Research Article

INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH

ISSN: 2395-6429, Impact Factor: 4.656
Available Online at www.journalcmpr.com
Volume 7; Issue 02(A); February 2021; Page No.5579-5585
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr202102968

PLATELET RICH PLASMA (PRP) THERAPY: A PERSPECTIVE INTO TREATING GYNAECOLOGICAL DISORDERS

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ARTICLE INFO

Article History:
Received 13th November, 2020
Received in revised form 11th December, 2020
Accepted 8th January, 2021
Published online 28th February, 2021

Key words:
PRP, Platelet-rich plasma, ovarian rejuvenation, pre-menopause, thin endometrium, regenerative medicine

ABSTRACT

Platelet Rich Plasma therapy commonly addressed as PRP therapy is widely used for the treatment of vast majority of diseases currently. The platelet concentrate derived from autologous blood has a unique potential to orchestrate the natural healing cascade at the site of the wound and hence PRP therapy is one of the promising facets of regenerative medicine. The ease of preparation and application of PRP towards various kinds of treatment, have been a major force in its popularity. We also discuss our signature protocol for PRP preparation which can be applied for the treatment of a diverse set of conditions. In this review, while we indulge into understanding PRP and its mechanism of action, special focus is given to its contribution in treatment of gynaecological disorders. The insights have been provided into treating the causes of pre-menopause which is highly prevalent in today's scenario. The remarkable recovery rate observed after using PRP, has led many scientists to unravel the mechanism of action. However, the exact course of action is yet to be elucidated. Nevertheless, PRP therapy continues to gain attention due to negligible adverse effects associated with its application in the light of the benefits that it provides towards disease management.

INTRODUCTION

History of Platelet-Rich Plasma

The use of PRP which is described as plasma with higher platelet count than that of peripheral blood dates back to 1970s when hematologists used it to treat thrombocytopenia. Platelet-Rich Plasma (PRP) is also commonly termed as PRF (Platelet rich Fibrin matrix), GF-s (Platelet- rich growth factors), and platelet concentrate [1, 2]. Over the years, the field has witnessed the use of PRP widely for tissue regeneration, skin rejuvenation, scars and wound healing, and for alopecia treatment owing to its property to kick start healing cascade. [3, 4, 5, 6, 7, 8].

The success of PRP in maxillofacial surgery as PRF (Platelet Rich Fibrin), a decade later, was due to the potential of fibrin for adherence and homeostatic properties, and of platelet rich plasma to stimulate cell proliferation [9]. Subsequent studies had shown remarkable recovery and complete pain relief when PRP injections were given for athletic injuries [10]. Hence, the use of PRP therapy for the treatment of musculoskeletal

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diseases such as arthritis, tendonitis, tears, and ligament sprains was promoted, thereby, making PRP therapy highly prevalent in orthopedic and sports medicine [11].

Histological evidence suggested that when PRP is injected in deep dermis and immediate sub-dermis, it induces activation of fibroblasts, soft-tissue augmentation, new collagen deposition, adipose tissue formation, and formation of new blood vessels. This led PRP therapy to become a popular and reliable procedure in cosmetic dermatology field [12,13]. With the remarkable success of PRP due to its natural healing properties, other medical fields that use PRP are gynecology, pediatric surgery, cardiac surgery, ophthalmology, plastic surgery, and urology [14, 15].

Understanding PRP

Platelets are tiny blood cells called thrombocytes which are made in bone marrow. Initially, the only property attributed to platelets was to maintain homeostasis, however, with time, the research has shown that these cells have a plethora of functions and the abilities to their name. Platelets are known to be rich in cytokines, coagulation factors, adhesion molecules, immunologic molecules, and regulators of growth and angiogenesis which have peculiar roles in inflammatory processes, coagulation and immunity modulation. They promote angiogenesis, tissue remodelling, and aid in wound healing process [16]. It is due to these aspects, that PRP represents a novel therapeutic option for the treatment of a large number of diseases.

