Journal of Experimental and Basic Medical Sciences 2023;4(2):110-115

Review

Innovative Approach: Platelet-Rich Plasma and In Vitro Fertilization

Büşra Alan[1], Ayşe Safiye Genç[1], Oytun Erbaş[1]

ABSTRACT

Over the years, the number of people suffering from infertility has increased globally. Individualized therapies are used in infertility therapy, unlike in other medical disciplines. Infertility instances might be of female or male origin, or both female and male origin, with the etiology of certain cases unexplained. Supportive therapy is utilized in individuals who have a poor ovarian response, have had several unsuccessful cycles, or are undiagnosed. The platelet-rich plasma (PRP) technique promotes cell proliferation by using the growth factors found in platelets. While the PRP approach is actively employed in a variety of industries, it is currently being used as an adjunct therapy in assisted reproductive procedures. Nonetheless, as this is a relatively novel application, there is ongoing contention regarding the standardization of PRP preparation methods, the frequency of its administration to patients, and the question of its effectiveness as a beneficial treatment. As a consequence of this analysis, it is believed that further prospective randomized clinical trials are required before PRP can be classified as a therapy. This review will explore the advantages and disadvantages of employing PRP for addressing endometrial receptivity and managing premature ovarian failure.

Keywords: *In vitro* fertilization, infertility, platelet concentrate, platelet-rich plasma application

Infertility is defined by the World Health Organization as the lack of pregnancy after at least one year of regular, unprotected intercourse. Infertility diagnosis and treatment, unlike other disciplines of medicine, are ways in which couples are assessed jointly. The reason for infertility is exclusively female in 40% of instances, only male in 30%, both male and female in 15%, and unknown in 15% of cases.[1] Unexplained infertility refers to situations that have not been diagnosed. Female infertility can be caused by ovarian, tubal, corpus, cervical, or peritoneal problems. Male infertility can arise due to problems with both sperm count and function. Furthermore, anatomical deviations, along with characteristics of the ejaculate and immunological factors, can also play a role.[1,2]

The histological structure of the female reproductive system organs differs between childhood, adolescence, and old age. Menstruation begins with puberty, influenced by hormones generated by the hypothalamus, pituitary, and ovaries. Internal genital organs undergo cyclical modifications throughout this time. The uterus is a specialized organ that helps the fetus develop, thrive, and protect itself throughout pregnancy. Many of the cyclical changes occur in the uterine endometrium. The endometrium prepares for pregnancy every month under the influence of estrogen and progesterone. Endometrium thickening, growth, change, and shedding are examples of cyclical changes. The thickness of the endometrium in an adult woman is anticipated to be between 7 and 14 mm for the embryo to adhere to and survive. Endometrial thickness of less than 7 mm might reduce the chances of embryo implantation and cause repeated pregnancy losses.[3,4]

During menstruation, the ovaries generate one or two mature oocytes in response to gonadotropin-releasing hormone (GnRH) produced from the hypothalamus, as well as follicle-stimulating hormone (FSH) and luteinizing hormone (LH) released

[1]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Türkiye

Correspondence: Büşra Alan. Institute of Experimental Medicine, 41470 Gebze-Kocaeli, Türkiye

E-mail: busraalan0@gmail.com

Cite this article as: Alan B, Genç AS, Erbaş O. Innovative Approach: Platelet-Rich Plasma and In Vitro Fertilization. JEB Med Sci 2023;4(2):110-115.

