embryo transfer (FET) in patients with repeated implantation failure.

Patients and methods

Study design and settings: This multicenter study is a double armed, non-blinded, randomized controlled trial conducted from December, 2018 October 2021 at Egyptian Consultants fertility center, Adam & Hawa fertility center, Ingab fertility center and Al-Yasmin fertility center.

Patients: One hundred and ten patients with history of prior ICSI failure were recruited from 4 fertility centers. Eligible patients were enrolled according to fulfillment of inclusion. The inclusion criteria were (a) patients with prior implantation failure prepared for FET (b) age of 20-35 years, (c) thin endometrium with thickness ≤ 7 mm at day 11. The exclusion criteria were (a) hepatic disorders, (b) platelet count of <150 000/mm3, (c) patients with abnormal uterine cavity septate uterus, bicornuate uterus or uterine myoma, (d) patients wishing fresh embryo transfer (e) patients with abnormal embryos grade B or C (f) patients with immunological disorders as autoimmune thyroiditis or systemic lupus or rheumatoid arthritis.

Sample size: The current study included independent cases and controls with 1:1 ratio. Previous studies showed that failure rate was 0.1 among controls. Assumption was made that true failure rate among study group to be 0.33. In that case, the appropriate sample required was 49 patients for study and similar 49 patients for control group. This sample is just enough to reject null hypothesis (N0) denoting equal failure rates for study and control groups with probability (power) 0.8 and Type I error of 0.05. Uncorrected chi-squared statistics were used to evaluate this null hypothesis.

Randomization and allocation: Randomization was done using computer based program with letter P denoting PRP group and letter S denoting control group receiving saline infusion. These letters were enveloped and patients were allocated into either group

after opening of the envelope. Envelope opening didn't change allocation. Allocation was with equal ratio 1:1.

Interventions

Endometrial preparation: Hormonal preparation of endometrium was done in all patients in both groups with estradiol oral tablets (white tablets of Cycloprogynova) with 2 mg estradiol in each white tablet. The endometrial preparation started on day 3 of menstrual cycle and continued in fixed hormonal protocol. The dose was one tablet three times daily. Endometrial thickness was measured on days 3, 7, 11, 13 and at day of embryo transfer. Vaginal progesterone 400µg twice daily was given on day 13 continuously along with estradiol oral tablet.

PRP preparation: Fifteen CC of venous blood was taken from patients allocated into PRP study group. The blood is collected in specified tubes for PRP (Acti-PRP tube, Taiwan). The blood is better collected at a temperature between 21-24 C and first centrifugation was performed at 1200 rpm for 12 minutes. The upper layer is transferred into another sterile tube and second centrifugation at 3300 rpm for 7 minutes was done. The upper 2/3 of the tube is discarded while the remaining 1/3 is homogenized and a total of 1 mL of PRP will obtained. (9) The platelet concentration in each 1 ml will 400×10^3 to 900×10^3/ml.

In study group, PRP (1 ml) was infused inside the uterine cavity immediately after preparation with embryo transfer catheter (Kitazato Medical Co., Ltd.) under ultrasound guidance at day 11^{th} of menstrual cycle and may be repeated at day 13 if endometrial thickness is still<7mm. In the control group 1 ml of normal saline 0.9% will performed on day 11 using the same embryo transfer catheter.

Embryo transfer: Good quality (2-3) grade (A) blastocyst stage were transferred on the 18^{th} day. Serum pregnancy test was done 2 weeks after embryo transfer.

Outcomes of the study: The primary outcome was occurrence of pregnancy evidenced by positive hCG, 14 days following Embryo transfer. The secondary outcomes included endometrial thickness on FET day, implantation evidenced by presence of gestational sac at 6 weeks by ultrasound examination. Clinical pregnancy rate (CPR) is obtained by dividing sum of viable fetal poles at 6-week ultrasound by the sum of transferred embryos. Implantation rate is obtained by dividing the sum of gestational sacs at 6-week ultrasound by the sum of transferred embryos.

Data collection: The demographic data, basal hormonal profiles, number of prior failed ICSI cycle, endometrial thickness at day of embryo transfer, pregnancy rate, implantation rate and any complications.

Study registration and ethical issues: Patients were provided through explanation about objectives, benefits and risks of the study and a written consent was obtained from all participation. The study was conducted according to principles of the Declaration of Helsinki. This study was approved by Tanta University ethical committee (Approval No. 34803), registered on clinicaltrials.gov, and given the unique ID: NCT03734042 and is available on the following link: https://register.clinicaltrials.gov/prs/app/action/ViewOrUnrelease?uid=U000404W&ts=18&sid=S0008G0D&cx=-qthfns

Statistical analysis: Continuous data distribution was evaluated using the Shapiro-Wilk test, and normally distributed variables were analyzed by descriptive statistics as mean, standard deviation and tested with the Student t-test for independent pairs. Non-normally distributed data were expressed as median (25th and 75th percentiles). Categorical data were analyzed and expressed as numbers and percentages. Comparison of categorical data was done by Chi-square test or Fisher exact test. Univariable logistic regression analysis was used to identify factors affecting the occurrence of pregnancy. Stata 16.1 (STATA

Corp, USA) was used for statistical analyses. P-value ≤ 0.05 was considered statistically significant.