Studies have shown that growth factors are present in significantly higher amounts in PRP as compared to platelet poor plasma and whole blood. PRP has been shown to promote changes in monocyte-mediated proinflammatory chemokine/ cytokine release [17]. The levels of Lipoxin A4 (LXA4) are also found to be significantly higher in PRP compared to whole blood. LXA4 is an endogenous lipoxygenase-derived eicosanoid mediator that has been shown to possess dual pro-resolving and anti-inflammatory properties. According to the study, PRP suppresses the cytokine release, limits inflammation and henceforth promotes tissue regeneration [17].

Platelet growth factors are responsible for only a part of platelet bioactivity. Along with the growth factors and other signaling molecules, platelets function with red blood cells and leukocytes to ignite the repair process and the duration and magnitude of the inflammatory response is dictated by their cooperative engagement.

PRP for the treatment of thin endometrium and ovarian rejuvenation

Premature ovarian failure (POF) is one of the leading causes of premature menopause and is diagnosed in approximately 1% women aged under 40 years. The onset of premature menopause is also attributed several other factors such as family history, behavioral habits like smoking, chemotherapy or pelvic radiation treatments for cancer, autoimmune diseases, chronic fatigue syndrome etc [18]. Women who experience premature menopause are at a higher risk of neurological diseases, psychosexual dysfunction, osteoporosis, mood disorders, ischemic heart disease, infertility and premature death [19]. The treatments that are readily available at hand to mitigate some of these adverse outcomes include estrogen treatment which can be initiated after the onset of menopause or hormone replacement therapy.

In scenarios where patients with irregular menstrual cycles or showing the symptoms of menstruation absence wish to address the concern of infertility, may consider the option of oocyte cryopreservation to preserve their fertility or in-vitro fertilization treatment (IVF) but the success of these treatments in the light of premature menopause onset is almost impossible to achieve. In such cases, the patients turn to oocyte donation or adoption as their only options available. Such kind of alternative options may not be welcomed by some patients based on their personal values and desire [20].

Another cause for infertility could be premature ovarian insufficiency (POI) which occurs before a woman turns 40 years of age. The women witness elevated levels of serum follicle stimulating hormone (FSH) (FSH >40 IU/l) and an associated cessation of menstruation. In addition, profound hypoestrogenism is observed which has detrimental effects in the body [21]. Patients with POI face the challenge of reproducing using their own gametes and oocyte donation has been the only recommended and proven treatment for women with POI. Taking the defined course of these treatments, it is still difficult to predict pregnancy outcome post assisted reproductive technology (ART). The other parameters which affect the outcome are maternal age, ovarian reserve measurement and endometrial receptivity (ER). ER is evaluated with a traditional 2D ultrasound which assesses Endometrial thickness (Eth) and Endometrial pattern (EnP). Eth of <7mm on ultrasound is considered as a thin endometrium which usually results in cycle cancellation and hence is non-responsive to standard treatments posing a challenge in ART [22]. Numerous strategies have been utilized for the treatment of thin endometrium such as use of low-dose aspirin, use of exogenous estrogen, vitamin E, electroacupuncture, vaginal sildenafil citrate, and application of G-CSF (Granulocyte colony stimulation factor). Ironically despite performing these remedies, many women do not respond to the ART [23, 24, 25].

PRP in treating thin endometrium

The successful use of PRP in improving endometrium thickness in the patients undergoing IVF treatment was first reported in 2015 by Chang *et al* [26]. According to the study, after standard hormone replacement therapy, five patients still had to cancel embryo transfer cycle due to poor endometrial response (Eth < 7mm). The group performed intrauterine infusion of PRP post which endometrial expansion was observed. Embryos were transferred and successful pregnancy was observed in all the patients [26]. Another study performed by Zadehmodarres *et al*. [27] reported the effectiveness of PRP for endometrial growth in patients with a thin endometrium. This group performed the study with 10 patients with a history of cancelled cycles because of inadequate endometrial growth (Eth<7 mm). They found that at 48 hours post first PRP application, endometrial thickness increased which reached more than 7 mm after the second PRP application in all the patients. Five patients became pregnant (50%) after FET, and in four of them the pregnancy progressed normally [27].

