Review Article

Platelet-rich plasma in female infertility: A comprehensive review of current literature

Pandey Divya

Department of Obstetrics and Gynaecology, Vardhman Mahavir Medical College and Safdarjung Hospital, Ansari Nagar West, New Delhi, India

Abstract

Platelet-rich plasma (PRP) is a novel approach in regenerative medicine. Being autologous, it is free from immunogenic reaction, cross-infection, easy to prepare, and easily accessible to physicians as well as patients. It has a rich milieu of multiple growth factors and bioactive molecules with capacity of regenerating tissues. Though there exist multiple protocols for PRP preparation, the common principle remains achievement of enriched plasma with platelet concentration approximately 4 to 5 times more than the circulating blood. Autologous PRP has found its potential application in different medical specialties including reproductive medicine. This study will review the current literature on potential PRP application in female infertility.

Keywords: Growth factors, ovarian rejuvenation, ovarian torsion, recurrent implantation failure, refractory endometrium, thin endometrium

Address for correspondence: Dr Divya Pandey, Department of Obstetrics and Gynaecology, Vardhman Mahavir Medical College and Safdarjung Hospital, Ansari Nagar West, New Delhi, India.
E-mail: dr_devya1@yahoo.co.in
Submission: 1–06–2021, **Accepted:** 6–06–2021, **Published:** 30–06–2021

Key Messages: PRP is platelet-enriched plasma which has a cocktail of multiple bioactive growth factors with tissue regenerating ability. It has upcoming role in treating female infertility due to endometrial and ovarian factor. The current evidence is mostly from descriptive studies, pilot studies (single–arm, self-controlled trials) and a few randomized controlled trials with small sample size. There is a need for well-designed, large-scale randomized trials on this subject.

INTRODUCTION

Platelet-rich plasma (PRP) is "plasma volume with high platelet count."[1] It is obtained after centrifuging whole blood to remove red and white blood cells so as to obtain platelet concentrated plasma, hence, aptly called as autologous conditioned plasma. This blood-derived product's use has gained momentum since last decade of 20th century in regenerative medicine, including oral and maxillofacial surgery, orthopedics, sports, and veterinary medicine.[2]

This study briefly reviews the science behind PRP, principle of PRP preparation, and its potential application in management of female infertility.

BIOLOGY OF PRP

The platelets whose concentration is enhanced four to five times in PRP contain around 1100 proteins with

Access this article online

Quick Response Code:

Website: www.fertilityscienceresearch.org

DOI: 10.4103/fsr.fsr_21_21

How to cite this article: Divya P. Platelet-rich plasma in female infertility: A comprehensive review of current literature. Fertil Sci Res 2021;8:30-5.

numerous post-translational modifications, leading to formation of more than 1500 bioactive factors.[3,4] The major functions of these factors are immune system messengers, enzymes, and their inhibitors and growth factors helping in promoting tissue repair, healing, and regeneration. PRP is prepared from autologous whole blood and contains an array of bioactive growth factors and cytokines such as fibroblast growth factor, platelet-derived growth factor, vascular endothelial growth factor, transforming growth factor, epidermal growth factor, and interleukin-8.[5]

The important factor behind its easy applicability is potentially no risk of cross-contamination, immunologic reaction, or disease transmission. This is by virtue of being an autologous product.[6] Moreover, it has a low cost, noninvasive, and easily accessible modality for both patients and physicians.

PRINCIPLE AND METHOD OF PREPARING PRP

There are multiple available methods of PRP preparation but the preparation method is not yet standardized. Although there is variation in speed, duration of centrifugation, and type of anticoagulant used, yet all are based on single principle of improving process and purity of PRP and common aim of achieving a final product with specific bio-function so as to have a specific clinical application.