Results:

A total of (n=117) patients were assessed for eligibility. Patients who were excluded were (13) either not fulfilling inclusion criteria (n=8) or declined to participate (n=5). The consort flow chart is presented in figure 1.

Baseline data:

We compared patients who had PPR (treatment group) to a control group. Baseline data were nearly similar with no significant difference between both groups. (Table 1)

Outcome data:

Regarding duration of endometrial preparation, there was no significant difference in between both groups. The endometrial thickness on the 11th day did not differ between groups, while the thickness was significantly higher in the treatment group at FET day. The clinical pregnancy rate was 10.92% in the control group versus 16.81% in the treatment group (P= 0.22). The implantation rate was 15.97% in the control group versus 21.24% in the treatment group (P= 0.36). (Table 2)

Factors affecting the occurrence of pregnancy:

Pregnancy was lower in patients with tubal factors [OR=0.15 (0.03- 0.79)] p-value=0.02. Endometrial thickness at FET also was positively correlated to occurrence of pregnancy. No other factors affected the occurrence of pregnancy. (Table 3)

Discussion

Repeated implantation failure (RIF) remains a big frustrating condition facing reproductive medicine specialists. There are no definite causes in most cases and the proposed treatment plans are unable to solve this problem in many cases. (1,2) Endometrium had a built-in program for reception or rejection of embryos and this endometrial receptivity allows an appropriate environment for implantation and placenta development. Endometrial receptivity is the main player in (RIF) and has a crucial role in implantation. [10]

Appropriate assessment of endometrial receptivity was studied and several markers were investigated in a large meta analysis including 88834 women. The studies included in that meta analysis advocated the use of certain markers and others didn't, so no marker is superior to others. Endometrial receptivity array (ERA) and endometrial thickness (ET) could denote appropriate endometrium or window of implantation (WOI). (11-13)

Several treatment strategies were introduced for solving RIF.[14] Away from embryo quality and stimulation protocols, the investigated strategies were antibiotics, [15] immunosuppressive drugs eg. Tacrolimus, [16] hCG-activated human peripheral mononuclear cells, [17] hysteroscopic endometrial injury [18] vitamin D, [19] IVIG, [20] G-CSF, [21] salpingectomy, [22] Intravenous intralipid infusion [23], LMH, [24] and Platelet rich plasma [25,26].

In the current study, autologous PRP injection was infused in the uterine cavity on day 11 and repeated at day 13 if endometrial thickness is still<7mm. The control group were infused by 1 ml saline. Regarding endometrial thickness, it was significantly increased in the treatment group on day of FET with P-value=0.04. Our results are in agreement with Nazari et al [25], Zamaniyanet al [26], Chang et al [27], Kusumi et al,[28], Obidniak et al.[29], Mehrafza et al.[30], Coksuer et al.[31], Nazari et al [1, 32] and Eftekhar et al [33].

On the other hand, Allahveisi et al conducted a study on 50 infertile patients with RIF and found that PRP infusion didn't increase endometrial thickness (ET) in study or control group where ET was 9.36 ± 0.27mm in con-

trol and 9.6 ± 0.27mm in study group with p-value= 0.54.[34] and similarly Madhavan et al.[35]

In the current study, although rates of chemical pregnancy, implantation and clinical pregnancy were higher in treatment group with PRP rather in control group but didn't reach to clinical significance with p-value 0.40, 0.49, and 0.38 respectively.

Our data are in agreement with Allahveisi et al who reported that pregnancy rate in control group was 36% and was 28% in treatment group (p-value= 0.83). They concluded that PRP had no significant role on improving pregnancy following FET. [34] Also Madhavan et al conducted a cohort study on ninety-eight patients with 42 patients allocated in PRP group and 56 patients allocated in the control group. The authors reported no difference in clinical pregnancy rate (CPR) in patients with primary infertility while in patients with secondary infertility the difference didn't reach to clinical significnace.[35]

Similar to our results, Aghajanzadeh et al conducted a study on 30 cases with RIF. They infused PRP 48 hours prior to embryo transfer. They found that implantation rate was 6.7% in PRP group. They also found that no significant differences regarding implantation rate, CPR, and miscarriage rates following FET with and without PRP infusion. [36]