doi: 10.5606/jebms.2023.1053

Received : June 29, 2023
Accepted : July 5, 2023
Published online : August 31, 2023

from the pituitary anterior lobe.[5] Ovulation begins on the 14th day of menstruation with the peak of LH hormone and the formation of the corpus luteum. The mature oocyte is released into the fallopian tube during ovulation. If the oocyte drifting in the fallopian tube comes into contact with a sperm cell, the sperm cell penetrates the oocyte and starts a chain of events, i.e., fertilization, by causing cellular activation. Fertilization and pregnancy will not occur in the absence of sperm in the fallopian tubes, and the corpus luteum, which safeguards the integrity of the endometrium, will atresia, and the endometrium, which has prepared itself for pregnancy, will shed. There are around 450 oocyte follicles in an adult woman that can be released during ovulation. The restricted number of follicles, age-dependent deterioration of oocyte quality, and age-dependent reduction in sensitivity to gonadotropins all contribute to the lengthening of oocyte maturation time. As a result, the rate of fertilization drops, and embryonic development suffers.[4,6]

Platelet-rich plasma (PRP), or platelet concentrate, was initially defined in hematology as the synthesis of platelets from peripheral blood in a lower volume and higher concentration. Platelets carry growth factors that aid in blood clotting, wound healing, and cell proliferation. This technique has gained popularity in the fields of regenerative medicine, dentistry, orthopedics, dermatology, cosmetic plastic surgery, and hair loss therapy. [7]

There are several techniques for preparation since there is no defined protocol for the production and delivery of plasma fluid. The primary premise, however, is to take some blood from the patient and centrifuge it to obtain a platelet concentrate, as shown in Figure 1.

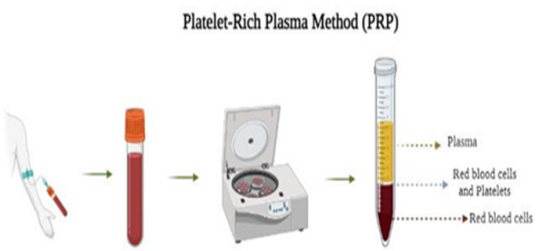

Figure 1: Platelet-rich plasma application

Pregnancy rates have increased due to the advancement of reproductive medicine and the advent of assisted reproductive procedures.

Endometrial receptivity is critical for successful embryo implantation. Despite breakthroughs in reproductive medicine, managing and treating endometrial receptivity in infertile individuals with thin endometrium continues to be difficult. Over the years, the number of people suffering from infertility has increased globally. Infertility has increased due to the increasing age of marriage, socioeconomic improvements, and contraceptive techniques.[8]

Poor ovarian reserve (POR) is one of the variables that contribute to infertility in women of advanced reproductive age. Despite having access to assisted reproductive technologies such as *in vitro* fertilization (IVF), these women have poor pregnancy and live birth rates, as well as a high repeat pregnancy rate. The levels of anti-Müllerian hormone (AMH) and antral follicle count (AFC) are critical measures of ovarian reserve.[9]

In assisted reproductive procedures, the PRP approach is utilized for a variety of applications. It is employed in the recycling of old oocytes, as well as the age-dependent fall in fertility. Premature ovarian failure, oocyte quality improvement, and increased implantation success are all possible outcomes.[10-12] However, due to the lack of uniformity in the control group and the fact that it has not been applied to a significant number of patients, the effect of PRP treatment on assisted reproductive procedures is still being contested.

CLINICAL RESEARCH FINDINGS

When excellent-quality embryos fail to implant numerous times after transfer, this is referred to as recurrent implantation failure (RIF). Nazari et al.[13] investigated if intrauterine injections PRP in RIF patients may enhance pregnancy outcomes. This research comprised 438 RIF women. The patients were randomly assigned to one of two groups, with the control group receiving normal IVF therapy. The second group received 0.5 ml PRP intrauterinally 48 hours before the transfer. Chemical pregnancy, clinical pregnancy, and live birth rates were greater in the PRP-treated group than in the control group, whereas spontaneous abortion rates were lower. According to their study, PRP can be utilized to enhance RIF. Intrauterine injection of platelet-rich plasma fluid is depicted in Figure 2.