The main process to prepare PRP is "differential centrifugation" where different constituents are separated by a certain accelerating force according to their specific gravity. Amid various available methods of PRP preparation, the main one is the PRP method. The anticoagulated whole blood is subjected to centrifugation in two steps. The first spin (soft) separates the whole blood in three layers. The bottom most layer has red blood cells with leukocytes accumulated in a layer just above it. The middle layer corresponds to PRP, whereas the uppermost layer has platelet-poor plasma (PPP). The supernatant plasma is separated, transferred to other tube without anticoagulant, and subjected to second spin (hard) to achieve concentrated platelet as pellet. Thus, the second centrifugation helps in concentrating platelets. Finally, the PPP is removed and pellet is suspended in smallest final plasma volume.[7]

TYPES OF PRP

There are four types of PRP based on Dohan Ehrenfest classification based on the amount of leukocyte (white blood cell) and fibrin.[8] This classification has been recommended by multidisciplinary consensus committee.[9] Accordingly there are P-PRP (pure PRP with poor leukocytes and low fibrin), leukocyte and PRP with rich leukocytes and low fibrin, pure platelet-rich fibrin with poor leukocytes and high fibrin content, and leukocyte- and platelet-rich fibrin.[10,11] Of all these types, P-PRP has been used extensively in reproductive medicine.

Recently, there has been an upsurge in the application of PRP in different medical specialties pertaining to regenerative medicine. It has been used even in female infertility successfully. The major use of PRP has been seen in cases of thin/refractory endometrium, recurrent implantation failure (RIF), and premature ovarian insufficiency (POI).

THIN ENDOMETRIUM

Thin endometrium (most often taken as <7 mm) is a clinical challenge to tackle when treating infertility patients especially those who are undergoing *in vitro* fertilization (IVF) treatment. The refractory thin endometrium not responding to conventional medical treatment can infact lead to or can be the etiology of RIF .Autologous PRP with its growth factors and cytokines has the potential for tissue regeneration. Though use of PRP is listed under management of thin endometrium in assisted reproduction of the clinical guideline published in July 2019 from the Canadian Fertility and Andrology Society, but the level of evidence recommended is weak.[12]

The first clinical use of PRP for thin endometrium was reported by Chang *et al.* from China in 2015. It was a descriptive study carried out on five women undergoing IVF who had thin endometrium after conventional hormone therapy. Intrauterine PRP instillation was performed, one to two times per cycle. The endometrial thickness (ET) improved in all and four women had successful conception. After this, many descriptive studies (case reports and series) and pilot studies were published and showed promising results.[13] In 2016, Farimani *et al.* conducted a single-blind pilot study to test hypothesis that intrauterine PRP can enhance the pregnancy outcomes of frozen-thawed embryo transfer (FET). They recruited nine women with a history of RIF, six (66.6%) women achieved clinical pregnancy.[14] In 2017, Farimani *et al.* reported a successful pregnancy after the use of intrauterine PRP to improve endometrial receptivity in a 45-year-old woman with primary infertility with the history of two IVF failures.[15] In the same year, Zadehmodarres *et al.* did a pilot study on 10 patients with a history of refractory

endometrium in FET cycles. Intrauterine PRP instillation resulted in optimum endometrial growth in all 10 women after two instillations.[16]

Subsequently in 2018, two studies were published. Wang *et al.* in his prospective study administered intrauterine PRP infusion after hormone replacement therapy on 20 women undergoing IVF with refractory thin endometrium history.[17] They demonstrated a significant endometrial improvement and 60% rise in pregnancy rate. They also observed a dose-dependent cell proliferation and migration, induced by PRP with maximum proliferation at a 2% PRP dose. Eftekhar *et al.* conducted a randomized clinical trial on 83 women with poor endometrial response to standard hormone replacement therapy (endometrium thickness <7 mm) in the 13th day of the cycle in a FET.[18] All 40 women in intervention group received intrauterine PRP instillation compared to no intervention in control group ($n = 43$). They observed significant improvement in ET ($P = 0.001$) with significantly higher implantation rate and per-cycle clinical pregnancy rate ($P = 0.002$).

