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The current use of the regenerative properties of platelet-rich-plasma in different medical conditions with particular emphasis on gynecology and obstetrics

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Abstract

Platelet-rich-plasma (PRP) is a concentrate of plasma containing high levels of platelets and different growth factors, involved in various cellular and regenerative processes, i.a. wound healing and tissue regeneration. Currently, due to its regenerative properties, PRP is widely used in different medical conditions. This paper summarizes knowledge about types of PRP, its preparation and current possibilities of PRP treatment in many fields of medicine with a particular emphasis on gynecology and obstetrics.

Key words: *platelet-rich-plasma, gynecology, obstetrics*

Introduction

Platelet-rich plasma (PRP) is a platelet concentrate found in a small amount of plasma. In addition to platelets, it is also rich in growth factors, chemokines, and cytokines. PRP is obtained by centrifugation of blood drawn from the patient. Platelets are small (~1-3 μm), elongated and nucleated cytoplasmic shreds formed in the bone marrow by the fragmentation of megakaryocytes. The average platelet count ranges from 1.5 to 3.0 × 10-5 / ml of circulating blood, and the half-life of platelets in vivo is about 7 days. They release more than 800 different proteins into the surrounding environment, exerting paracrine effects on tendon cells, mesenchymal stem cells, chondrocytes, osteoblasts, fibroblasts, and endothelial cells [1].

In addition to participating in hemostasis, platelets are also involved in the regeneration of damaged tissues. When damage occurs, a number of chemokines and cytokines are released into the bloodstream to convey information about the state of the damaged tissue and to activate different cells: monocytes, neutrophil granulocytes, fibroblasts, and platelets. Activated thrombocytes (platelets) release cellular granules from their interior, containing growth factors and clotting factors. The coagulation cascade is activated and the healing process begins. The main growth factors involved in the aforementioned process are: transforming growth factor β (TGF-ß),

platelet-derived growth factor (PDGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF). In addition, interleukin 8, keratinocyte growth factor (KGF), insulin-like growth factors 1 and 2 (IGF-1 and IGF-2), and connective tissue growth factor (CTGF) are also released from alpha granules. Growth factors and chemokines are proteins whose function is to stimulate repair and regenerative processes. They induce DNA synthesis, stimulate fibroblasts to produce collagen and synthesize the intercellular matrix, affect cell proliferation and migration to the site of injury and the formation of new blood vessels [2, 3]. In addition, they regulate collagenase secretion and are responsible for the differentiation and growth of keratinocytes. In vitro studies show an increase in proteoglycan and collagen synthesis after administration of PRP compared to platelet-poor plasma. Dense granules (corpuscles) δ, containing high levels of histamine, adenosine, serotonin, dopamine, and calcium, which modulate inflammatory processes, are also important in the regeneration process [3, 4]. There are also reports confirming that platelets release antimicrobial peptides, suggesting an antibiotic effect of PRP [5].

This paper is a narrative review of the current literature on the use of PRP in different medical conditions with a particular emphasis on gynecology and obstetrics. A review was conducted by searching through PubMed, Cochrane, and Web of Science databases. Search terms included: platelet-rich plasma, PRP, gynecology, obstetrics, aesthetic medicine, and wound healing with different combinations in order to find as many recently published articles as possible.

Wound healing and different types of PRP

Wound healing can be divided into three general phases: exudative, proliferative, and remodeling. The initial exudative phase is characterized by a local inflammatory response and hemostasis in which thrombocytes form a clot while releasing growth factors that chemotactically attract neutrophils and macrophages to the area of injury. The proliferative phase involves actual tissue regeneration and involves granulation, myofibroblast contraction,

epithelialization, and angiogenesis. Finally, the remodeling phase is associated with the synthesis of collagen and scar tissue. The above-mentioned processes are directly regulated by cytokines and growth factors, high concentrations of which can be found in PRP [6].

