Platelet-Rich Plasma (PRP) in Obstetrics and Gynecology

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ABSTRACT

Background: Platelet-rich plasma PRP is being used as a new therapeutic option for different pathologies in the field of dermatology, such as trichology, wound healing, and cosmetic medicine. Platelet-rich plasma is an exciting new technology that may have the potential to serve as an alternative or adjuvant treatment to surgery in many common injuries/conditions in sports medicine. The growth factors provided by platelets and plasma are essential to the tissue repair process. It could have its effect due to the microenvironment of the tissue. It is used within, the tissue's specific processes for healing, or PRP's possible ability to enchange stem cell proliferation, depending on its preparation, activation, and variable contents. Accordingly, it may be effective treatment for some gynecological and obstetrical conditions. **Aim of the work:** We conducted this essay to confirm PRP efficacy and safety in varous obstetric and gynecological disorders. **Methodology:** Relevant citations were extracted from Pubmed, Google scholar, Clinical key, Scopus, Med-line, Embase and Cochrane to identify studies investigating the uses of PRP in gynecology from 2010 to 2020.

Conclusion: PRP is an innovative therapeutic modality, as it is affordable, simple, easily performed, and effective. In the field of gynecology, the risks of PRP therapy as infection, bleeding, and nerve damage, appear to be minimal.

Keywords: Platelet-Rich Plasma, Obstetrics and Gynecology.

INTRODUCTION

Platelet-rich plasma (PRP) is defined as a portion of the plasma fraction of autologous blood having a platelet concentration above baseline. Platelet-rich plasma (PRP) is becoming more popular as a nonoperative treatment option for a broad spectrum of medical disorders. It is an emerging treatment in the modern health sector known as 'orthobiologics'. The articles on PRP in the field of gynecology were mainly case series, pilot studies or case reports. PRP is currently considered a new therapeutic modality for some disorders that are refractory to conventional drugs [(1)]. The goal of this discipline is to enhance the body's innate ability to repair and regenerate. PRP therapy has lately gained a lot of attention as a safe, non-surgical, biological treatment [(2)].

PRP is widely used in orthopedic and sports medicine to relieve pain through the natural promotion of healing in musculoskeletal diseases [(3)]. Autologous PRP is derived from an individual's whole blood then centrifuged to remove red blood cells. The remaining plasma has a 5- to 10-fold higher concentration of growth factors than whole blood. These growth factors have been found to promote natural healing responses by researchers across multiple specialties, such as dentistry, dermatology, urology, and gynecology [(4)].

The theory underlying this treatment modality was derived from natural healing processes, as the body's first response to tissue injury is to deliver platelets to the injured area.

Platelets promote healing and attract stem cells to the site of the injury.

Moving from basic science to clinical practice. PRP injections have been applied to diseased ligaments, tendons, and joints, with outcomes in terms of repair [(5)]. The aim of this work was to be aware of this new line of therapy for many resistant diseases. To know the most recent update of this modality in literature. To know to what extent this modality can be practically applied in gynecology.

METHODOLOGY

Relevant citations were extracted from Pubmed, Google scholar, Clinical key, Scopus, Med-line, Embase and Cochrane to identify studies investigating the uses of PRP in gynecology from 2010 to 2020. RCTs, observational studies (cohort and case control), case series and case reports was included, also systematic reviews or comprehensive reviews was included.

Platelet physiology and function:

The main physiological role of platelets is to contribute to primary hemostasis, a defense mechanism aimed at preventing blood loss when the continuity of the vasculature is interrupted. In addition to their critical role in hemostasis, platelets may exert other functions in regulating the immune response, promoting inflammation and cancer metastasis [(6)].

- Adhesion.
- Activation.
- Secretion.
- Aggregation.

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Platelet function disorders:

Disorders of platelet function can be divided into those of congenital and those of acquired origin. Although congenital disorders are uncommon, acquired disorders are encountered frequently in clinical practice.

- Defects in platelet receptors.
- Defect in granule content/storage pool deficiency.
- Release defects.
- Abnormalities in plasma factors affecting platelet function.
- Abnormalities of platelet interaction with plasma coagulation factors by impaired platelet coagulant activity.
- Miscellaneous congenital disorders [7].

