



Effectiveness of Intrauterine Infusion of Autologous Platelet-Rich Plasma in the Treatment of Thin Endometrium of Infertile Women

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Study Protocol

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ABSTRACT

One of the key factors in implantation and pregnancy is endometrium. Sufficiently great percentage of in vitro fertilization failure is because of the endometrial receptivity therefore, high quality embryo and adequate receptive endometrial growth are important for successful implantation. Platelet rich plasma has beneficial effect in advancement of endometrial thickness for women with thin endometrial thickness. PRP can be used in various medical conditions including patients with refractory endometrium as a complementary therapy to conventional treatment.

Aim: To determine the effectiveness of intrauterine infusion of autologous platelet-rich plasma in the treatment of thin endometrium of infertile women.

Objectives:

1. To identify infertile female patients with inadequate endometrial growth (less than 7 mm) in the past frozen embryo transfer (FET) cycles despite standard treatments.

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2. To observe intrauterine infusion of autologous platelet-rich plasma (PRP) in these infertile female patients with thin endometrium.
3. To determine the effectiveness of intrauterine infusion of autologous PRP in the treatment of thin endometrium of infertile women during In vitro fertilization (IVF).

Methods: It is a prospective observational study. Present study will be carried out with 30 patients. Women having inappropriate endometrial thickness of less than 7 mm, in past FET cycles will be included. Sonographic machine will be used; to measure endometrial thickness by an expert Gynecologist, where thickest part of uterus will be measured in longitudinal axis.

Expected Results: It is expected that intra uterine infusion of PRP will be effective in thickening of endometrial wall in patients with thin endometrium. Once the results are satisfactory it can be helpful for endometrial preparation in reproduction techniques.

Conclusion: Present study is purposed to testify PRP as a novel method for advancement of reproductive medicine, it will be helpful to overcome with the issues such as inadequate thickness of endometrium, poor response to conventional therapy and increase clinical pregnancies and live births positively.

Keywords: Platelet-rich plasma; thin endometrium; infertile female patients; in-vitro fertilization.

1. INTRODUCTION

The percentage of couples suffering from infertility is about 13%, hence infertility became a global public health issue. Since the first in vitro fertilization (IVF) attempts in the mid1970s, various study states the vital role of endometrium with embryo itself in achieving pregnancy [1]. It also states only a good quality of embryo can provide good coordination between mother and fetus implantation and pregnancy.

One of the key factors in implantation and pregnancy is endometrium. Sufficiently great percentage of in vitro fertilization failure is because of the endometrial receptivity therefore, high quality embryo and adequate receptive endometrial growth are important for successful implantation [2,3]. In order to improve pregnancy rates it is necessary to increase endometrial thickness. In numerous studies conducted for embryo transfer, minimum endometrium thickness was found to be 7mm [4,5,6].

Platelet- rich plasma has been introduced in reproductive medicine as a novel treatment, after its beneficial effect are found out in thickening of endometrial wall in women with thinner endometrium. Human blood is when centrifuged there is presence of soaring concentration of platelet, it is known as PRP. It is extracted from patients own blood, it contains growth factors and cytokines which can be helpful in reformation of endometrial and embryonic development [7,8,9,10].

PRP is used because it can be obtained easily, it is cheap and is rich in growth factors. As it is autologous, it is nontoxic and no allergenic. Therefore, it can be used in various medical conditions including patients with refractory endometrium as a complementary therapy to conventional treatment, with generally decent results [11].

Positive and promising result are noticed in between the uterine environment and implantation of embryo after administering platelet growth factors. Present study is aimed, in order to evaluate the effectiveness of intrauterine infusion of PRP in the treatment of thin endometrium in IVF.

1.1 Objectives

1. To identify infertile female patients with inadequate endometrial growth (less than 7 mm) in the past frozen embryo transfer (FET) cycles despite standard treatments.
2. To observe intrauterine infusion of autologous platelet-rich plasma (PRP) in these infertile female patients with thin endometrium.
3. To determine the effectiveness of intrauterine infusion of autologous PRP in the treatment of thin endometrium during In vitro fertilization (IVF).

2. METHODS

2.1 Study Design

It is a prospective interventional study.

2.2 Study Setting

It will be carried out in the department of Obstetrics and Gynecology of tertiary care hospital.

2.3 Duration of the Study

June 2021 to December 2022

2.4 Sample size Calculation

Cochran Sample size formula with desired error of margin:

- Formula For Calculating A Sample For Proportions
- For populations that are large, Cochran (1963:75) developed the Equation 1 to yield a representative sample for proportions

$$\text{Equation 1: } n_0 = \frac{Z^2 pq}{e^2}$$

Where;

$Z_{\alpha/2}$ is the level of significance at 5% i.e. 95% confidence interval = 1.96

p = Incidence rate of infertility = 13/100
= 130 per 1000 population
= 0.130

d = Error of margin = 8% = 0.08

$$n = \frac{1.96^2 * 0.130 * (1-0.130)}{0.08^2}$$

=29.80 = 30 patients needed in the study

2.5 Study Reference

Chang Y, Li J, Chen Y et al. [9] Autologous platelet-rich plasma promotes endometrial growth and improves pregnancy outcome during in vitro fertilization. *Int J Clin Exp Med* 8:1286–1290.

2.6 Formula Reference

Cochran, W. G. (1977). *Sampling techniques* (3rd Ed.) New York: John Wiley & Sons.

2.7 Study Population

Present study will be carried out with 30 patients. Women having inappropriate endometrial thickness of less than 7 mm, in past FET cycles will be included. Sonographic machine will be

used; to measure endometrial thickness by an expert Gynecologist, where thickest part of uterus will be measured in longitudinal axis from each participant written informed consent will be taken for participation in study after explaining the procedure in detail. Institutional Ethical Committee (IEC) clearance for the study has been obtained.