Chang *et al.*, later in 2019, conducted a prospective cohort study on 64 participants and demonstrated a positive impact of PRP in enhancing endometrium proliferation, improving embryo implantation rate and clinical pregnancy rate for women with thin endometrium in FET cycles.[19] They concluded that PRP has a positive role in promoting endometrium proliferation and improving embryo implantation rate and clinical pregnancy rate for women with thin endometrium in FET cycles. Significant improvement in endometrium vascularity has also been described.[20]

Other authors also showed significant increase in ET in women with thin endometrium.[6,21,22] However, this needs to be confirmed by large randomized and controlled trials.

In 2020, in a pilot study, Agarwal *et al.* studied a novel approach of hysteroscopic instillation of PRP into endomyometrial junction in 32 women with a history of embryo transfer cancellation due to thin endometrium to see the effect on endometrial vascularity and thickness. They demonstrated an improvement of ET and vascularity with higher pregnancy rates in cases of previously cancelled embryo transfer due to a thin endometrium.[23]

Hence, there is a role of PRP in improving ET, vascularity, and enhancing clinical pregnancy rates but the level of evidence is low.

RECURRENT IMPLANTATION FAILURE

The RIF is a clinically challenging situation for ART physicians.

Implantation failures are due to either poor embryo quality or defect in endometrial receptivity. There is an emergence of new trends in managing RIF via interference with endometrial receptivity. Different therapies have been suggested for managing RIF, but the most effective treatment modality is yet to be given consensus upon. These approaches are hysteroscopy, endometrial scratching, blastocyst transfer, and assisted hatching. Off late, intrauterine PRP instillation has been suggested as a modality to promote endometrial growth and receptivity.[24] Nazari *et al.* did a randomized controlled trial on 138 women who failed to conceive after three or more, high-quality embryo transfers and candidate for FET. Intrauterine infusion of 0.5 ml PRP was given. The study group had significantly higher chemical as well as clinical pregnancy rate. Thus they concluded that intrauterine PRP may be effective in the improvement of pregnancy outcome in RIF.[25]

Similar results were also observed by Zamaniyan *et al.* in RCT carried out on 98 women with RIF.[26]

Aghajanzadeh *et al.* did study on 30 women with RIF submitted to FET cycles to see the effect of intrauterine PRP on reproductive outcomes. The implantation rate observed in the PRP group was 6.7%. No significant difference was found between the implantation, clinical pregnancy, ongoing pregnancy, and miscarriage rates of FETs with and without PRP infusion. But the effect size of PRP infusion on implantation rates showed a medium strength relationship.[27]

In 2019, a meta-analysis carried out by Maleki-Hajiagha *et al.* to evaluate the effect of the intrauterine infusion of PRP on the outcome of embryo transfer in women undergoing IVF/intracytoplasmic sperm injection (ICSI) included seven studies on 625 patients (311 cases and 314 controls). Three were randomized controlled trials and four were cohort studies. The probability of chemical pregnancy ($P < 0.001$), clinical pregnancy ($P < 0.001$), and implantation rate ($P < 0.001$) was significantly more in patients who received PRP therapy compared with control. There was significant improvement in ET. This meta-analysis suggested PRP as an alternate treatment approach in patients with thin endometrium and RIF.[28]

In 2021, Tehraninejad *et al.* in a randomized controlled trial on 85 women with RIF (42 cases and 43 in control group) undergoing FET cycle received intrauterine PRP instillation 48 hours prior to embryo transfer. The pregnancy outcomes, including biochemical, clinical, and ongoing pregnancy (≥20 weeks of gestation) rates, were similar between the PRP (35.7%, 31.0%, and 26.8%, respectively) and control (37.2%, 37.2%, and 25.6%, respectively) groups. They concluded that PRP is not an effective adjuvant treatment for IVF of patients with RIF and normal ET undergoing embryo transfer. As per their findings, even if PRP has any positive effect on the endometrial function and receptivity, it should be given only to individuals with features of endometrial growth failure and a thin endometrium.[29]

