Review

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Thrombocyte-rich Plasma in Gynecology: A Review

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ABSTRACT

Platelet-rich plasma (PRP) is a specialized plasma preparation containing extremely high concentrations of platelets. The medical use of PRP has been accepted for many years and has produced favorable and better outcomes for disease management and prognosis in various fields. PRP has been widely used in orthopedics, plastic surgery, and many other fields since the early 1970s, but in recent years, its use in gynecology has become increasingly common. In gynecology, regenerative medicine was among the first areas to adopt PRP therapy, with largely positive results, which led to more extensive research in other areas of gynecology. The results of these studies demonstrate the importance of PRP in the treatment of gynecologic disorders, including genitourinary syndrome, urinary retardation, vesical vaginal fistulas, thin endometrium, and lymphatic sclerosis. This review summarizes the various uses of PRP in gynecology.

Keywords: Gynecology, thrombocyte-rich plasma, PRP

INTRODUCTION

Platelet-rich plasma (PRP) is an autologous plasma preparation enriched by increased concentrations of thrombocytes compared to those in full blood.[1] PRP is obtained by the centrifugation of whole blood.[2] It maakes use of the endogenous growth factors present in the thrombocyte granules to support the regeneration and repair processes of damaged tissues, cells, and organs. It is one of the most commonly used preparations in regenerative medicine today.[3] Depending on the preparation and method of thrombocyte activation, the following types of preparation are available: standard PRP and platelet-rich fibrin (PRF).

In 2014, Dohan Ehrenfest et al.[4] proposed the division of PRP presented in Table 1. There are four classifications of PRP: pure platelet-rich plasma (P-PRP), leukocyte- and platelet-rich plasma (L-PRP), pure platelet-rich fibrin (P-PRF), and leukocyte- and platelet-rich fibrin (L-PRF).[5] In order to categorize platelet products, they are separated according to their leukocytes concentration and the presence or absence of solid fibrin architecture. Pure P-PRP products are preparations with a low-density fibrin network, existing in the form of a liquid solution or activated gel, devoid of leukocytes.[5] Similarly, L-PRP products also exist in liquid or activated gel form, but these products also contain higher concentrations of leukocytes.[5,6] In contrast to plasma products, fibrin products exist exclusively as strong fibrin matrices, which can be handled as solid materials rather than liquids or gels. Within this category exist two subsets of PRF products: pure P-PRF as well as L-PRF products.[5] Due to the polymerization technique of these PRF products, the stable matrix allows for an extended, continuous release of growth factors for up to 28 days, which was hypothesized to enhance healing.[7] Delong et al.[8] created a new PRP classification system called platelet, activation, and white blood cells (WBC), which is based on the following parameters: the absolute number of platelets; the form of activation adopted; and the presence or absence of white cells. In this classification, the authors defined four different levels of platelet concentration: P1 (≤ baseline); P2 (> baseline-750,000 cells/μL); P3 (>750,000-1,250,000 cells/μL); and P4 (>1,250,000 cells/μL). Other

Table 1. Dohan Ehrenfest et al.[4] PRP classification

Preparation	Acronym	Leukocytes	Fibrin density
Pure platelet-rich plasma	P-PRP	Poor	Low
Leukocyte and platelet-rich plasma	L-PRP	Rich	Low
Pure platelet-rich fibrin	P-PRF	Poor	High
Leukocyte and platelet-rich fibrin	L-PRF	Rich	High

P-PRP: Platelet-rich plasma, L-PRP: Leukocyte- and platelet-rich plasma

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considerations relate to the use or not of platelet activators, the presence of WBC, and neutrophils (above or below the basal value present in whole blood). According to the authors, the precise identification of the cellular components and the use and type of activator adopted are important information when comparing studies with PRP.[8] Mautner et al.[9] identified some variables for which none of the previously published PRP classifications showed all the characteristics that could influence PRP activity and efficacy. In this context, the authors showed that it is important to define platelet count (absolute number/μL), leukocyte content (as positive or negative) and percentage of neutrophils when present, red blood cells (RBCs) content (as positive or negative), and activation (yes or no for exogenous activation) in the platelet, leukocyte, red blood cell and activation classification.