There are four main types of PRP based on leukocyte and fibrin content: leukocyte-rich PRP (L-PRP), pure or leukocyte-reduced PRP (P-PRP), leukocyte-rich PRP with high fibrin content and pure PRP with high fibrin content [7].

The aforementioned fibrin is formed from fibrinogen under the influence of thrombin, then it polymerizes into long insoluble fibrils, forming a platelet--fibrin clot together with blood morphotic elements. It is essential for proper wound healing, thus high concentrations of fibrin can increase the effectiveness of PRP therapy [7].

On the other hand, leukocytes present in L-PRP prevent different infections, e.g., E. coli and methicillin-resistant Staphylococcus aureus. Moreover, they support tissue regeneration, where each type of leukocyte has a different function in this process [8]. Neutrophils are involved in the inflammatory phase of wound healing. Monocytes and macrophages, on the other hand, facilitate tissue repair by purifying and phagocytosing fragments of damaged tissue. Similar to thrombocytes, macrophages release key growth factors in tissue repair. They support tissue regeneration to such an extent that in the case of thrombocytopenia in mice, they are able to almost completely compensate for the release of VEGF, FGF-2, TGF 1, KGF, and EGF, allowing for efficient reepithelialization, collagen synthesis, and angiogenesis [9]. Although leukocytes can potentially prevent bacterial infections and accelerate wound healing, they also have pro-inflammatory and immunostimulatory properties that could lead to local tissue damage, thus counteracting the positive effects of PRP therapy. To prevent this, the leukocyte concentration of PRP should be kept low enough [10]. Moreover, according to the study by Akhundov et al., reducing leukocyte concentrations in PRP may be more important than maximizing thrombocyte concentrations in terms of the efficacy of PRP therapy [11].

The PRP preparation techniques

Various techniques for preparing PRP can be found in the literature. The final product of each method differs in bioactivity and in consequence also in the possible application into the clinical practice. However, most of the described methods of PRP preparation involve similar procedures, such as blood collection in the presence of an anticoagulant and immediate centrifugation [12]. A brief centrifugation at medium speed is designed to separate the blood into three layers: a supernatant corresponding to cell-free plasma, an intermediate "leukocyte-platelet sheepskin" containing leukocytes and concentrated platelets, and a final, lower sediment rich in red blood cells. The first centrifugation may be followed by a second, faster and longer centrifugation to further isolate the "leukocyte-platelet bed." Finally, an activating agent, such as thrombin, may be added to the preparation when it is administered into the surgical treatment site or wound to stimulate platelet degranulation and exocytosis of factors stored in the cytoplasmic granules [12].

It is possible to observe individual variability in the total number of thrombocytes in each patient. The overall goal of PRP preparation is to achieve a high platelet density index. Methods that allow a sevenfold concentration of thrombocytes are commonly used [13].

The simpler method of preparing PRP described in the literature eliminates the need for both an anticoagulant and an activating agent used to activate platelets. In this case, a clot of leukocytes and platelet-rich fibrin (L-PRF) should be collected after one step centrifugation and applied directly into the wound. In this method, platelets can be activated by mechanical stresses during centrifugation [14].

Determination of platelet concentration in the final material can be done with a hemocytometer or hematology analyzer. Most hematological analyzers use the impedance method with hydrodynamic focusing to count the platelets. In this method there is a risk of classifying some thrombocytes as erythrocytes and vice versa, since they are differentiated between each other only on the basis of different volume. This can result in misrepresentation of the results.

However, there are commercially available analyzers that can assess platelet count using an optical method, based on the fluorescent staining of thrombocyte RNA. This way, the platelet number is not falsely elevated or reduced, allowing for more reliable results [13, 14].