Abnormalities in platelet interaction:

Glanzmann's thrombasthenia is platelet disorder caused by an absence or decrease in platelet receptors for fibrinogen 11b-111a. The platelet count, size, shape and lifespan are normal in this disorder. Bernard-soulier syndrome is rare syndrome characterized by large platelets that may also be mildly decreased in number [8].

Defect in granule storage pool:

A small number of patients have an inheritable deficiency of platelet a-granules (a-SPD); a condition termed the gray platelet syndrome [9].

Defect in platelet release reactions:

Abnormalities of platelet release can be divided into deficiencies of one or more of the platelet granules, disorders of thromboxane A., synthesis from membrane arachidonic acid, or conditions in which altered cAMP metabolism changes the reactivity to platelet agonists. In a number of patients, a deficiency in platelet cyclo-oxygenase has been confirmed. This condition is characterized by defective platelet aggregation to collagen as well as absent second-phase aggregation to ADP and epinephrine [10].

Abnormalities of platelet interaction with plasma coagulation factors by impaired platelet coagulant activity:

Scott syndrome is perhaps the best described defect in platelet function in this category. In Scott syndrome, platelets have defective binding of factor va-x and factor v111a-1xa complexes this result in impaired activation of factor x and prothrombin, platelet dependent fibrin formation, and abnormality in platelet factor 3 activity [11].

Definition of platelet-rich plasma:

PRP is a biological product defined as a portion of the plasma fraction of autologous blood with a platelet concentration above the baseline (before centrifugation). As such, PRP contains not only a high level of platelets but also the full complement of clotting factors, the latter typically remaining at their normal, physiologic levels [12].

Biology:

Platelets were thought to have only hemostatic activity, although in recent years, scientific research and technology has provided a new perspective on platelets and their functions [13]. PRP is a natural source of signaling molecules, and upon activation of platelets in PRP, the P-granules are degranulated and release the GFs and cytokines that will modify the pericellular microenvironment [14].

PRP preparation:

The preparation of PRP is an outpatient procedure that involves a blood draw, preparation of the PRP, and the injection of PRP into the diseased area. Multiple methods have been developed for PRP preparation, with variation in the speed and timing of centrifugation. PRP is prepared either manually or by the use of automated devices, in a day care setting just prior to the procedure [15].

Manual double spin method:

Platelet-rich plasma is separated from whole blood by 'light-spin' centrifugation and subsequently the platelets are concentrated by 'heavy-spin' centrifugation with removal of the supernatant plasma. The centrifugation process separates blood components owing to their different specific gravities, i.e., RBCs being the heaviest, followed by WBCs, whereas platelets are the lightest [16].

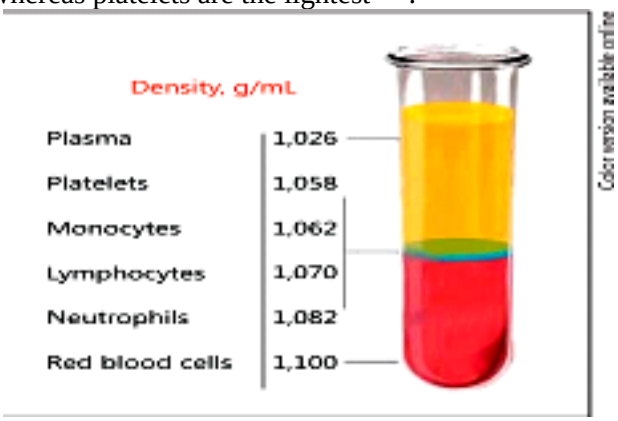

Figure (1): After centrifugation, the blood components (red blood cells, leukocytes, and platelets) are separated from the plasma due to their different densities. The platelets have the lowest density

The double spin method is preferred over the earlier prevalent single spin method, (49) as the therapeutic concentration of platelets was not achieved by the latter. PRP must be used on the treated site within 10 minutes of activation. The concentrated platelets remain viable for up to 8 hours and sterile if placed on a sterile surgical table [17].

Automated devices:

Numerous commercial devices of varying standards are available for the preparation of PRP, but their application has been confusing because each lead to a different product with potentially dissimilar biology, technique and unknown relative efficacy. Various devices have been approved by US Food and Drug Association (FDA) e.g., Smart PReP® (Harvest Technologies Inc, Plymouth, MA), PCCS® (3i Implant Innovations Inc, West Palm Beach, FL), BioMet GPSII® etc [18].