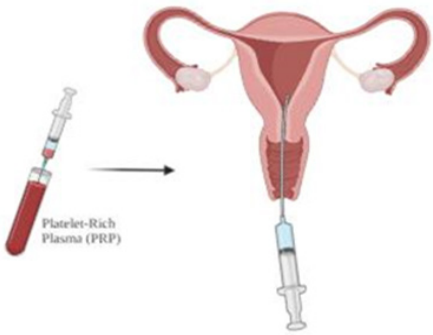

Figure 2: Intrauterine injection of platelet-rich plasma fluid

In double-blind clinical research done in 2022, Bakhsh et al.[14] split 100 women with RIF into two groups. One group was given 0.5 CC PRP, while the other got normal care. According to their findings, whereas the pregnancy rate in the PRP group was 20%, the pregnancy rate in the conventional therapy group was 13.33%. Platelet-rich plasma can be utilized to enhance RIF.

Zamaniyan et al.[15] split 98 RIF women into two groups. The experimental group was given 0.5 ml of PRP intrauterinally 48 hours before embryo transfer, whereas the control group was given conventional care. They discovered that the experimental group had a considerably greater clinical pregnancy rate, continuing pregnancy rate, and implantation rate than the control group.

The endometrium must be at least 7 millimeters thick for the embryo to connect and develop.[16] Before embryo transfer, the endometrium is measured to see if it is thick enough. If the endometrium is not thick enough, the embryo is not transplanted and the cycle is postponed until the following cycle. Eftekhar et al.[17] intended to conduct a randomized clinical study to evaluate the effectiveness of PRP in patients with thin endometrium. The trial comprised 83 women, 40 of whom got 0.5-1 cc PRP in the intrauterine cavity in addition to hormone replacement treatment, while the remaining 43 women did not. They concluded that the group that received PRP in addition to hormone replacement therapy had greater endometrial thickness, implantation rate, and pregnancy rate per cycle than the group that received normal hormone replacement therapy.

Chang et al.[18] used a prospective cohort trial to determine the effectiveness of PRP for endometrium thickness in 64 patients with thin endometrium who would undergo frozen embryo transfer. While hormone replacement treatment was used in the control group, PRP was used intrauterinally in the other group, and the results showed that the PRP group had a higher implantation rate and clinical pregnancy rate.

Tehraninejad et al.[19] wanted to see how PRP, which has been shown to enhance pregnancy outcomes in women with RIF, affected individuals with normal endometrial thickness. They enrolled 85 women with RIF and a minimum endometrial thickness of 7 mm in this study. Forty-two individuals were given PRP two days before embryo transfer, while the remaining 43 were placed in a control group. There was no significant difference in biochemical, clinical, or continuing pregnancy results between the control and PRP groups, and they concluded that PRP is not a useful therapy for RIF in women with normal endometrium.

Ershadi et al.[20] separated 85 women with endometrial thickness of 8 mm and a history of RIF into two groups, one receiving normal IVF and the other receiving intrauterine PRP injection 48 hours before embryo transfer and observing if it had any influence on pregnancy. According to the findings of this study, they found that the chemical pregnancy rate was 40% in the PRP-treated group and 27% in the control group. When the clinical pregnancy rates were evaluated, they found 33% in the PRP group and 24% in the control group, with no significant difference between the two groups. As a consequence, it was reported that PRP injection did not affect fertilization in women with endometrial thickness of 8 mm or greater who underwent RIF.

Xu et al.[21] intended to see if PRP intrauterine perfusion before frozen-thawed embryo transfer was successful in 288 women with RIF. The PRP-treated group included 138 women, while the control group included 150 women. They found that the PRP group had more live births, clinical pregnancies, greater implantation rates, and fewer spontaneous abortions than the control group, although the difference was not statistically significant.