Dieamant *et al.* studied the concept of a protocol labeled as PRIMER.[30] They conducted a randomized controlled trial on 66 women using this new protocol for endometrial receptivity improvement (PRIMER**)** based on PRP and granulocyte colony-stimulation factor (G-CSF) in women with RIF to improve pregnancy rates. As per this protocol, intrauterine PRP injection along with subcutaneous G-CSF-injection was given. The study group patients were given 0.7 ml of intrauterine PRP injection 48 hours before the embryo transfer. G-CSF (300 mg/0.5 ml) was started simultaneously to PRP and thereafter given as subcutaneous injection every week. The use of PRIMER in women with RIF achieved similar ongoing pregnancy and live birth rates as in women with first IVF/ICSI cycle ($P = 0.99$). Thus concluded that this therapeutic protocol (PRIMER) is simple, free of complications, and has promising outcome. More studies are awaited on this protocol.

Hence, though the existing literature is limited, but over last few years, the quality of study design has seen an improving trend. This needs to be enhanced further. There is an evident need of well-powered and well-designed randomized trials to support PRP therapy for RIF treatment.

PREMATURE OVARIAN FAILURE

Recent times are witnessing a large increase in the age of first conception due to career-oriented approach of modern women .Hence, they are likely to land in ovarian insufficiency by the time they plan to have baby. With rising age, both quality and quantity of the oocytes decline. The remedy to resultant infertility due to ovarian insufficiency has been either IVF treatment with donor oocyte or adoption. The aged oocytes have tendency to give rise to errors in cell division, leading to higher rates of aneuploidy and congenital malformations. Lately, attempts to restore or rejuvenate function of ovary have been made and are under investigation to circumvent these events. The use of autologous PRP is one such modality which is being used in poor ovarian reserve (POR) or diminished ovarian reserve, POI, etc.[31] This is based on the theory of presence of oogonia stem cells which in experimental models have shown potential to differentiate into newer follicles and oocytes.

Again, the data addressing this issue is very limited. In 2020, Panda *et al.* conducted a systematic review to evaluate the efficacy of intraovarian infusion of autologous PRP in patients with POR or ovarian insufficiency.[32] This review analyzed four studies.[33-36] Melo *et al.* (Venezuela) conducted a nonrandomized clinical trial on 46 infertile women (against 37 controls) planning for intrauterine insemination (IUI)/IVF with (i) age ≥38 years, (ii) baseline follicular-stimulating hormone (FSH), day 3 of the menstrual cycle > 12 mIU/ml, (iii) anti-Müllerian hormone (AMH) <0.8 ng/ml. Intraovarian (cortex) (200 μl) PRP injection was given once between day 7 and day 9 of the menstrual cycle for three consecutive cycles (cycles 1, 2, and 3).[33] After treatment completion with PRP, participants were advised to undergo IVF/ICSI, IUI, or timed intercourse as soon as the next menstrual cycle started. Post-treatment, there was significant improvement observed in ovarian reserve parameters (increase in median value of AMH and antral follicle count [AFC] and decrease in FSH) ($P < 0.001$) compared to pretreatment.

In 2020, Cakiroglu *et al.*, Sfakianoudis *et al.*, and Sills *et al.* did quasi-experimental (single-arm study, pre- and post-treatment) study at Turkey, the United States, and Greece, respectively.[33-36] Cakiroglu *et al.* did study on 311 infertile women with POI. Trans-vaginal intraovarian injection of about 2 to 4 ml PRP was administered in both ovaries. The injection was given on random day in amenorrheic women, whereas in those with oligomenorrhea, PRP was injected within 10 days after completion of menstruation bleeding. Post-treatment, a significant rise in AMH and AFC was observed, but decrease in FSH was not significant. On the one hand, Sfakianoudis *et al.* conducted four pilot studies, on cohort of 30 each of women with POR, POI, perimenopause, and menopause. On the other hand, Sills *et al.* did the study on 182 women with POR with at least one previous failed IVF cycle in perimenopausal or menopausal age. Both these authors evaluated postintraovarian PRP injection, ovarian reserve

parameters (AFC and AMH), and observed a significant increase.