Smart PReP® (Harvest Technologies Inc)

BIOMET GPS2

SELPHYL

Regenlab

Figure (2): Devices used in preparation of PRP

The platelet-poor plasma (PPP) is removed, and PRP is obtained. Platelets can be activated before application of the PRP. Although there is no consensus on whether or not platelets must be previously activated before their application and with which agonist [19].

Types of PRP preparation:

First classification:

After centrifugation of whole blood, four types of preparations can be obtained [20].

Table (1): Platelet-containing preparations [19]

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

Second classification:

Another classification of PRP preparations was proposed by **Mishra *et al.*** [21] based on the presence or absence of white blood cells, their activation status, and platelet concentration .

Third classification:

A newer classification of PRP preparations was called the DEPA (dose of injected platelets, efficiency of production, purity of the PRP, activation of the PRP) classification. The DEPA classification is based on 4 different components [22].

Table (2): DEPA classification of PRP preparations [23]

DEPA classification	Subgroup	Description
Dose of injected platelets	Very high	>5 Billion injected platelets
	High	3–5 Billion injected platelets
	Medium	1–3 Billion injected platelets
	Low	<1 Billion injected platelets
Efficiency of production	High device efficiency	Recovery rate in platelets >90%
	Medium device efficiency	Recovery rate in platelets 70%–90%
	Low device efficiency	Recovery rate in platelets 30%–70%
	Poor device efficiency	Recovery rate in platelets <30%
Purity of the PRP	Very pure PRP	Platelets in the PRP >90%
	Pure PRP	Platelets in the PRP 70%–90%
	Heterogeneous PRP	Platelets in the PRP 30%–70%
	Whole-blood PRP	Platelets in the PRP <30%
Activation process	Autologous thrombin Calcium chloride	-

Activation procedures:

The term "activation" refers to two key processes within PRP preparations that may be initiated: (1) Degranulation of platelets to release α-granules containing growth factors. (2) Fibrinogen cleavage to initiate matrix formation [24]. Accordingly, rapid platelet activation can be achieved by addition of calcium chloride and thrombin, freeze/thaw cycles and direct exposure to collagen in vivo [24].

Platelet-rich plasma products:

Several key biological mediators are present in a PRP. The more studied growth factors contained in platelet-rich plasma that are important during tissue repair include IGF-I (Insulin-like Growth Factor type I), TGF-β1 (Transforming Growth Factor β type 1), PDGF (Platelet Derived Growth Factor), HGF (Hepatocyte Growth Factor), VEGF (Vascular Endothelial Growth Factor), EGF (Epithelial Growth

Factor) and bFGF (basic Fibroblastic Growth Factor) [25].

Table (3): Growth factors in platelet-rich plasma [25]

Growth factor	Function
Transforming growth factor-β (TGF-β)	Stimulates undifferentiated mesenchymal cell proliferation
	Regulates endothelial, fibroblastic, and osteoblastic mitogenesis
	Regulates collagen synthesis and collagenase secretion
	Regulates mitogenic effects of other growth factors
	Stimulates endothelial chemotaxis and angiogenesis
	Inhibits macrophage and lymphocyte proliferation
Fibroblast growth factor (FGF)	Promotes growth and differentiation of chondrocytes and osteoblasts
	Mitogenetic for mesenchymal cells, chondrocytes, and osteoblasts
Platelet-derived growth factor a and b (PDGF)	Mitogenetic for mesenchymal cells and osteoblasts
	Stimulates chemotaxis and mitogenesis in fibroblast, glial, or smooth muscle cells
	Regulates collagenase secretion and collagen synthesis
	Stimulates macrophage and neutrophil chemotaxis
Epidermal growth factor (EGF)	Stimulates endothelial chemotaxis or angiogenesis
	Regulates collagenase secretion
	Stimulates epithelial or mesenchymal mitogenesis
Vascular endothelial growth factor (VEGF)	Increases angiogenesis and vessel permeability
	Stimulates mitogenesis for endothelial cells
Connective tissue growth factor (CTGF)	Promotes angiogenesis
	Cartilage regeneration
	Fibrosis and platelet adhesion
Insulin like growth factor (ILGF 1 and 2)	Chemotactic for fibroblasts and stimulates protein synthesis
	Enhances bone formation
Platelet factor 4 (PF-4)	Stimulate the initial influx of neutrophils into wounds
	Chemo-attractant for fibroblasts
Interleukin 8 (IL-8)	Pro-inflammatory mediator
	Recruitment of inflammatory cells
Keratinocyte growth factor (KGF)	Promote endothelial cell growth, migration, adhesion and survival
	Angiogenesis