The use of PRP in different medical conditions

PRP was first extracted in the 1970s and used in 1987 during cardiac surgery [12]. Therapy with PRP gained popularity in the mid-1990s. Attempts have been made to implement PRP in many fields of medicine, including cardiac surgery, plastic surgery, dentistry, sports medicine, and pain management. Therefore, nowadays, PRP is widely used in the treatment of many conditions, including plastic surgery, orthopedics, periodontics, dermatology, aesthetic medicine, gynecology, aesthetic, and reconstructive surgery. It can be used for maintaining hemostasis during surgery and surgical wound closure, as well as in the treatment of chronic wounds – chronic ulcers in patients with diabetic foot syndrome or vascular type of chronic lower leg ulcers [3, 8, 15–17]. The usefulness of PRP in stimulating wound healing is particularly relevant to ligaments, tendons, and cartilage, whose repair processes are extremely slow due to limited blood supply and slow cell renewal [18, 19].

In cardiac surgery, PRP has been shown to be an effective support in intraoperative autologous transfusion [20].

In dentistry, PRP can be used to accelerate the formation of bone fusion in bone grafts, in the treatment of tendonitis and after reconstructive ligament surgery. Anitua showed that the use of PRP in alveolus after extracted teeth helps in bone regeneration [21]. In reconstructive maxillofacial surgery, on the other hand, Marx et al. evaluated the effect of PRP on the maturation rate and density of bone after transplantation, showing that the addition of PRP to grafts results in increased bone formation [22]. PRP, as a biological surgical additive, is successfully used in many procedures in regenerative dentistry. However, some applications of PRP in this field remain controversial, as there is a lack of studies determining its exact therapeutic effect [23].

Currently, PRP therapy has become notably attractive in sports medicine and musculoskeletal disorders due to its beneficial effects on tissue regeneration, enabling significantly quicker return to the active live, especially in professional athletes [24]. The number of scientific publications on the use of PRP in this field has grown significantly and many clinical trials confirmed both its efficacy and safety [2]. The effectiveness of PRP has been reported for the healing process of muscle injuries. Muscle tissue recovery includes a number of complex and long-term processes characterized by various overlapping phases, leading finally to the restoration of continuity and anatomical function of the muscle. This process is modulated by various growth factors that are present in PRP, which is the basis for its therapeutic use. There are many experimental and clinical studies that show the positive role of PRP in the healing process of muscle injuries. Moreover, Borrione et al. concluded that PRP injection is able to reduce the pain intensity and discomfort caused by muscle injury, as well as to significantly decrease the time required for full recovery [25].

There are available reports suggesting the potential use of PRP in transplantation medicine. Using a canine, Gimbrone et al. demonstrated that in vitro perfusion of the thyroid gland and kidney with PRP provides improved vascular preservation and tissue survival. According to the authors, thrombocytes "appear to somehow 'nurture' the microcirculation" and these attributes had far-reaching effects in both short- and long-term organ preservation [26].

PRP can be considered an autologous source for tissue engineering applications [16]. The use of PRP as a scaffold for intracerebral delivery of bone marrow stem cells resulted in significant neurological improvement in experimental animals with induced intracerebral hemorrhage. In addition, post-mortem histological analysis showed that animals that received PRP scaffolds had stem cells integrated into damaged tissues and exhibited endogenous neurogenesis, measured by the expression of specific glial proteins and neuronal nuclei [27].

Another potential field for the use of PRP is dermatology. By stimulating angiogenesis, collagen synthesis and adipogenesis, PRP may be particularly useful for hair restoration and skin rejuvenation. Applications in aesthetic

medicine and dermatology include the treatment of acne scars and alopecia. Repeated microinjections, due to penetration into the deep layers of the skin, also allow for effective smoothing of wrinkles. They can be used in combination therapy or as an alternative to fillers [28]. The use of PRP in combination with other treatments, such as lasers or dermal fillers, results in significant improvements in skin appearance, pigmentation, and texture. The use of PRP is currently recommended in combined treatment with other modalities and further studies are needed to confirm its efficacy in skin diseases [29]. Noteworthy, PRP, due to its autologous origin, can be administered to patients with allergies to other types of fillers.