The outcome of the ICSI cycle was also studied in three studies.[33-35] There was significant improvement in total number of oocytes retrieved, number of two-pronuclei (2Pn) embryos, fertilization rate, number of cleavage stage embryos, number of good quality embryos, and lower cycle cancellation rate postintraovarian PRP infusion when compared with the cycle without PRP infusion.[33-35]

Petryk and Petryk did a single-arm study on 38 women between 31 and 45 years of age with POR and at least two unsuccessful attempts to receive their oocytes through IVF. The ovarian rejuvenation was performed by injecting under ultrasound guidance or laparoscopic approach. They observed that higher platelet concentration in PRP being injected (about 1×10^6 µl) gives long-lasting results, within 12 months, after a single injection.[37]

Due to absence of homogeneity in the existing studies on role of intraovarian PRP therapy, meta-analysis is lacking. Thus again there is need of better quality study designs and trials.

OVARIAN TORSION

Torsion in ovaries can be a common cause of ischemic injury leading to decreased follicular function and infertility. PRP which has growth factors has demonstrated cytoprotective action in animal (rat) model, where 60 adult female rats were exposed to ischemia and bilateral adnexal torsion for 3 hours. Intraperitoneal PRP was given 30 minutes before ischemia in one group. This was followed by de-torsion. The oxidative stress levels, histopathologic changes, and reperfusion injuries were lower in the PRP group. The authors concluded that PRP led to ischemia prevention and reperfusion damage in rat ovary.[38] This use of PRP in animal model strengthens the regenerative potential of PRP.