Kim *et al* (2019) [28] conducted a pilot study to unravel the effect of PRP therapy on thin endometrium. They considered women who presented with a history of failed IVF cyclesatleast twice, refractory thin endometrium (EMT < 7mm), undergone more than two cycles of previous therapy for increasing the EMT, such as, hysteroscopic adhesiolysis following hormone replacement therapy, high dose estradiol

valerate, transvaginal sildenafil administration, or pentoxifylline combination with vitamin E, and frozen embryo available for embryo transfer. Intrauterine autologous PRP administration was performed at the estrogen-primed FET cycle. The first autologous PRP infusion was performed on menstrual cycle day 10 which was repeated at 3 days intervals until the thickness of endometrium reached 7 mm. ET was conducted 3 days after the final autologous PRP administration. The serum β-hCG levels were measured from peripheral blood 2 weeks after ET. The authors found that the use of autologous PRP significantly improved implantation, pregnancy, and live birth rates of the patients with refractory thin endometrium [28].

Furthermore, a study conducted using an animal model by Jang *et al*., [29] investigated the role of PRP in the endometrium regeneration after ethanol-induced damage. They observed that intrauterine administration of autologous PRP not only stimulated but it also accelerated regeneration of the endometrium which was coupled with decreasing fibrosis in a murine model of endometrial damage [29].

PRP in Ovarian Rejuvenation

PRP therapy is an emerging promising treatment in the reproductive context as it enhances the development of primordial and primary preantral follicles [30]. PRP has not only been proven to prevent possible ischemia following ovarian injury but it is explicitly clear that the use of PRP to target various issues regarding the reproductive system is highly positive and beneficial. According to a report by Sfakianoudis *et al* in 2019 [31], autologous PRP application lead to pregnancy in menopause for a woman aged 40 and diagnosed with premature menopause. The patient chose PRP therapy with the aim to rejuvenate the ovarian tissue to enable the employment of her own gametes through IVF. The results showed a significant reduction in FSH levels after six weeks following the autologous PRP treatment [31].

Recently Melo *et al* in 2020 [32] studied the impact of intracortical injections of autologous PRP on ovarian reserve markers in women observed with low ovarian reserve before undergoing ART. A significant improvement in the levels of FSH, AFC, and AMH was seen with no change in the control group. The group concluded that PRP injections improved these markers of low ovarian reserve and the therapy was safe and effective [32].

Sfakianoudis *et al* in 2020 [33] performed a study to investigate the impact of PRP application for ovarian rejuvenation. Four pilot studies were conducted on poor ovarian response (POR), premature ovarian insufficiency (POI), perimenopause, and menopause, respectively. Primary outcome measures for the POR pilot study were levels of anti-müllerian hormone (AMH), antral follicle count (AFC) and oocyte yield. For the POI, perimenopausal and menopausal pilot studies primary outcome measures were restoration of menstrual cycle, and Follicle Stimulating Hormone (FSH) levels. A significant improvement on the hormonal profile and the ovarian reserve status was noted, along with improved intracytoplasmic sperm injection (ICSI) cycle performance concerning POR participants. Menstruation recovery was observed along with a statistically significant improvement on levels of AMH, FSH, and AFC. Similarly, significant number of menopausal women positively responded to PRP treatment. Finally, menstruation regularity, improved hormonal levels and AFC were reported for perimenopausal women. The group concluded that PRP infusion shows promising results in addressing ovarian insufficiency [33].

Preparation of PRP

There is no consensus regarding PRP preparation.PRP is prepared through a process known as differential centrifugation, which separated the components of blood based on different specific gravity [34]. The preparation of PRP depends on the type of device chosen and should be done according to the manufacturer's instructions. There are different PRP systems that facilitate the preparation of PRP in a reproducible manner. All operate on a small volume of drawn blood and on the principle of centrifugation. (Table 1).

Even though most devices aim to obtain the best PRP, the systems differ widely in their ability to collect and concentrate platelets depending on the methodology, speed and time of centrifugation. Consequently, suspensions of different concentrations of platelets and leucocytes are obtained[34].