In their 2020 trial, Çakıroğlu et al.[22] enrolled 311 women with primary ovarian insufficiency (POI). They wanted to see how PRP affected ovarian stimulation response and IVF results in these women, thus they injected PRP intraovarially. A rise in AFC and AMH was found following the intraovarian PRP injection, but no significant increase in FSH was noted. According to their findings, 23 of the 311 women treated with PRP had spontaneous pregnancies, while 201 produced

antral follicles and underwent IVF. Antral follicle formation did not occur in the remaining 87 women. Overall, 25 (8%) of the 311 women treated with PRP had live births/ongoing implantation, while another 25 (8%) had cryopreserved embryos. Platelet-rich plasma application, according to them, might be regarded as an alternative experimental therapy for women with POI.

Çakıroğlu et al.[23] evaluated if intraovarian PRP injection influenced ovarian reserve and IVF outcomes in 510 women with POR and an average age of 40 years in 2022. As a consequence, 22 of the 510 women fell pregnant spontaneously between the first and seventh cycles, with 12 (54.5%) giving birth. Following PRP administration, they noticed a rise in the ovarian reserve measures AFC and AMH as well as a reduction in FSH. In this research, 474 women had IVF and controlled ovarian stimulation, with 424 (89.5%) receiving oocyte retrieval. In 324 (86.6%) of the women, at least one mature oocyte was obtained. The number of oocytes collected before and after PRP increased significantly. They also found that a woman's age had a detrimental impact on the success of IVF with PRP. Finally, they believe that intraovarian PRP injection can be used in women with POR; however, it has been reported that the ideal population that can benefit should be patients younger than 40 years of age, with FSH levels under the 21.2 mIU/mL, AMH level higher than 0.2 ng/ml, at least one antral follicle, and mean ovarian volume bigger than 4.30 cm^3. According to them, the therapeutic effectiveness of PRP should be established in prospective randomized clinical studies before it can be suggested as standard therapy for women with POR.

Hosseinisadat et al.[24] evaluated the intra-ovarian infusion of PRP in addition to IVF treatments in 22 women with POR using a GnRH agonist regimen. They discovered a considerable rise in AMH following intra-ovarian infusion of PRP, but no change in the number of antral follicles at the conclusion of the research. According to them, PRP may considerably boost AMH levels in women with inadequate ovarian reserve, thereby increasing fertility chances.

Keikha et al.[25] intended to see if intra-ovarian injection of autologous PRP affected oocyte count in POR patients. In this study, 12 patients with POR had two IVF cycles 70 days apart. Following the oocyte pick-up one ovary underwent a 4 cc PRP multifocal intramedullary injection. The other ovary was not subjected to any control procedures. The second IVF cycle was done after 70 days, and a substantial rise in the number of antral follicles was seen in the PRP-treated ovary, but no significant change in the number of embryos was observed before and after PRP administration. In comparison to the first cycle, there was a considerable rise in AMH and FSH during the PRP-treated cycle. Except for an increase in the number of antral follicles, they found that intra-ovarian treatment of women with POR with PRP did not affect embryo number, oocyte number, or FSH/AMH levels.

Hsu et al.[26] studied 12 early menopausal individuals to see if PRP is beneficial in restoring ovarian function in women during early menopause. They injected PRP and recombinant FSH (rFSH) into the ovaries and then monitored them for six months. According to reports, 11 of the women who had PRP and rFSH injections resumed menstruation. They found that by utilizing autologous oocytes, PRP can temporarily restore ovarian function and enhance the chance of conception in women in early menopause.

In conclusion, the notion of reproduction has remained relevant over the years. Infertility is the decline or loss of reproductive function. Many people all around the world are affected by infertility. Looking at the world as a whole, it is clear that the number of people suffering from infertility has risen over time. Infertility is becoming more common due to factors such as increasing marriage age, socioeconomic advancements, and contraceptive techniques. Unlike in other medical professions, tailored therapies are developed for assisted reproductive procedures. Infertility can be of female or male origin, or of both male and female origin, with the reason unexplained in certain situations. In situations of poor implantation chance, failure of endometrial receptivity, or undiagnosed cases, supportive treatments are used. Platelet-rich plasma promotes cell proliferation by using the growth factors found in platelets. While this technology is now being utilized in dentistry, orthopedics, dermatology, and plastic surgery, it is also being employed as an adjuvant treatment in assisted reproductive procedures. Yet, due to its recent adoption, there remains ongoing debate regarding the standardization of PRP preparation procedures, the frequency of its administration to patients, and the determination of its effectiveness as a treatment. It is believed that further prospective randomized clinical studies are needed to qualify PRP application as a therapy.