CONCLUSION

Although the literature is limited, yet demonstrates promising effect of PRP therapy in infertile women by increasing ET and vascularity, improving AMH, recovering AFC, and decreasing FSH levels, as well as increasing chemical and clinical pregnancy rates. There is definitely dearth of standardized protocol for PRP preparation. With the encouraging results of existing studies, it is necessary to standardize PRP preparation protocols for various therapeutic functions. Moreover, issue of lack of well-designed, high-quality, large randomized controlled trials needs to be addressed in future studies. Till then, PRP use is more of experimental therapy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Marx RE. Platelet-rich plasma (PRP): what is PRP and what is not PRP? Implant Dent 2001;10:225-8.
2. Hanson B, Johnstone E, Dorals J, Silver B, Peterson CM, Hotaling J. Female infertility, infertility-associated diagnosis and co-morbidities: a review. J Assist Reprod Genet 2017;34:167-77.
3. Knezevic NN, Candido KD, Desai R, Kaye AD. Is platelet-rich plasma a future therapy in pain management? Med Clin North Am 2016;100:199-217.
4. Boswell SG, Cole BJ, Sundman EA, Karas V, Fortier LA. Platelet-rich plasma: a milieu of bioactive factors. Arthroscopy 2012;28:429-39.
5. Nazari L, Salehpour S, Hoseini S, Zadehmodarres S, Azargashb E. Effects of autologous platelet-rich plasma on endometrial expansion in patients undergoing frozen-thawed embryo transfer: a double-blind RCT. Int J Reprod Biomed 2019;17:443-8.
6. Marques LF, Stessuk T, Camargo IC, Sabeh Junior N, dos Santos L, Ribeiro-Paes JT. Platelet-rich plasma (PRP): methodological aspects and clinical applications. Platelets 2015;26:101-13.
7. Dhurat R, Sukesh M. Principles and methods of preparation of platelet-rich plasma: a review and author's perspective. J Cutan Aesthet Surg 2014;7:189-97.
8. Dohan Ehrenfest DM, Andia I, Zumstein MA, Zhang CQ, Pinto NR, Bielecki T. Classification of platelet concentrates (platelet-rich plasma-PRP, platelet-rich fibrin-PRF) for topical and infiltrative use in orthopedic and sports medicine: current consensus, clinical implications and perspectives. Muscles Ligaments Tendons J 2014;4:3-9.
9. Dohan Ehrenfest DM, Bielecki T, Mishra A, *et al.* In search of a consensus terminology in the field of platelet concentrates for surgical use: platelet-rich plasma (PRP), platelet-rich fibrin (PRF), fibrin gel polymerization and leukocytes. Curr Pharm Biotechnol 2012;13:1131-7.
10. Pavlovic V, Ciric M, Jovanovic V, Stojanovic P. Platelet rich plasma: a short overview of certain bioactive components. Open Med 2016;11:242-7.
11. Bielecki T, Dohan Ehrenfest DM, Everts PA, Wiczkowski A. The role of leukocytes from L-PRP/L-PRF in wound healing and immune defense: new perspectives. Curr Pharm Biotechnol 2012;13:1153-62.
12. Liu KE, Hartman M, Hartman A. Management of thin endometrium in assisted reproduction: a clinical practice guideline from the Canadian Fertility and Andrology Society. Reprod Biomed Online 2019;39:49-62.
13. Chang Y, Li J, Chen Y, *et al.* Autologous platelet-rich plasma promotes endometrial growth and improves pregnancy outcome during in vitro fertilization. Int J Clin Exp Med 2015;8:1286-90.
14. Farimani M, Bahmanzadeh M, Poorolajal J. A new approach using autologous platelet-rich plasma to treat infertility and to improve population replacement rate. J Res Health Sci 2016;16:172-3.