Table 1 ACD, acid citrate dextrose. Courtesy of Dr. Jeremy Magalon, adapted from Dohan Ehrenfest

Devices	Blood collection/ anticoagulant	Centrifugation		
		number of times	speed/time	centrifuge
Selphyl®	Tube 9 mL/sodium citrate	1	1,100 g/6 min	Classic
PRGF Endoret®	Tube 9 mL/sodium citrate	1	270 g/7 min	Classic
Cascade®	Tube 9 mL/sodium citrate	2	1,100 g/6 min 1,450 g/15 min	Classic
Plateltex®	Tube 9 mL/ACD	2	180 g/10 min 1,000 g/10 min	Classic
Regenkit®	Tube 9 mL/sodium citrate	1	1,500 g/9 min	Classic
ACP Arthrex®	Syringe 15 mL/ACD or no anticoagulant	1	1,500 rpm/5 min	Adapted
GPS III®	Syringe 30 or 60 mL/ACD	1	3,200 rpm/15 min	Adapted
Genesis®	Syringe 12 mL/ACD	1	2,400 rpm/12 min	Adapted
SmartPrep 2®	Syringe 20 or 60 mL/ACD	2	2,500 rpm/4 min 2,300 rpm/10 min	Adapted
Proteal®	Syringe 20 mL/sodium citrate	1	1,800 rpm/8 min	Adapted
Magellan®	Syringe 30–60 mL/ACD	–	–	Adapted devic
Angel®	Syringe 40–180 mL/ACD	–	–	Adapted devic

METHODOLOGY

We follow our own protocol for PRP preparation for conducting our studies which is as follows:

1. Venous blood (15-50 mL) is drawn from the patient's arm in anticoagulant-containing tubes;
2. The recommended temperature during processing is 21˚C-24˚C to prevent platelet activation during centrifugation of the blood;
3. The blood is centrifuged at 1,800 rpm for 12 minutes;
4. The blood separates into three layers: an upper layer that contains platelets and white blood cells, an intermediate thin layer (the buffy coat) that is rich in white blood cells, and a bottom layer that contains red blood cells; (Figure 1)
5. The upper and intermediate buffy layers are transferred to an empty sterile tube. The plasma is centrifuged again at 3,200 rpm for 6 minutes to help with the formation of soft pellets (erythrocytes and platelets) at the bottom of the tube;
6. The upper two-thirds of the plasma is discarded because it is platelet-poor plasma;
7. Pellets are homogenized in the lower third (5 mL) of the plasma to create the PRP;
8. The PRP is now ready for injection. Approximately 30 mL of venous blood yields 3-5 mL of PRP;
9. We then inject the prepared PRP either laproscopically (2.5cc in each ovary) at multiple site but preferably at cortex stromal site and sometimes in medulla of ovary in case of ovarian atrophy.

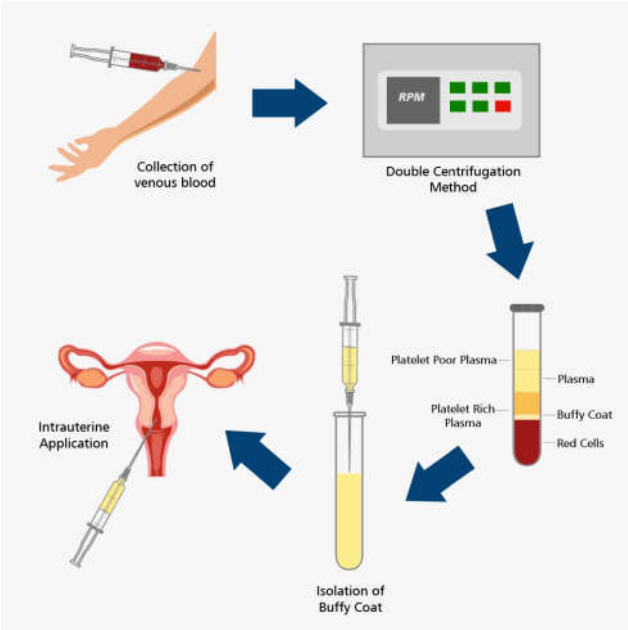

Figure 1 Schematic representation of the protocol for PRP preparation and collection for application. Venous blood is collected and subjected to double centrifugation method to separate the components of the blood. After centrifugation, the blood components (red blood cells, leukocytes, and platelets) are separated from the plasma due to their different densities. The platelets have the lowest density and hence float on top. The yellow part consisting of Platelet Rich Plasma is then collected via syringes and to heal pre-menopausal issues, is subjected to intrauterine application.