Mechanisms of action of PRP:

A. PRP as a hemostat:

Through thrombin and fibrin generation, PRP gels are significant in hemostasis and have been applied during surgery across various medical areas to prevent blood loss and allogeneic blood transfusions [26].

B. Clinical implications of PRP role in inflammation:

A molecular process that works well in inflammation is destined to be aligned with desired outcomes in pain. The analgesic properties of PRP therapies have been assessed not only after surgical trauma but also in chronic painful conditions, mainly in cardiology, plastic and reconstructive surgery, dermatology, orthopedics and ophthalmology [27].

C. Neovascularization Injury, pathology and angiogenesis:

Vascular damage is an expected effect of injury and inflammation. Moreover, angiogenic deficits associated with lack of or excess promoters/inhibitors have been reported in several clinical conditions. Pathologic angiogenesis is often related to chronic inflammation. Angiogenesis involves two consecutive biological stages, induction and resolution. The first is regulated by the presence of VEGF, TGF - b1, bFGF, PDGF and EGF (secreted from PRP or produced by stromal cells), inducing activation and migration of

endothelial cells [27]. The notion that PRP regulates angiogenesis is attributed largely to the observation that platelet activation results in the release of proangiogenic proteins such as VEGF, HGF, TGF - b1, platelet-derived growth factors (PDGF-A, -B or -C) and other soluble cytokines (namely, chemokines IL-8, angiopoietin and CXCL12) and metalloproteases MMP-1, -2 and -9 [28]. Overall, proangiogenic molecules influence the migration and proliferation of vascular cells, and vessel organization and stabilization. By contrast, PRPs provide a range of inhibitors, including endostatin, fibronectin, PF4, TSP-1, a2-macroglobulin, PAI-1 and angiostatin, as well as the tissue inhibitors of metalloproteases (TIMP-1–4) [29].

Indications of PRP in various gynecological disorders:

1) PRP in skin lesions and wound healing: Due to the ability of PRP to promote angiogenesis and wound healing, it is widely used in dermatology for purposes including the treatment of ulcers, scars, and alopecia [30].

2) PRP in cervical ectopy:

Autologous PRP application appeared promising for the treatment of cervical ectopy in symptomatic women, as it yielded a shorter tissue healing time and milder adverse effects than laser treatment [31].

3) PRP in vulvar dystrophy: PRP has been tried in many dermatological and autoimmune conditions nonresponsive to corticosteroids, such as lichen sclerosus (LS) and eczema. LS affect the vulva and causes extensive scarring, with progressive loss of the labia minora, sealing of the clitoral hood, and burying of the clitoris. LS also cause progressive pruritus, dyspareunia, and genital bleeding. It has a considerable impact on the quality of life of affected patients by disturbing physical activity, sexual pleasure, and causing emotional and psychological problems [32].

4) PRP in reconstructive surgery for vulvar cancer: Platelet gel application before vulvar reconstruction represented an effective strategy for preventing wound breakdown after surgery to treat locally advanced vulvar cancer [33].

5) Role of PRP in cancer treatment: Platelets have been assumed to have decisive function in cancer metastasis. PRP administration is a promising approach to enable tissue repair, since it has cytokines and growth factors capable of enabling stem cell proliferation and differentiation. PRP use for tissue regeneration purposes may also impair tumor growth [33].