The use of PRP in gynecology and obstetrics

The PRP activity enabling skin and mucosal revitalization can be implemented in aesthetic gynecology patients. The goal of the therapy may be to rejuvenate the skin of the intimate area: smoothing and unifying the skin tone, improving skin elasticity and density, or remodeling scars. It is also possible to inject PRP into the vaginal mucosa to accelerate its regeneration, increase tension and elasticity. By reconstructing the vaginal epithelium, it is possible to reduce the incidence of inflammation and improve the comfort of patients with vaginal dryness [30]. Clinical reports indicate that this method is also effective in patients with premenopausal symptoms, such as chronic itching and vaginal dryness. In the absence of effective treatment with estrogens, emollients, and testosterone gels, attempts have been made to administer PRP to the affected areas (mainly the vaginal vestibule area). Improvements in perceived symptoms and satisfaction with sexual life were reported in female patients two months after the treatment. The treatment showed satisfactory results in terms of both pain and comfort in sexual life [31, 32]. Runels et al. also investigated the efficacy of PRP in the treatment of sexual dysfunction in women. The majority of patients showed significant improvements in the perception of sexual arousal, vaginal lubrication, and orgasm. PRP is also used in filling the labia majora. These procedures are performed to improve the quality of life of patients who do not accept the appearance of their external genitalia

or experience discomfort during intercourse. The presence of this type of disorder is associated with reduced sexual function and a negative impact on the psycho-emotional condition of patients. Positive results have stimulated researchers both gynecologists and sexologists, to further investigate this issue [33].

The proven effect of PRP in the treatment of chronic ulcers and the pathophysiological basis for the role of platelets and platelet-derived growth factors in the healing process have encouraged the use of PRP for the treatment of high-risk surgical wounds. Attempts have been made to use PRP to stimulate the healing process in the treatment of scars after a cesarean section (CS), perineal incision, or plastic gynecology procedures [34]. Impaired wound healing after cesarean sections is still an on-going problem, especially in the face of rising incidence of obesity, often leading to postpartum morbidity. In a randomized controlled study, Tehranian et al. showed a statistically significant reduction in swelling around the wound after a cesarean section and also a reduction in the level of pain on the VAS scale, starting on the fifth day after surgery, with a stable trend at the end of the eighth week in the group where PRP was applied [35]. In a study published recently by our group, PRP application during a CS significantly improved wound healing in both short- and long-term assessment. Although it did not influence postoperative pain intensity, it reduced the use of analgesics after surgery [36]. The finding of reduced nociception due to the use of PRP is a relatively new scientific report, and needs to be confirmed by further clinical follow-up. The first scientific results in this field, as well as the own experience of many centers, are promising; further randomized studies are needed for objective evaluation of the method. Another target group for potential use of PRP in wound healing in gynecology are patients with gynecological malignancies, especially undergoing treatment by laparotomy, because they are at high risk of postoperative wound dehiscence. PRP application during abdominal closure in gynecological cancer patients may improve wound healing, as well as reduce pain and the use of analgesics in the early postoperative period [37].

Recent reports of the potential application of PRP in autoimmune skin diseases have led to the research on the use of this therapy in the treatment