The main advantage of using PRP is that the preparation is autologous and thus there is no risk of immune response and infection of microorganisms from other donors.[10] Another important advantage is that its preparation is simple and fast (about 30 minutes from blood extraction to application), and its cost is low.[11]

It is known that growth factors play an important role in the healing process and tissue regeneration.[12,13] This resulted in research examining various growth factors and their role in tissue repair.[12,14] However, there are conflicting reports about potential benefits. While some authors reported improved tissue healing with PRP, other researchers were less successful.[12,15,16] Alpha granules are storage units in platelets containing pre-packaged growth factors in inactive form. The growth factors contained in these granules are transformative growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and epithelial growth factor (EGF) (Table 2). These growth factors are essential for increasing cell recruitment, proliferation, and differentiation during tissue regeneration, vascular remodeling, angiogenesis, inflammatory processes, and coagulation.[17]

Table 2. Growth factor chart

Platelet-derived growth factor	Stimulates cell replication
	Promotes angiogenesis
	Promotes epithelialization
	Promotes granulation tissue formation
Transforming growth factor	Promotes formation of extracellular matrix
	Regulates bone cell metabolism
Vascular endothelial growth factor	Promotes angiogenesis
Epidermal growth factor	Promotes cell differentiation and stimulates re-epithelialisation, angiogenesis and collagenase activity
Fibroblast growth factor	Promotes proliferation of endothelial cells and fibroblasts
	Stimulates angiogenesis

PRP Preparation

Different blood separation devices have different preparation stages but basically similar purposes. The Biomet Biologics GPS III (Platelet Concentration System, the patient's own platelets can be separated into a highly concentrated formula) system is briefly described. Approximately 30-60 mL of venous blood is taken from an anti-cubital vein by aseptic technique. It is recommended to use a butterfly needle of 18 or 19 g to prevent irritation and trauma to resting platelets. The blood is then placed in the Food and Drug Administration (FDA)-approved device and centrifuged for 15 minutes at 3200 rpm. Subsequently, the blood platelets are divided into weak platelet-poor plasma (PPP), RBC, and PRP. PPP is then removed through a dedicated port and discarded from the device. While the PRP is in a vacuumed space, the device is shaken for 30 seconds to re-suspend the platelets. The PRP is then withdrawn. Approximately 3 cc or 6 cc of PRP is obtained.[18]

The properties of PRP preparation systems are given in Table 3.[19] There were no significant differences between PRP separation systems in average PRP thrombocytes, RBCs, active TGF-β1, or fibrinogen concentrations (Table 4). There was only a significant difference in the effectiveness of thrombocyte capture.

The highest thrombocyte capture efficiency was achieved with Cascade, which is comparable to Magellan but significantly higher than GPS III. Significant differences in concentrations of WBC, PDGF-αβ, PGDF-ββ, and VEGF were observed among all systems. The cascade system concentrated weak PRP compared to leukocyte-rich PRP from the GPS III and

Table 3. PRP preparation system properties

Manufacturer	Device	Whole blood volume (mL)	Anticoagulant	Procedure	Centrifuge	Centrifuge time	mL
Emcyte	Genesis CS	54	ACD-A, 6 mL	Single spin	3600 RPMx10 min	10 min	6.0±0.0
Harvest	Smart PRP	54	ACD-A, 6 mL	Double spin	2500±150 RPMx1-3 min 2300±140 RPMx6-9 min	14 min	7.0±0.0
Arteriocyte	Magellan	52	ACD-A, 8 mL	Double spin	2800 RPM 3800 RPM	17 min	5.3±1.6
Biomet	GPS III	54	ACD-A, 6 mL	Single spin	3400 RPMx15 min	15 min	6.1±0.2

PRP: Platelet-rich plasma

Table 4. Mean platelet-rich plasma growth factor concentrations, ng/mL°

		PDGF-αβ	PDGF-ββ	TGF-β1	VEGF
Separation system, company	Cascade, MTF	9.7±3.6	14.8±2.5	0.1±0.08	0.3±0.3
	GPS III, Biomet	18.7±12.8	23.1±10.1	0.1±0.08	2.4±1.1
	Magellan, Arteriocyte	34.4±10.7	33.0±8.2	0.2±0.1	1.2±0.8
Comparison (p-values)	Among all systems (analysis of variance)	0.006	0.009	0.37	0.005
	Cascade vs. GPS III	0.52	0.33	0.99	0.004
	Cascade vs. Magellan	0.006	0.008	0.97	0.28
	GPS III vs. Magellan	0.08	0.20	0.54	0.12