Acknowledgments

The Figures (Figure 1 and Figure 2) used in this review were created with BioRender (BioRender.com).

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Carson SA, Kallen AN. Diagnosis and Management of Infertility: A Review. JAMA. 2021 Jul 6;326:65-76.
2. Starc A, Trampuš M, Pavan Jukić D, Rotim C, Jukić T, Polona Mivšek A. Infertility and sexual dysfunctions: A systematic literature review. Acta Clin Croat. 2019 Sep;58:508-15.
3. Sternberg AK, Buck VU, Classen-Linke I, Leube RE. How Mechanical Forces Change the Human Endometrium during the Menstrual Cycle in Preparation for Embryo Implantation. Cells. 2021 Aug 6;10:2008.
4. Artunc-Ulkumen B, Pala HG, Pala EE, Yavasoglu A, Yigitturk G, Erbas O. Exenatide improves ovarian and endometrial injury and preserves ovarian reserve in streptozocin induced diabetic rats. Gynecol Endocrinol. 2015 Mar;31:196-201.
5. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012–. Gonadotropins. 2018 Mar 26. PMID: 31644163.
6. Blanco-Breindel MF, Singh M, Kahn J. Endometrial Receptivity. 2022 Dec 4. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 36512665.
7. Lin Y, Qi J, Sun Y. Platelet-Rich Plasma as a Potential New Strategy in Endometrial Treatment in Assisted Reproductive Technology. Front Endocrinol (Lausanne). 2021 Oct 18;12:707584.
8. Paichitrojjana A, Paichitrojjana A. Platelet Rich Plasma and Its Use in Hair Regrowth: A Review. Drug Des Devel Ther. 2022 Mar 10;16:635-45.
9. Sharara FI, Lelea LL, Rahman S, Klebanoff JS, Moawad GN. A narrative review of platelet-rich plasma (PRP) in reproductive medicine. J Assist Reprod Genet. 2021 May;38:1003-12.
10. Atkinson L, Martin F, Sturmey RG. Intraovarian injection of platelet-rich plasma in assisted reproduction: too much too soon? Hum Reprod. 2021 Jun 18;36:1737-50.
11. Poulios E, Mykoniatis I, Pyrgidis N, Zilotis F, Kapoteli P, Kotsiris D, et al. Platelet-Rich Plasma (PRP) Improves Erectile Function: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial. J Sex Med. 2021 May;18:926-35.
12. Hortu I, Ozceltik G, Ergenoglu AM, Yigitturk G, Atasoy O, Erbas O. Protective effect of oxytocin on a methotrexate-induced ovarian toxicity model. Arch Gynecol Obstet. 2020 May;301:1317-24.
13. Nazari L, Salehpour S, Hosseini S, Sheibani S, Hosseinirad H. The Effects of Autologous Platelet-Rich Plasma on Pregnancy Outcomes in Repeated Implantation Failure Patients Undergoing Frozen Embryo Transfer: A Randomized Controlled Trial. Reprod Sci. 2022 Mar;29:993-1000.
14. Bakhsh AS, Maleki N, Sadeghi MR, SadeghiTabar A, Tavakoli M, Zafardoust S, et al. Effects of Autologous Platelet-Rich Plasma in Women with Repeated Implantation Failure Undergoing Assisted Reproduction. JBRA Assist Reprod. 2022 Jan 17;26:84-7.
15. Zamaniyan M, Peyvandi S, Heidaryan Gorji H, Moradi S, Jamal J, Yahya Poor Aghmashhadi F, et al. Effect of platelet-rich plasma on pregnancy outcomes in infertile women with recurrent implantation failure: a randomized controlled trial. Gynecol Endocrinol. 2021 Feb;37:141-5.