On the other hand Chang et al found that pregnancy rate was 44.12% in study group while it was 20% in control group with p value= 0.036. Chang et al concluded that PRP has beneficial role in endometrial proliferation, and improving implantation and pregnancy rates for women with thin endometrium in FET cycles. Nazari et al reported 90% pregnancy rate in PRP group. [25]

Zamaniyan et al. conducted a randomized clinical trial on 98 patients with RIF. Patients were allocated in PRP group (n=55) and in the control group (n=43). They found that clinical pregnancy was significantly higher in study group than in control group (48.3% versus 23.26) respectively with p=0.001. The implantation rate was 58.3% versus 25%; p=0.001) in study and control groups respectively. They concluded that rates of implantation, clinical pregnancy and ongoing pregnancy were improved following PRP use. [26]

Kusumi et al conducted a randomized self-controlled study on 39 patients. They found that endometrial thickness was improved significantly and on the same side clinical pregnancy rate was improved following PRP infusion (15.6%) in patients with FET. They reported no adverse events and concluded that PRP therapy was safe and increased both endometrial thickness and clinical pregnancy rate.[28]

The strengths of this study were the randomized controlled design and blinding of participants while the weakness point was the small sample size.

Conclusion:

Autologous PRP is a cheap office procedure and doesn't require great experience in its handling and preparation with high safety. It is a new modality of treatment in the field of reproductive medicine which was investigated in many conditions. In Repeated implantation failure, although it significantly increased endometrial thickness at FET day, but the increase in clinical pregnancy rate, and implantation rated didn't reach to clinical significance. A larger studies are required to reach to an evidence based solid conclusion regarding the use of PRP in RIF.

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Conflict of interest:

no conflicts do exist for all authors

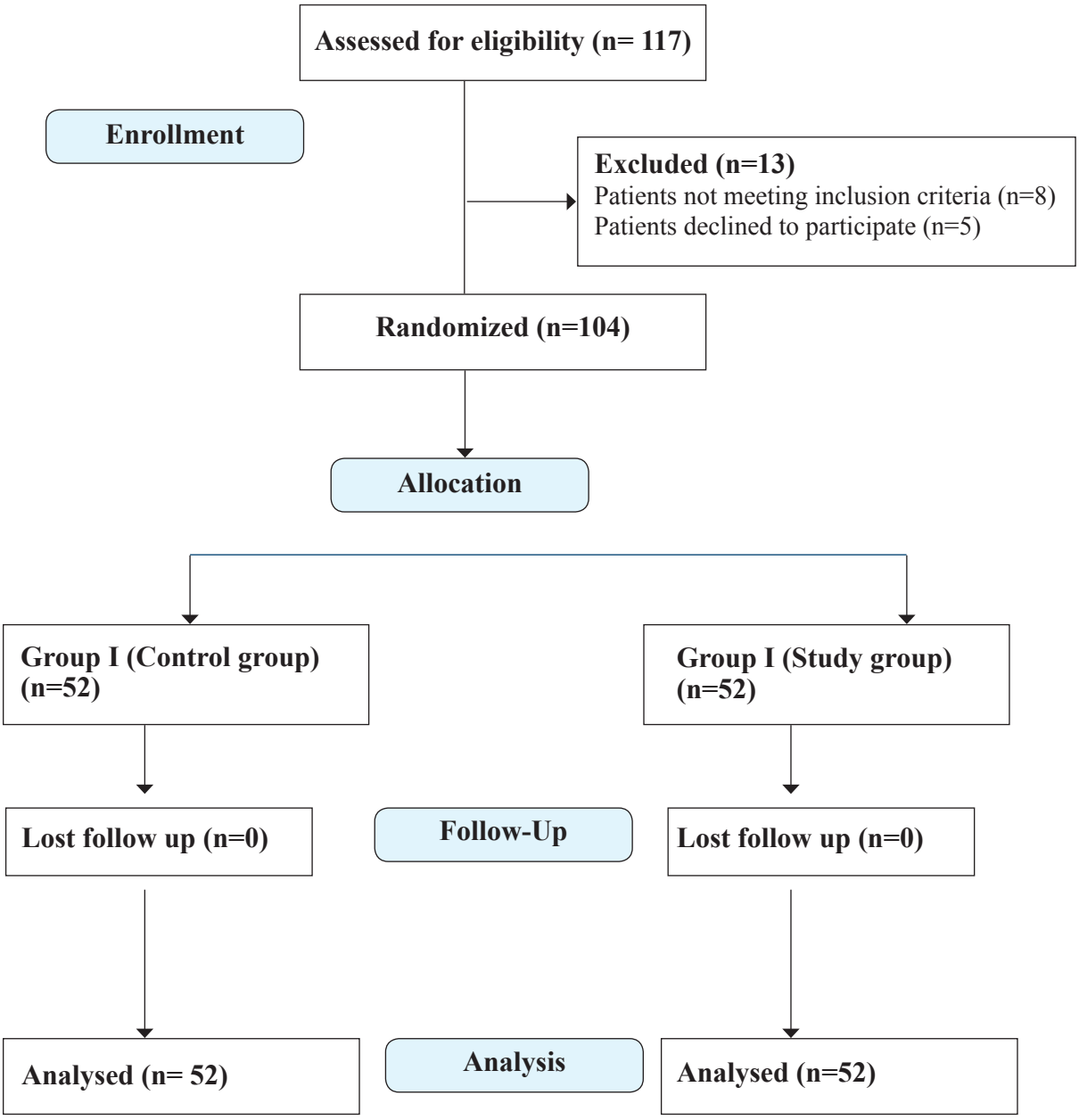

Figure 1: CONSORT Flow chart of cases through the study

Table 1: Baseline data of enrolled patients

Variables	Control group (n= 52)	Treatment group (n= 52)	P
Age (years)	30.52± 3.381	29.60± 2.99	0.14
Gravidity Zero One Two Three	 27 (51.92%) 14 (26.92%) 7 (13.46%) 4 (7.69%)	 28 (53.85%) 15 (28.85%) 8 (15.38%) 1 (1.92%)	0.66
Parity Zero One	 40 (76.92%) 12 (23.08%)	 34 (65.38%) 18 (34.62%)	0.19
BMI (kg/m2)	25.2 (23.5- 28.35)	27.65 (25- 29.65)	0.06
Type of infertility Primary Secondary	 27 (51.92%) 25 (48.08%)	 28 (53.85%) 24 (46.15%)	>0.99
Duration of infertility (years)	6.65 (5- 8.5)	5.25 (4.5- 7)	0.08
Indication of ICSI Endometriosis Male factor PCOS Tubal factor Unexplained	 6 (11.54%) 20 (38.46%) 12 (23.08%) 11 (21.15%) 3 (5.77%)	 6 (11.54%) 19 (36.54%) 13 (25%) 9 (17.31%) 5 (9.62%)	0.95
Number of failed ICSI One Two Three Four	 23 (44.23%) 19 (36.54%) 8 (15.38%) 2 (3.85%)	 32 (61.54%) 10 (19.23%) 6 (11.54%) 4 (7.69%)	0.16
FSH	8 (6.9- 8.6)	8 (6.65- 8)	0.66
AMH	2.8 (2.25- 3.5)	3 (2.85- 3.6)	0.08

AMH: Antimullerian hormone; BMI: body mass index; FSH: follicular stimulating hormone; ICSI: Intracytoplasmic sperm injection; PCOS: polycystic ovary syndrome

Table 2: Comparison of the fertilization and outcomes between both groups.

Variables	Control group (n= 52)	Treatment group (n= 52)	P
Days of endometrial preparation	12.56± 1.16	12.46± 1.29	0.69
Endometrial thickness day 11 (mm)	8.5± 1.34	8.18± 1.35	0.23
Endometrial thickness at FET (mm)	12 (11.55- 13.4)	12.5 (12- 14)	0.04
Difference in endometrial thickness	3.71± 1.65	4.60± 1.43	0.004
Number of embryos Two Three	 37 (71.15%) 15 (28.85%)	 43 (82.69%) 9 (17.31%)	0.16
Number of sacs One Two	 9 (64.29%) 5 (35.71%)	 12 (66.67%) 6 (33.33%)	>0.99
Chemical Pregnancy rate	14 (26.92%)	18 (34.62%)	0.40
Clinical pregnancy rate	10.92%	16.8 %	0.38
Implantation rate	15.97%	21.24%	0.49

Table 3: Univariable logistic regression analysis for factors affecting pregnancy

	(OR (95% confidence interval	P-value
Treatment	1.44 (0.62- 3.32)	0.40
Age	0.95 (0.84- 1.09)	0.47
Gravidity	0.80 (0.48- 1.31)	0.37
Parity	0.95 (0.38- 2.39)	0.91
BMI	1.03 (0.89- 1.20)	0.69
Type of infertility	0.68 (0.29- 1.59)	0.38
Duration of infertility	0.97 (0.77- 1.23)	0.82
Tubal factor	0.15 (0.03- 0.79)	0.02
Number of failed ICSI	0.94 (0.59- 1.50)	0.80
FSH	1.34 (0.90- 2.00)	0.14
AMH	1.04 (0.76- 1.42)	0.82
Endometrial thickness (11 day)	0.83 (0.60- 1.13)	0.23
Endometrial thickness at FET	0.92 (0.69- 1.22)	0.03
Difference in thickness	1.07 (0.82- 1.40)	0.01

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