°PDGF-αβ: Platelet-derived growth factor alpha-beta, PDGF-ββ: Platelet-derived growth factor beta-beta, TGF-β1: Transforming growth factor-beta 1 VEGF: Vascular endothelial growth factor

Magellan systems. GPS III and Magellan leukocytes were compared from Cascade to leukocytes poor PRP to increase concentrations of rich PRP, WBCs, PDGF-αβ, and VEGF.[20]

PRP injection is a relatively recent treatment modality, and therefore, robust data on the dosing of treatment, the location, frequency, and duration of its administration are scarce. Nevertheless, the adverse events of PRP therapy, such as infection, bleeding, and nerve damage, appear to be minimal.[21] It can be prepared manually, or there are different FDA-approved commercial PRP preparation kits, such as the GPSIII, Cascade and Magellan. With these kits, PRP substrates with different concentrations, using different coagulation activators, and with different leukocyte contents are obtained. Choukroun and Ghanaati[22] investigated growth factor release and total leukocyte and platelet counts for the first time in relation to the systematic variation of relative centrifugal force (RCF) exposure. The data showed that reducing RCF from a high range to a low spectrum in autologous PRF-based matrices resulted in a significant increase in leukocyte and platelet count as well as growth factor concentration of VEGF and TGF-β1. Furthermore, PRF clots produced with glass tubes showed higher weight (average 1.9±0.4 g) compared to silica-coated plastic tubes (average 1.6±0.3 g), although this difference was not significant. Recently, the importance of centrifuge tubes in the final production of PRF matrices has been reported.[23] Yamaguchi et al.[24] reported different platelet distributions in the concentrated growth factor (CGF) matrix when prepared with silica-coated plastic tubes or glass tubes. Platelets were distributed mainly on the distal side of the CGF matrix prepared with glass but homogeneously in the CGF matrix prepared with plastic.

In 2014, Ghanaati et al.[25] proposed a new protocol increasing the time of centrifugation and decreasing speed (A-PRF, RCFclot, 193 g, RCFmax: 276 g for 14 minutes) using glass tubes for blood collection. Recently, the same group introduced another modification by reducing centrifugation speed and duration even further (A-PRF+, RCFclot 145 g, RCFmax 208 g for 8 minutes). Reducing RCF resulted in an increase in the release of growth factors and in the concentration of leucocytes and platelets.[22]

REVIEW

In a case report by Kim et al.,[26] a 67-year-old woman who had been complaining of vaginal itching, irritation, and the appearance of her external genitalia for five years initially tried estrogen therapy but failed to achieve symptomatic relief. A total of 36 cc of autologous fat was collected from the abdomen using a 10 cc Luer-Lok syringe and a blunt-tipped two-hole cannula. A total of 4 cc autologous PRP was prepared from 30 cc whole blood using SmartPreP® APC-30 kit. A total of 40 cc autologous fat mixed with PRP was transferred into 1 cc syringes and injected aseptically into the subcutaneous layer of the labia majora through four ports injected into the subcutaneous layer of the labia majora. Within a month, itching and irritation disappeared, and there was a noticeable increase in volume in the labia majora in the immediate postoperative period.[26]

A prospective phase II pilot study conducted by Hersant et al.[27] enrolled twenty breast cancer survivors affected by vulva vaginal atrophy. Patients with a Gloria Bachman vaginal health index (VHI) score <15 received an A-PRP+HA (Regenkit A-PRP) combination intramucosally. Clinical evaluations were performed using VHI and female sexual distress (FSD) scores at months 0, 1, 3, and 6. Improvement in vaginal dryness and dyspareunia symptoms was observed, with a significant increase in VHI scores at six months ($p<0.0001$) and a significant decrease in FSD scores during the study ($p<0.0001$).[27]

A pilot study conducted by Long et al.[28] investigated the efficacy of A-PRP injections for the treatment of women with stress urinary incontinence (SUI). Twenty women with SUI received A-PRP injections through the anterior vaginal wall, near the middle of the urethra. Symptom severity was assessed using self-reported questionnaires before and six months after treatment. The study found a significant improvement in incontinence symptoms at both time points, with no adverse reactions. The treatment did not show a significant effect on sexual function. These results suggest that A-PRP injections may be a mildly effective, safe treatment for mild to moderate SUI in women and may open avenues for further research in this area.[29] Prodromidou et al.[29] conducted a systematic review to evaluate the efficacy of PRP in the treatment of urogynecologic disorders. The review included studies with patients who had vaginal atrophy, pelvic organ prolapse,

urinary incontinence, vaginal fistulas, and mesh exposure. The results suggested that PRP was a viable alternative method, especially when hormone therapy was contraindicated.