6) PRP in urogenital disorders:

Small fistulae could be treated conservatively with various therapies, including PRP, with success rates ranging from 67% to 100%. 104 PRP has been tried in the treatment of vesicovaginal fistulae as a novel and minimally invasive approach for the closure of genital fistulae. PRP injection was moderately successful in Crohn disease fistulae, with a success rate of 70%, and suggested that further studies were needed. Both absorbable and nonabsorbable vaginal implants used in pelvic floor reconstructive procedures have numerous serious adverse effects. PRF is a mixture of platelets, leukocytes, cytokines, and circulating stem cells that is optimal for stimulating fibroblast migration and proliferation. This mixture causes rapid remodeling and connective tissue growth after vaginal surgery [34].

Side effects and possible complications:

There is no chance of having an allergy or immune reaction. Side effects or complications of PRP injection are extremely rare. The main risks include local infection (< 1% chance) and pain at the site of injection. Patients tend to experience 2 or 3 days of mild bruising, edema, erythema and may feel pruritic for short while. The risks of PRP therapy as infection, bleeding and nerve damage appear to be minimal [35].

Conclusion:

PRP is an innovative therapeutic modality, as it is affordable, simple, easily performed, and effective. It is also a noninvasive modality with promising results and no side effects. The risks of PRP therapy as infection, bleeding, and nerve damage, appear to be minimal.

References:

1. **Dhurat R, Sukesh M (2014):** Principles and methods of preparation of platelet-rich plasma: A review and author's perspective. J Cutan Aesthet Surg., 7: 189-97.
2. **Wasterlain A, Braun H, Dragoo J (2016):** Contents and formulations of platelet rich plasma. Platelet Rich Plasma in Musculoskeletal Practice. https://www.researchgate.net/publication/307523183_Contents_and_Formulations_of_Platelet_Rich_Plasma
3. **Dhillon R, Schwarz E, Maloney M (2012):** Platelet-rich plasma therapy-future or trend? Arthritis Res Ther., 14 (4): 219.
4. **Lai L, Stitik T, Foye P *et al.* (2015):** Use of platelet-rich plasma in intra-articular knee injections for osteoarthritis: a systematic review. PMR., 7 (6): 637-48.
5. **Wang S, Chang Q, Lu J *et al.* (2015):** Growth factors and platelet-rich plasma: promising biological strategies for early intervertebral disc degeneration. Int Orthop., 39 (5): 927–934.
6. **Yu W, Wang J, Yin J (2011):** Platelet-rich plasma: a promising product for treatment of peripheral nerve regeneration after nerve injury. The International Journal of Neuroscience, 121 (4): 176-80.
7. **Caen J, Castaldi P, Leclerc J *et al.* (1966):** Congenital bleeding time and normal platelet count-I. Glanzmann's thrombasthenia (report of 15 patients). Am J Med., 7: 15-22.
8. **Weiss H (1980):** Congenital disorders of platelet function. Sem Hematol., 17: 228-241.
9. **Raccuglia G (1971):** Gray platelet syndrome: a variety of qualitative platelet disorders. Am J Med., 51: 818–28.