2.8 Sample Allocation

Convenient sampling will be used.

Autologous PRP preparation:

Autologous PRP preparation involves drawing of patients' blood, preparation of autologous PRP and injecting PRP into uterine cavity by skilled gynecologist. It is an outpatient procedure. Method for preparation is given below [5,6]:

1. Sterile tubes having anticoagulant will be taken, for venous blood (15–50 mL) which will be drawn from the patient's arm.
2. Temperature required during processing will be 21°C–24°C, it will help to prevent activation of platelet during blood centrifugation.
3. Blood will be centrifuged at 1200 rpm for 12 minutes
4. there will be three layers of blood after centrifugation -
 - i. white blood cells and platelets will be at the upper layer
 - ii. an intermediate thin layer (the buffy coat) this layer will be rich in white blood cells,
 - iii. bottom layer will contain red blood cells;
5. Empty sterile tube will be used for pouring of the upper and intermediate buffy layers. After that remaining plasma will be centrifuged at 2200 rpm for 10 minutes to help with the formation of soft pellets (erythrocytes and platelets) at the bottom of the tube;
6. platelet poor plasma will be discarded by discarding the upper two thirds of the plasma
7. in the lower third, pallet will be homogenized (5 mL) of the plasma to create the PRP;
8. the PRP will be now ready to inject. Around 30 mL of venous blood can yield 3–5 mL of PRP;
9. the affected area will be disinfected before the PRP injection;
10. Assurance and care will be given to patients after discussion of procedure, to

make the injection easier and less painful.

11. 0.5 ml of PRP will be infused into the uterine cavity with catheter by expert Gynecologist on day 11-12 of menstrual cycle [12,13]
12. There will be little swelling on injected site and painful for next 3 days. As the PRP stimulates a series of biological responses.

Hormone replacement therapy (HRT) will be made for endometrial preparation in all participants: estradiol valera 6 mg/dl administration will be started on the 2nd or 3rd day of the menstrual cycle and it will be gradually increased to 8 mg/dl on 9th -10th day, due to insufficient endometrial growth (<7 mm).

During the cycle, when the endometrial thickness will be 7 mm, suppository progesterone should be started, 400 mg twice-a-day and embryo transfer (ET) will be carried out per embryonic stage. B-hCG value will be checked after day 14 of embryo transfer. Estradiol valerate and progesterone supplementation will be continued for 2 weeks after ET and once the serum β HCG will be positive, supplementations of the hormones will be continued until 12 weeks of conception.

The primary outcome will be measured by endometrial expansion as observed by skilled gynecologist and the secondary outcomes will be chemical and clinical gestations, determined by positive serum β HCG, 2 weeks after ET and the presence of fetal heart beat in the transvaginal ultrasound 5 weeks after ET.

Effectivity of intrauterine infusion of autologous PRP in the treatment of thin endometrium during In vitro fertilization (IVF) will be determined based on primary and secondary outcome of this study.

2.9 Statistical Methods

Student's paired and unpaired t test, one way ANOVA, Pearson's correlation coefficient.

Software: SPSS 27.0 version.

2.10 Expected Outcome

It is expected that intra uterine infusion of PRP will be effective in thickening of endometrial wall in patients with thin endometrium. Once the results are satisfactory it can be helpful for

endometrial preparation in reproduction techniques.

3. DISCUSSION

Samy A, Abbas AM, Elmoursi A, Elsayed M, Hussein RS [14] states the locally administered PRP shows remarkable effect as it increases gestation rates of infertile women with refractory endometrium with ET < 6 mm, as growth factors and other cytokines present in PRP have positive effects on local tissue repair and endometrial receptivity; it helps to increase endometrial receptivity and vascularity.

Farimani M, Poorolajal J, Rabiee S, Bahmanzadeh M [12] found that the local administration of PRP shows effectiveness in successful implantation. Although to justify its benefits and application clinically, further studies will be looked-for in infertility treatment

According to Colombo GV, Fanton V, Sosa D, Lotti J, Aragona SE, Lotti T [15] due to the inefficient expression adhesion molecules, after PRP administration, multiple implantation failures were seen, which can be more represented hypothetically.

According to Zadehmodarres S, Salehpour S, Saharkhiz N, Nazari L [13] PRP was effective for endometrial growth in patients with thin endometrium and had a history of cycle cancellation due to thin endometrium. Administration of PRP is a harmless process, with negligible risks in spread of infectious disease and immunological reactions as it is made from autologous blood samples.

Eftekhar M, Neghab N, Naghshineh E, Khani P [16] study found the significant increase in endometrial thickness to $8.67 \pm$ in PRP group than in controls.

Different studies conducted worldwide showed beneficial effect of PRP administration in improving the endometrial growth and possibly pregnancy outcomes in women with a thin endometrium.

4. CONCLUSION

Present study is purposed to testify PRP as a novel method for advancement of reproductive medicine, it will be helpful to overcome with the issues such as inadequate thickness of

endometrium, poor response to conventional therapy and increase clinical pregnancies and live births positively.

PRP is used because it can be obtained easily, it is cheap and is rich in growth factors. As it is autologous, it is nontoxic and no allergenic. Therefore, it can be used in various medical conditions including patients with refractory endometrium as a complementary therapy to conventional treatment, with generally decent results

CONSENT

As per international standard or university standard, Participants' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

FUTURE SCOPE AND IMPLICATIONS

It is expected that intra uterine infusion of PRP will be effective in thickening of endometrial wall in patients with thin endometrium. Once the results are satisfactory it can be helpful for endometrial preparation in reproduction techniques.

SOURCE OF FUNDING

Intramural funding from the institute has been applied for.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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