However, the study also concluded that more extensive, randomized trials are needed to fully establish the efficacy of PRP in these treatments.

In a meta-analysis by Maged et al.[30] in 2023, intrauterine and subendometrial PRP injection was proven to improve in vitro fertilization (IVF) cycle outcomes, such as rates of implantation, clinical pregnancy, live birth, and endometrial thickness in previously implantation failure and refractory infertile women with thin endometrium.

In obstetrics and gynecology, several different studies with small sample sizes have been conducted to investigate the effects of PRP injection into the uterus and ovaries.[31] The first reviews of intraovarian injections of PRP were published by Sills et al.[31] They reported improvement in laboratory values after intraovarian PRP in four women with premature ovarian failure. Later, Sfakianoudis et al.[32] reported the first pregnancy in a menopausal woman after intraovarian PRP injection.

The other indication for PRP administration is Asherman syndrome. According to studies by Aghajanova et al.,[33,34] treatment with intrauterine PRP infusion has been shown to improve endometrial function, as demonstrated by successful conception and ongoing clinical pregnancies without short- or long-term side effects. Together with robust *in vitro* data on human endometrial cells, these pilot clinical results were very reassuring, but the primary results obtained after a pilot study of 30 patients were not very instructive compared to standard therapy. Shen et al.[35] recruited women with moderate to severe intrauterine adhesions and randomly assigned them to either the PRP group or the control group. The results showed that intrauterine infusions of PRP did not improve clinical pregnancy rates. In contrast, Wang et al.[36] reported a significant improvement in clinical pregnancy rates and menstrual duration in the PRF group compared to the control group. PRF is a second-generation platelet concentrate containing mainly fibrin, platelets, and leukocytes.[37] Unlike PRP, PRF does not use anticoagulant in the preparation process and has a weak, flowing gel structure.[37] In the study, no significant difference was found between the cytokine concentrations measured in PPP supernatant and those measured in the actual PRF clot. Moreover, PRF may prolong cytokine lifespan by promoting the slow release of cytokines.[38] However, further research is needed to assess whether the therapeutic effect of PRF is superior to PRP.

Molina et al.[39] followed 19 patients with resistant endometrium, aged between 33 and 45 years, who had undergone IVF and in whom PRP was infused into the uterine cavity via a catheter. PRP was used twice, after the 10th day of hormone replacement therapy and 72 hours after the first administration. The endometrial thickness was reported to be >7.0 mm after the first application, and in all cases, the endometrial thickness was >9.0 mm after the second application. The entire study group was qualified for embryo transfer at the blastocyst stage. Pregnancy tests were positive in 73.7% of cases, 26.3% of which resulted in live births; 26.3% had ongoing pregnancies; 10.5% had biochemical pregnancies; and 5.3% had fetal death by 16 weeks.[39] In another publication, Zadehmodarres et al.[40] reported that they enrolled ten patients with a history of insufficient endometrial thickness in frozen-thawed embryo transfer cycles. In each patient, PRP treatment increased endometrial thickness, and embryo transfer was performed. Five patients became pregnant after treatment, and in four cases, the pregnancy progressed normally.

PRP is emerging as a promising therapeutic modality that shows promise in the treatment of refractory conditions.[41,42] PRP is rich in growth factors that have been implicated in cellular growth, differentiation, angiogenesis, and tissue repair.[43] The administration of PRP into the ovaries is thought to stimulate the activation of potential ovarian stem cells, resulting in the secretion of factors that facilitate follicular growth and development.[44] Furthermore, PRP may augment ovarian blood flow through the promotion of angiogenesis, thereby improving the delivery of oxygen and nutrients to developing follicles.[43,45] In cases where ovarian dysfunction makes it difficult to conceive, PRP injection into both ovaries has been attempted. The effect of the administration was an increase in the number of ovarian oocytes.[45] Autologous intraovarian PRP treatment in women with poor ovarian reserve and early menopause also increased anti-Müllerian hormone levels and decreased follicle-stimulating hormone concentrations; clinical and live birth rates tended to increase.[47,48] In a related study, Farimani et al.[46] published a study involving 19 women. The mean number of oocytes before and after PRP injection was 0.64 and 2.1, respectively. A spontaneous pregnancy occurred in two patients.