10. **Malmsen C, Hamberg M, Svensson J *et al.* (1975):** Physiological role of an endoperoxide in human platelets: Hemostatic defect due to platelet cyclooxygenase deficiency. Proc Natl Acad Sci USA., 72 (4): 1446–1450.
11. **Harker L, Slichter S (1972):** The bleeding time as a screening test for evaluation of platelet function. N Engl J Med., 287: 155–158.
12. **Andia I, Rubio-Azpeitia E, Martin J *et al.* (2015):** Current concepts and translational uses of platelet rich plasma biotechnology. https://www.intechopen.com/books/biotechnology/current-concepts-and-translational-uses-of-platelet-rich-plasma-biotechnology
13. **Girao L (2016):** PRP and other applications in dermatology; in Alves R, Grimalt R (eds): Clinical Indications and Treatment Protocols with Platelet-Rich Plasma in Dermatology. Barcelona, Ediciones Mayo, Pp: 73-78.
14. **Alves R, Grimalt R (2018):** A review of platelet-rich plasma: history, biology, mechanism of action, and classification. Skin Appendage Disord., 4: 18-24.
15. **Dawood A, Salem H (2018):** Current clinical applications of platelet-rich plasma in various gynecological disorders: An appraisal of theory and practice. Clin Exp Reprod Med., 45 (2): 67–74.
16. **Kumaran MS.** Platelet-rich plasma in dermatology: Boon or a bane? Indian J Dermatol Venereol Leprol., 1: 5-14.
17. **Dohan Ehrenfest D, Bielecki T, Mishra A *et al.* (2012):** 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., 7: 1131-7.
18. **Magalon J (2016):** Medical devices for the production of PRP: main aspects to be considered; in Alves R, Grimalt R (eds): Clinical Indications and Treatment Protocols with Platelet-Rich Plasma in Dermatology. Barcelona, Ediciones Mayo, Pp: 17-28.
19. **Magalon J, Chateau A, Bertrand B *et al.* (2016):** DEPA classification: a proposal for standardising PRP use and a retrospective application of available devices. BMJ Open Sport Exerc Med., 2: 60-6.
20. **Du Cros D (1993):** Fibroblast growth factor and epidermal growth factor in hair development. J Invest Dermatol., 101: 106S-113S.
21. **Takabayashi Y, Nambu M, Ishihara M *et al.* (2016):** Enhanced effect of fibroblast growth factor-2-containing dalteparin/protamine nanoparticles on hair growth. Clin Cosmet Investig Dermatol., 9: 127-134.
22. **Mishra A, Harmon K, Woodall J *et al.* (201):** Sports medicine applications of platelet rich plasma. Curr Pharm Biotechnol., 13: 1185-1195.
23. **Yakar S, Courtland H, Clemmons D(2010):** IGF-1 and bone: new discoveries from mouse models. Journal of Bone and Mineral Research, 15: 32-36.
24. **Mamer S, Chen S, Weddell J *et al.* (2017):** Discovery of high-affinity PDGF-VEGFR interactions: redefining RTK dynamics. Scientific Reports, 6: 17-22.
25. **Everts P, Hoogbergen M, Weber T *et al.* (2012):** Is the use of autologous platelet-rich plasma gels in gynecologic, cardiac, and general, reconstructive surgery beneficial? Curr Pharm Biotechnol., 8: 22-26.
26. **Tehranian A, Esfehani-Mehr B, Pirjani R *et al.* (2016):** Application of autologous platelet-rich plasma (PRP) on wound healing after caesarean section in high-risk patients. Iran Red Crescent Med J., 6: 17-22.
27. **Fanning J, Murrain L, Flora R *et al.* (2007):** Phase I/II prospective trial of autologous platelet tissue graft in gynecologic surgery. J Minim Invasive Gynecol., 5: 132-136.
28. **Hua X, Zeng Y, Zhang R *et al.* (2012):** Using plateletrich plasma for the treatment of symptomatic cervical ectopy. Int J Gynaecol Obstet., 3: 47-52.
29. **Wang Y, Zhang H (2008):** Platelet-induced inhibition of tumor cell growth. Thromb. Res., 123: 324–330.
30. **Andrade S, Sumikawa J, Castro E *et al.* (2017):** Interface between breast cancer cells and the tumor microenvironment using platelet-rich plasma to promote tumor angiogenesis: Influence of platelets and fibrin bundles on the behavior of breast tumor cells. Oncotarget, 8: 7-12.
31. **Peterson J, Zurakowski D, Italiano J *et al.* (2010):** Normal ranges of angiogenesis regulatory proteins in human platelets. Am. J. Hematol., 85: 56-60.
32. **Mongardini M, Iachetta R, Cola A *et al.* (2009):** Low rectovaginal fistula treated with platelet-rich plasma (PRP). G Chir., 30 (11-12): 507-9.
33. **Medel S, Alarab M, Kufaishi H *et al.* (2015):** Attachment of primary vaginal fibroblasts to absorbable and nonabsorbable implant materials coated with platelet-rich plasma: potential application in pelvic organ prolapse surgery. Female Pelvic Med Reconstr Surg., 23: 978–992.
34. **Pantos K, Nitsos N, Kokkali G *et al.* (2015):** Ovarian rejuvenation and folliculogenesis reactivation in peri-menopausal women after autologous plateletrich plasma treatment. Proceedings of the 32nd Annual Meeting of ESHRE; Helsinki, Finland. www.medicopublication.com › ijphrd › article › download
35. **Lewi L, Liekens D, Heyns L *et al.* (2009):** In vitro evaluation of the ability of platelet-rich plasma to seal an iatrogenic fetal membrane defect. Prenat Diagn., 29 (6): 620-5.