PRP composition and activation

Since PRP has high level of platelets, it is abundant in chemokines, growth factors, cytokines, plasma proteins which are stored within α-granules and other biomolecules such as fibronectin, vitronectin, and sphingosine 1-phosphate. The growth factors includeinsulin-like growth factor, platelet derived growth factor, platelet-derived angiogenic factor, vascular endothelial growth factor, fibroblast growth factor, transforming growth factor beta, connective tissue growth factor, epidermal growth factor, and interleukin-8. Altogether, the vast variety of active signaling molecules found in PRP is responsible for the onset of inflammation, stem cell migration, angiogenesis, and cell proliferation [35, 36, 37].

PRP is composed of neutrophils, monocyte macrophages which are highly motile and migrate to the site, fibroblasts: produce collagen, glycosaminoglycans, reticular fibres, and glycoprotein; endothelial cells which act as permeability barrier, regulate vascular reactivity, vasoconstrictors, vasodilators, inflammation, and immunity; keratinocytes whose main function is to act as barrier; hematopoietic stem cells (HSCs) which are multipotent in nature [36, 38].

PRP activation can be done exogenously with the use of thrombin, calcium chloride, and collagen or through mechanical trauma. Each method of activation influences the physical form of PRP, bioavailability of PRP, the amount of growth factors released, and the kinetics of release. [39]

Proposed mechanism of action

With the success of PRP therapy in treating many diseases as documented in Table 2 in addition to gynaecological disorders, elucidating the molecular mechanism of action of PRP is crucial. According to the recent study, formation of regenerative matrix is supported by the fibrin framework present over platelets [40]. It is known that higher concentration of growth factors in platelet rich plasma promote the initiation of the healing cascade [38]. The ignition of the process starting from tissue necrosis resolution, chemotaxis, cell regeneration, cell proliferation and migration to extracellular matrix synthesis, remodeling, angiogenesis, and epithelialization is attributed to the release of various growth factors such as TGF-β, PDGF, IGF, VEGF, EGF and FGF-2, and differentiation factors like GDF-9 (growth differentiation factor 9) upon platelet activation (Figure 2). GDF-9 serves as a biomarker for oocyte maturation and its mutations have been linked to premature ovarian failure [41, 42, 43].

Ovary is highly angiogenic in structure and platelet derived factors play a crucial role in vascular activation and stabilization. The proposed mechanism of PRP application to treat ovarian insufficiency, premature menopause or thin endometrium, may involve the enrichment of the ovarian tissue with essential factors required for neoangiogenesis. Moreover, as shown in the studies Virant-Klun *et al* 2008 [44], embryonic-like stem cells (VSEL) and ovarian stem cells (OSCs) or germline stem cells (GSCs) are detected in human ovarian surface epithelium even in the case of post-menopausal and premature ovarian failure women. Surprisingly, these stem cells/ germline stem cells retain the ability to differentiate into oocytes under certain conditions which paves a new direction for the origin of PRP-derived follicles [44].

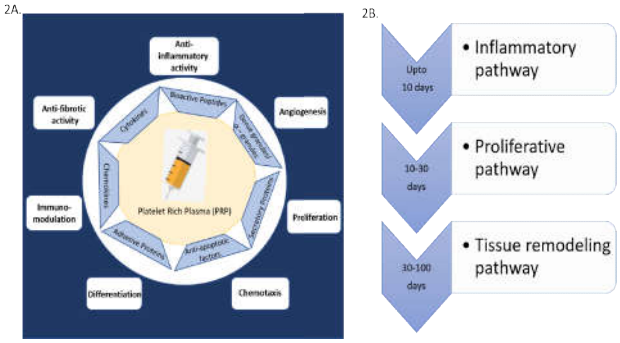

Figure 2 Mechanism of action of PRP. (2A) The figure depicts the composition of PRP and the various pathways that it is predicted to target to initiate the healing cascade. (2B). The timeline of the PRP induced process. The flowchart signifies when to repeat the next cycle of PRP.

Applications of PRP

PRP application has seen the light of success not only in ovarian rejuvenation and in treating premature menopausal conditions but it is applied for many other conditions as shown in Figure 3.