In the third case, clinical pregnancy was achieved, and a healthy baby was born.

PRP infiltrations may play a role in symptom relief in selected cases of patients with severe lichen sclerosis (LS) who have not responded to first-line therapy or for whom other treatments are poorly tolerated or contraindicated. Medina Garrido et al.[49] administered three PRP infiltrations to 28 postmenopausal female patients with biopsy-proven LS and an inadequate response to steroid therapy. The change in score according to the Clinical Scoring System for Vulvar Lichen Sclerosus was measured six times over the course of one year and they reported a statistically significant improvement. In another study involving the largest number of patients to date (94 patients), both female and male patients showed a significant reduction in symptoms and improvement in sexual function and quality of life after six months of PRP treatment.[50]

Sukgen et al.[51] investigated the effects of PRP injection into the lower third of the anterior vaginal wall on sexual function, orgasm, and genital perception in women with sexual dysfunction. The study revealed that PRP administration to the distal part of the anterior vaginal wall as a minimally invasive method can improve female sexuality and provide higher satisfaction. In another study of 68 women aged between 32 and 97 years, O-shot injection, the application of PRP to the vulvovaginal area, was found to be a satisfactory method for women with problems, such as stress incontinence, overactive bladder, lack of lubrication, and sexual dysfunction, such as

lack of libido, arousal, and dyspareunia. The results also showed that 94% of these patients were satisfied but did not show improvement in 6% of all patients with an overactive bladder.[52]

Gorlero et al.[53] evaluated the effect of PRP in patients with recurrent pelvic organ prolapse surgery. PRF was prepared in 10 patients using the Vivostat PRF system developed by Vivostat A/S and applied over the dissected pubourethral fascia before vaginal skin closure. The authors observed an anatomical success rate of 80%, and patients reported a 100% improvement in symptoms. Despite these excellent results, the authors did not go on to study a larger group of women affected by vaginal prolapse.

CONCLUSION

PRP has been one of the most widely used preparations in reconstructive medicine for over 20 years. Its growth factors and proteins have proven to be effective in wound healing and regeneration processes. Its low cost, ease of preparation, and minimally invasive application make the clinical use of PRP increasingly widespread. The absence of any risk of side effects is another reason for preference. Autologous PRP is a new alternative approach for the treatment and management of some etiologies of infertility, especially in women resistant to standard therapy. PRP is known to be effective in demonstrating endometrial regeneration, restoring the menstrual cycle, improving folliculogenesis, enhancing endometrial receptivity, and increasing clinical pregnancy and live birth rates. PRP has a wide range of applications in reproductive medicine, such as Asherman's syndrome, cases of thin endometrium, urinary incontinence, and adjunctive treatment of recurrent genitourinary fistulas. Although this would require a randomized controlled trial with a larger sample size, the small amount of information from the few studies currently published shows promise that PRP therapy, with the appropriate preparation, may in the near future be able to solve many of the challenges currently faced in obstetrics and gynecology. There are many factors in PRP applications that are not yet agreed upon. One of these is the effectiveness of serial injections. There are physicians who administer PRP injections at intervals of 2-4 weeks, as well as physicians who wait at least two months for a new injection or longer in chronic cases. The consequences of these differences in practice on the efficacy of PRP are not yet known. Other issues that have not been standardized are the buffering of PRP with the addition of bicorbanate and the addition of platelet activating agents, such as calcium chloride and thrombin to PRP for optimal release of growth factors from platelets. Other limitations include the shortcomings of existing PRP classification systems, the lack of standard protocols and definitions for centrifugation and preparation, cellular components such as platelet concentration, red and WBC counts, and the platelet activation procedure.

PRP injections are a new prospective treatment modality for chronic refractory diseases that we frequently encounter in gynecology practice and the treatment of which has failed with existing conservative methods.

The increasing popularity of PRP should not ignore the fact that there is still insufficient data concerning its use. In studies, groups are small, randomization is insufficient, and the level of evidence is low.

Larger scale, well-designed randomized controlled trials are needed to determine the efficacy of PRP in gynecological conditions.

Footnote

Author Contributions

Surgical and Medical Practices: H.G., S.H.K., Concept: H.G., S.H.K., Design: H.G., S.H.K., Data Collection and Processing: H.G., S.H.K., Analysis and Interpretation: H.G., S.H.K., Literature Search: H.G., S.H.K., Writing: H.G., S.H.K.

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