of lichen sclerosus and atrophic vulva. In lichen sclerosus, as a result of chronic inflammation during the progression of the disease, patients may develop multiple skin lesions, such as erosions, atrophic changes, scarring, formation of skin fistulas, obliteration of the vaginal vestibule, atrophy of the labia minora and complete covering of the glans clitoris by the affected skin of its prepuce – which often requires surgical interventions. Current recommendations for the treatment of lichen sclerosus include the use of topical corticosteroids for many months or even years, but its effectiveness for most patients is insufficient. In the case of the failure of corticosteroids therapy, supporting treatment such as calcipotriol, retinoids, tacrolimus, pimecrolimus, and photodynamic therapy are used. Since the majority of lichen sclerosus patients are postmenopausal, experiencing urogenital atrophy, chronic use of strong steroids has its limitations due to the possibility of increasing atrophy symptoms [38]. A new therapeutic option, that has emerged for the treatment of lichen sclerosus, is PRP. In a study by Behnia-Willison et al., 82% of symptomatic patients were able to achieve regeneration of the skin of the urogenital area with PRP and no further treatment with topical corticosteroids was needed. 28 patients with a diagnosis of steroid-resistant lichen sclerosus were treated with PRP. Patients received three PRP applications at 4 to 6 week intervals. In a 2-year follow-up, researchers showed complete remission of symptoms in 15 patients and improvement in 13 patients. The use of autologous adipose tissue transfer in combination with PRP (which prolongs the survival of fat cells and significantly prolongs the lipofilling effect) in lichen sclerosus patients, has contributed to a such spectacular therapeutical success [39]. In 2015, Boero et al. showed very promising results from the use of autologous fat grafts in combination with PRP in patients with lichen sclerosus who were resistant to traditional therapies [40]. Randomized studies with a greater number of patients are needed to objectively evaluate the clinical value of this new method.

As mentioned above, the use of PRP may improve the survival of autologous fat grafts. One of the most important factors affecting transplanted adipocytes (and stimulation of mesenchymal stem cells within the adipose tissue) is adding platelet-derived growth factors prior to transplantation [41]. After the harvested material is washed out, PRP is added to the graft at a rate

of about 5–10% for small-volume grafts and 10–20% for larger-volume grafts [42]. As platelet concentrations increase, we also have an increased concentration of seven essential proteins that are released from platelet granules to initiate the healing process [43]. These growth factors include three isomers of PDGF (PDGF-AA, PDGF-AB, and PDGF-BB), two types of TGFβ (TGFβ1 and TGFβ2), VEGF and EGF. These factors synchronize epithelialization, angiogenesis, and collagen matrix formation, which are fundamental steps in the healing process. In this case, the addition of PRP has also an anti-inflammatory effect. Based on clinical observations, the addition of PRP has been found to increase the rate of revascularization and the survival of transplanted cells. The addition of PRP is also associated with other beneficial effects, including, inter alia, reduced incidence of calcification and fat necrosis. The above observations were confirmed using radiological and ultrasound studies [41–43]. The potential improvement in the viability of the transplanted fat and the clinical outcome of the procedure, for both small and large graft volumes, indicates an important role for PRP in autologous fat grafting.

PRP is used to combine with fat tissue not only as a volumetric therapy, but also for dyspareunia and vulvodynia. Symptoms in female patients include cracking, itching, and bleeding from vaginal vestibule, together with the lack of response to topical estrogen therapy and/or laser therapy. In these cases, attempts to apply autologous fat tissue and PRP are being made [32, 34]. Noteworthy, in some postmenopausal patients with urogenital atrophy, hormonal treatment is contraindicated due to, e.g., breast or other hormonal sensitive cancer treatment. In this group of patients, PRP together with hyaluronic acid may be particularly useful, leading to a reduction in vaginal dryness and improvement in sexual function [32, 34, 44]. The results of such treatment are promising, but prospective randomized studies are needed to fully evaluate this method.

Good experiences with PRP injections in tendons and ligaments in orthopedics and plastic surgery, encouraged researchers to consider an attempt to treat uterine and vaginal prolapse by using PRP applications into the uterine ligaments and pelvic floor tissues. Injection of autologous adhesion factor into the ligaments could result in improvement in vaginal or uterine prolapse,

by stimulating the ligaments and restoring normal anatomy, with minimal, if any, complications. For patients with comorbidities, the initial approach of minimally invasive treatment before surgery seems to be the most beneficial [32, 34, 45]. Additionally, the effectiveness of using PRP-coated implants in reconstructive surgery for genital prolapse has been tested and the potential benefit of this type of therapy has been confirmed [46]. There are also hypotheses about the possible use of the PRP injections into the pubocervical ligament in the treatment of stress urinary incontinence. This would be a clinically important alternative for patients with contraindications to classical surgical methods of stress urinary incontinence. The use of PRP therapy carries significantly fewer complications compared to conventional surgical methods [47, 48].