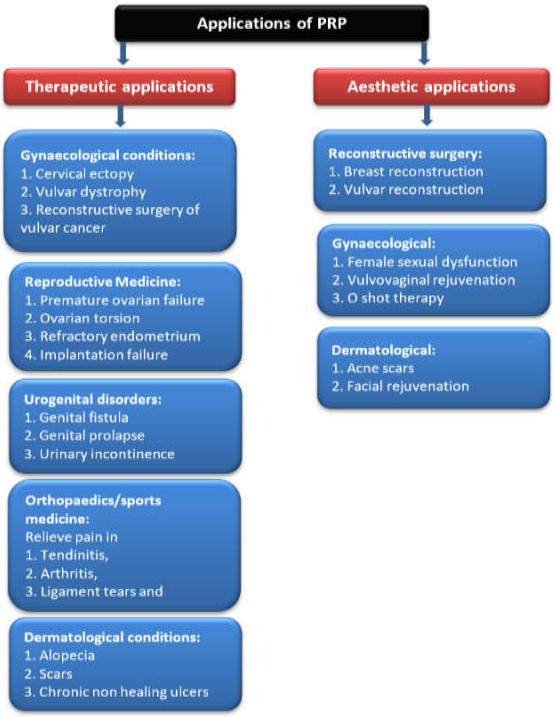

Figure 3 Applications of PRP. The figure shows various therapeutic and aesthetic application of PRP and the conditions it is used to treat under each of the areas.[10]

Furthermore, Table 2 provides the evidence-based studies where PRP related to applications of PRP.

Table 2 Evidence based studies related to the application of PRP

Application	Evidence based studies
PRP in skin lesion and wound healing	PRP to promote angiogenesis and wound healing and it was tested by Tehranian *et al.*[45] in wound healing in high-risk women undergoing cesarean sections. They applied PRP in 70 patients and compared them to 71 control cases without PRP application. They found a greater reduction in the redness, edema, ecchymosis, discharge, approximation score than in the control group
PRP in cervical ectopy	Hua *et al.* [46] conducted a randomized clinical study to compare the effectiveness of autologous PRP application to that of laser treatment for benign cervical ectopy. They applied PRP twice on the area of cervical erosion with a 1-week interval in 60 patients, while laser treatment was used in the other 60 patients. They found that the complete cure rate was 93.7% in the PRP group and the mean time to re-epithelialization was significantly shorter in the PRP and the rate of adverse treatment effects was much lower in the PRP group than in the laser group.
PRP in O shot therapy	Neto JB *et al.* [47] conducted a study to evaluate the safety, tolerability and clinical efficacy of "O-Shot" Platelets Rich Plasma (PRP) of the vulvo vaginal field among 68 women with symptoms of stress incontinence (13 patients), overactive bladder (15 patients), mixed (22 patients), lack of lubrication and sexual dysfunction (libido, arousal, dyspareunia). Treatment protocol was based on two sessions of Platelet Rich Plasma (O-Shot) two months apart. The study concluded that Platelet Rich Plasma, "O-Shot" is an in-office treatment that is safe, effective, non-surgical, and non-hormonal option for women having stress incontinence, overactive bladder, lack of lubrication, and sexual dysfunction, such as lack of libido, arousal or dyspareunia
PRP in Vaginal rejuvenation	Kim *et al.* [48]reported the use of PRP in a case of vaginal rejuvenation. They concluded that the application of autologous lipofilling mixed with PRP in a patient with vaginal atrophy produced relief of symptoms and contour restoration. The rejuvenated appearance of the external genitalia provided a pleasing cosmetic outcome to the patient.
PRP in Vulvar lichen sclerosis	Goldstein *et al.*[49] showed that among 15 patients with biopsy proven VLS received 2 separate treatments of PRP separated by 6 weeks. It was observed that out of 12 patients, 7 had decreased inflammation on their post-treatment biopsies which statistically significant.
PRP in Breast reconstruction	Gentile *et al.* [50] enrolled 100 patients aged between 19 and 60 years affected by breast soft-tissue defects. They divided the patients into two equally-sized groups. The study group was treated with fat grafting and PRP, while the control group was treated with fat grafting injections only. They found that the patients treated with PRP added to the autologous fat grafts showed a 69% maintenance rate of the restored contour and of three-dimensional volume after 1 year. They concluded that PRP mixed with fat grafts led to improvements in the maintenance of breast volume in patients affected by breast soft-tissue defects. Similar results were obtained by Salgarello *et al.*[51]
PRP in Premature ovarian failure	PRP therapy is investigated in women with POF, infertile women more than 35 years of age, and women with low ovarian reserve. PRP is injected into the ovary under ultrasound guidance, Pantos *et al.*[52] at the annual European Society of Human Reproduction and Embryology conference held in 2016 in Helsinki, Finland, introduced this modality (ovarian rejuvenation). They injected PRP in eight perimenopausal/ POF women with poor ovarian reserve. They found successful ovarian rejuvenation 1-3 months after PRP treatment. All cases underwent natural IVF cycles with follicles of 15.20±2.05 mm in diameter, the resulting oocytes were inseminated by intracytoplasmic sperm injection (ICSI), and all resulting embryos were cryopreserved.
PRP in Refractory endometrium	Colombo *et al.*[53] and Zadehmodarres *et al.*[27] in their respective studies, showed that endometrial thickness increased at 48 hours after the first PRP application and reached more than 7 mm after the second PRP application in all patients. They concluded that PRP was effective for endometrial growth in patients with a refractory endometrium.
PRP in Genital fistulae	Adler *et al.* [54] in his systemic review, that assessed conservative and surgical treatments found that small fistulae could be treated conservatively with various therapies, including PRP, with success rates ranging from 67% to 100%. Shirvan *et al.* [55] concluded that autologous PRP injection and PRF glue interposition offered a safe, effective, and novel minimally invasive approach for the treatment of vesicovaginal fistulae that obviated the need for open surgery.
PRP in Genital prolapse and urinary incontinence	PRP mixture causes rapid remodeling and connective tissue growth after vaginal surgery and because of this property Gorlero *et al.*[56] in his observational study of 10 consecutive women requiring surgery for prolapse recurrence were operated on the cases and performed PRF injections. The success rate was 80% with complete symptom relief. Sexual activity increased by 20% without dyspareunia. They concluded that the use of PRF for site-specific prolapse repair was associated with good functional outcomes.