16. Pala HG, Erbas O, Pala EE, Artunc Ulkumen B, Akman L, Akman T, et al. The effects of sunitinib on endometriosis. J Obstet Gynaecol. 2015 Feb;35:183-7.
17. Eftekhar M, Neghab N, Naghshineh E, Khani P. Can autologous platelet-rich plasma expand endometrial thickness and improve pregnancy rate during the frozen-thawed embryo transfer cycle? A randomized clinical trial. Taiwan J Obstet Gynecol. 2018 Dec;57:810-3.
18. Chang Y, Li J, Wei LN, Pang J, Chen J, Liang X. Autologous Platelet-Rich Plasma Infusion Improves Clinical Pregnancy Rate in Frozen Embryo Transfer Cycles for Women with Thin Endometrium. Medicine (Baltimore). 2019 Jan;98:e14062.
19. Tehraninejad ES, Kashani NG, Hosseini A, Tarafdari A. Autologous Platelet-Rich Plasma Infusion Does Not Improve Pregnancy Outcomes in Frozen Embryo Transfer Cycles in Women with a History of Repeated Implantation Failure Without Thin Endometrium. J Obstet Gynaecol Res. 2021 Jan;47:147-51.
20. Ershadi S, Noori N, Dashipoor A, Ghasemi M, Shamsa N. Evaluation of the Effect of Intrauterine Injection of Platelet-Rich Plasma on the Pregnancy Rate of Patients with a History of Implantation Failure in the In Vitro Fertilization Cycle. J Family Med Prim Care. 2022 May;11:2162-6.
21. Xu Y, Hao C, Fang J, Liu X, Xue P, Miao R. Intrauterine Perfusion of Autologous Platelet-Rich Plasma Before Frozen-Thawed Embryo Transfer Improves the Clinical Pregnancy Rate of Women With Recurrent Implantation Failure. Front Med (Lausanne). 2022 Mar 29;9:850002.
22. Cakiroglu Y, Saltik A, Yuceturk A, Karaosmanoglu O, Kopuk SY, Scott RT, et al. Effects of Intraovarian Injection of Autologous Platelet-Rich Plasma on Ovarian Reserve and IVF Outcome Parameters in Women with Primary Ovarian Insufficiency. Aging (Albany NY). 2020 Jun 5;12:10211-22.
23. Cakiroglu Y, Yuceturk A, Karaosmanoglu O, Kopuk SY, Korun ZEU, Herlihy N, et al. Ovarian Reserve Parameters

and IVF Outcomes in 510 Women with Poor Ovarian Response (POR) Treated with Intraovarian Injection of Autologous Platelet-Rich Plasma (PRP). Aging (Albany NY). 2022 Mar 22;14:2513-23.

24. Hosseinisadat R, Farsi Nejad A, Mohammadi F. Intra-Ovarian Infusion of Autologous Platelet-Rich Plasma in Women with Poor Ovarian Reserve: A Before and After Study. Eur J Obstet Gynecol Reprod Biol. 2023 Jan;280:60-3.
25. Keikha F, Shahsavari S, Salari Y, Roozbeh N, Haghollahi F, Tarazjani MD, et al. One-Side Ovarian Rejuvenation: A Quasi-Experimental Study of the Effect of Autologous Platelet-Rich Plasma in Poor Ovarian Responders in IVF. Ethiop J Health Sci. 2022 Nov;32:1133-40.
26. Hsu CC, Hsu I, Hsu L, Chiu YJ, Dorjee S. Resumed Ovarian Function and Pregnancy in Early Menopausal Women by Whole Dimension Subcortical Ovarian Administration of Platelet-Rich Plasma and Gonadotropins. Menopause. 2021 Mar 26;28:660-6.