A relatively new approach in the treatment of thin endometrium is the intrauterine injection of PRP. Endometrial thickness is an indicator for endometrial receptivity as well as a prognostic marker for pregnancy outcome following embryo transfer. It is reported that the minimum thickness of the endometrium for frozen embryo transfer (FET) is 7-8 mm, because beneath that value, pregnancy outcomes are significantly worse [49]. A thin endometrium is not optimal for embryo implantation and is associated with poor pregnancy outcomes, increase in recurrent pregnancy loss and in embryo transfer failure [50]. The management of thin endometrium still remains a challenge, and the use of PRP is one of the possibilities. One of the first studies in the field, performed by Zadehmodarres et al., was designed to determine the effectiveness of PRP in reconstructing and stimulating the endometrium to grow naturally in patients with a history of failed FET cycles due to thin endometrium. No abnormalities were detected in the uterine cavity prior to the cycle. Four of the ten patients underwent hysteroscopy due to Asherman syndrome and/or myomas. All participants were given PRP because of insufficient endometrial growth. Endometrial thickness increased 48 hours after PRP administration and reached more than 7 mm in all patients. Five patients were pregnant and in four of them the pregnancy continued with giving birth [51]. Eftekhar et al. conducted the first randomized controlled trial with 66 eligible participants with thin endometrium

despite estradiol therapy and revealed a rise of the endometrial thickness, as well as lower cycle cancelation rate and higher pregnancy rate among women who received PRP intrauterine infusion; however, this difference was not statistically significant [52]. Further studies also showed promising results; however, additional research needs to be done using larger-scale randomized controlled trials with larger sample sizes to demonstrate the utility of autologous PRP in clinical practice.

In the scientific literature of recent years, there have been reports of attempts to use PRP in patients with Asherman syndrome. In two patients with the diagnosed syndrome unsuccessfully trying to get pregnant, PRP was injected intrauterine via hysteroscopy and simultaneously oral treatment with 4 mg estradiol was applied. Endometrial rebuilding occurred in both of them. The patients were then prepared for in vitro fertilization (IVF). Both became pregnant (including one spontaneously) and gave birth to healthy children [53].

Recurrent implantation failure (RIF) is another condition, where PRP application may find its place. The first case of using PRP in a woman with primary infertility and two failed IVF cycles was published in 2017. After the diagnosis of RIF, it was decided to treat the patient with PRP to improve endometrial receptivity. Intrauterine injection of autologous PRP was performed 24 hours before the embryo transfer. As a result, the patient gave birth to a healthy boy weighing 2350 g after a cesarean section [54]. Other studies compared efficacy of PRP and granulocyte-colony stimulating factor (GCSF) on the pregnancy outcome in patients who suffered from RIF and demonstrated that, although implantation rates were similar for both therapies, the clinical pregnancy rates were significantly higher in the PRP group [55].

Intraovarian PRP therapy, where PRP is injected under ultrasound guidance into the ovarian cortex, is a novel alternative therapy for women with diminished ovarian reserve (DOR). An increasing number of studies suggest that PRP has the potential to improve folliculogenesis and thus increasing pregnancy and live birth rates. However, to date, the only two randomized controlled trials did not show an improvement in assisted reproduction techniques outcomes [50].

Summary

In recent years, the use of PRP in different medical conditions has gained a lot of attention. The main advantage of using PRP is the autologous nature of its preparation, providing no risk of immune reactions and transmission of microorganisms from other donors. This is important especially for patients with atopic skin or autoimmune disorders. Moreover, PRP preparation is simple and fast (about 30 min from blood withdrawal to its application) and the cost of preparation is quite low.

The results of available studies concerning the use of PRP application in different medical fields are promising, but there is a need for large prospective randomized trials that will be able to confirm the effectiveness of PRP therapies.

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