15. Farimani M, Poorolajal J, Rabiee S, Bahmanzadeh M. Successful pregnancy and live birth after intrauterine administration of autologous platelet-rich plasma in a woman with recurrent implantation failure: a case report. Int J Reprod Bio Med 2017;15:803-6.
16. Zadehmodarres S, Salehpour S, Saharkhiz N, Nazari L. Treatment of thin endometrium with autologous platelet-rich plasma: a pilot study. JBRA Assist Reprod 2017;21:54-6.
17. Wang X, Liu L, Mou S, *et al.* Investigation of platelet-rich plasma in increasing proliferation and migration of endometrial mesenchymal stem cells and improving pregnancy outcome of patients with thin endometrium. J Cell Biochem 2019;120:7403-11. https://doi.org/10.1002/jcb.28014
18. Eftekhar M, Neghab N, Naghshineh E, Khani P. Can autologous platelet rich plasma expand endometrial thickness and improve pregnancy rate during frozen-thawed embryo transfer cycle? A randomized clinical trial. Taiwan J Obstet Gynecol 2018;57:810-3.
19. 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;98:e14062.
20. Tandulwadkar SR, Naralkar MV, Surana AD, Selvakarthick M, Kharat AH. Autologous intrauterine platelet-rich plasma instillation for suboptimal endometrium in frozen embryo transfer cycles: a pilot study. J Hum Reprod Sci 2017;10:208-12.
21. Kim H, Shin JE, Koo HS, Kwon H, Choi DH, Kim JH. Effect of autologous platelet-rich plasma treatment on refractory thin endometrium during the frozen embryo transfer cycle: a pilot study. Front Endocrinol 2019;10:61.
22. Frantz N, Ferreira M, Kulmann MI, Frantz G, Bos-Mikich A, Oliveira R. Platelet-rich plasma as an effective alternative approach for improving endometrial receptivity − a clinical retrospective study. JBRA Assist Reprod 2020;24:442-6.
23. Agarwal M, Mettler L, Jain S, Meshram S, Günther V, Alkatout I. Management of a Thin endometrium by hysteroscopic instillation of platelet-rich plasma into the endomyometrial junction: a pilot study. J Clin Med 2020;9:2795.
24. Garcia-Velasco JA, Acevedo B, Alvarez C, *et al.* Strategies to manage refractory endometrium: state of the art in2016. Reprod Biomed Online 2016;32:474-89.
25. Nazari L, Salehpour S, Hosseini MS, Hashemi Moghanjoughi P. The effects of autologous platelet-rich plasma in repeated implantation failure: a randomized controlled trial. Hum Fertil (Camb) 2020;23:209-13.
26. Zamaniyan M, Peyvandi S, Heidaryan Gorji H, *et al.* Effect of platelet-rich plasma on pregnancy outcomes in infertile women with recurrent implantation failure: a randomized controlled trial. Gynecol Endocrinol 2021;37:141-5.
27. Aghajanzadeh F, Esmaeilzadeh S, Basirat Z, Mahouti T, Heidari FN, Golsorkhtabaramiri M. Using autologous intrauterine platelet-rich plasma to improve the reproductive outcomes of women with recurrent implantation failure. JBRA Assist Reprod 2020;24:30–3.
28. Maleki-Hajiagha A, Razavi M, Rouholamin S, Rezaeinejad M, Maroufizadeh S, Sepidarkish M. Intrauterine infusion of autologous platelet-rich plasma in women undergoing assisted reproduction: a systematic review and meta-analysis. J Reprod Immunol 2020;137:103078.
29. 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 history of repeated implantation failure without thin endometrium. J Obstet Gynaecol Res 2021;47:147-51.
30. Dieamant F, Vagnini LD, Petersen CG, *et al.* New therapeutic protocol for improvement of endometrial receptivity (PRIMER) for patients with recurrent implantation failure (RIF) − a pilot study. JBRA Assist Reprod 2019;23:250-4.
31. Amable PR, Carias RB, Teixeira MV, *et al.* Platelet-rich plasma preparation for regenerative medicine: optimization and quantification of cytokines and growth factors. Stem Cell Res Ther 2013;7:67.
32. Panda SR, Sachan S, Hota S. A systematic review evaluating the efficacy of intra-ovarian infusion of autologous platelet rich plasma in patients with poor ovarian reserve or ovarian insufficiency. Cureus 2020;12:e12037.
33. Cakiroglu Y, Saltik A, Yuceturk A, *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 2020;12:10211-22.
34. Melo P, Navarro C, Jones C, Coward K, Coleman L. The use of autologous platelet-rich plasma (PRP) versus no intervention in women with low ovarian reserve undergoing fertility treatment: a non-randomized interventional study. J Assist Reprod Genet 2020;37:855-63.
35. Sfakianoudis K, Simopoulou M, Grigoriadis S, *et al.* Reactivating ovarian function through autologous platelet-rich plasma intraovarian infusion pilot data on premature ovarian insufficiency, perimenopausal, menopausal, and poor responder women. J Clin Med 2020;9:1809.
36. Sills E, Sills E, Petersen J, Rickers N, Wood S, Li X. Regenerative effect of intraovarian injection of activated autologous platelet rich plasma: serum anti-Müllerian hormone levels measured among poor-prognosis in vitro fertilization patients. Int J Regen Med 2020;1:5.
37. Petryk N, Petryk M. Ovarian rejuvenation through platelet-rich autologous plasma (PRP)-a chance to have a baby without donor eggs, improving the life quality of women suffering from early menopause without synthetic hormonal treatment. Reprod Sci 2020;27:1975-82.
38. Bakacak M, Bostanci MS, İnanc F, *et al.* Effect of platelet rich plasma on experimental ischemia/reperfusion injury in rat ovary. Gynecol Obstet Invest 2016;81:225-31.