Contraindications and adverse effects

Individuals who smoke
Individuals who have skin cancer
Individuals who have liver disorders
Individuals who have problems with blood clotting

Adverse effects: It has been reported that PRP does not cause detectable adverse effects. There are minimal side effects or complications from PRP treatments. However, one may experience swelling, redness, and in rare cases mild bruising [57].

Future Perspective

The future of medicine lies in harnessing the body's own potential of healing and regeneration. The advancing technologies in the field like stem cells therapy and cell-based therapy are all centred around exploiting the body's natural capacity to fight against a disease and offer treatment. PRP application in such a scenario offers a promising direction and strategy to open new avenues for treatment of a vast majority of diseases. However, the prevailing concern today is the lack of a standard uniform procedure for PRP isolation and based on the procedure followed, PRP preparation from the peripheral blood has been classified into many categories like Leukocyte- rich/ poorand Fibrin-rich/ poor. Hence, there is a need to develop protocols which can either be indication specific or a standard protocol which can be personalized based on the indication for which treatment is sought. We have developed a standard procedure for PRP preparation and it is called O-Cell ® procedure. It yields an autologous concentrate of Plasma which is primarily rich in α-granules and dense granules. It is prepared by using differential centrifugation followed by double centrifugation method. The PRP prep obtained through this procedure has enhanced regenerative and neo-angiogenesis capacity.

CONCLUSION

The effectiveness of PRP is based on its high level of growth factors which are important in modulating mesenchymal cell proliferation, and extracellular matrix synthesis during the process of healing. PRP has shown to be effective at

propagating new healthy tissue growth in a wide range of medical conditions [49]. During the healing process, growth factors, cytokines, and chemokines are secreted from the α-granules inside platelets. The various secreted proteins have paracrine effects on different types of cells in the body *stimulating cell migration, cell proliferation, and angiogenesis* and consequently inducing tissue regeneration [28, 58].

PRP being autologous is biocompatible and non-immunogenic in nature. It is easy to harvest, process and associated less morbidity. Low expenses are associated with its administration and therefore, PRP therapy is more affordable than other procedures. However, scientific studies done till date are only pilot studies, case reports and case series study and it necessitates for large randomized controlled studies which are required to confirm its efficacy and safety in various gynaecological disorders.

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