

The Application of Platelet Rich Plasma in Gynecology

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Regenerative medicine combines elements of tissue engineering and molecular biology aiming to support the regeneration and repair processes of damaged tissues, cells and organs. The most commonly used preparation in regenerative medicine is platelet rich plasma (PRP) containing numerous growth factors present in platelet granularities. This therapy is increasingly used in various fields of medicine.

Keywords: platelet rich plasma ; platelet rich fibrin ; premature ovarian failure ; urogynecology

1. Endometrium

Endometrium status is one of the main factors of pregnancy implantation failure. In women with a thin endometrium, PRP was used as an intrauterine infusion in order to induce endometrial growth and increase clinical rates of pregnancies ^{[1][2]} ^[3]. This was described in several cases. Molina et al., for example, characterized 19 patients who had undergone in vitro fertilization, aged between 33 and 45 years, with refractory endometrium, to whom PRP was infused with a catheter into the uterine cavity. In the case histories, PRP was used twice, after the 10th day of the hormone replacement therapy, and then 72 h after the first administration. Endometrial thicknesses >7.0 mm was reported with the first use, and in all cases, endometrial thickness >9.0 mm was evident after the second administration. The entire study group qualified for embryo transfer at the blastocyst stage. There were 73.7% of positive pregnancy tests, of which 26.3% yielded live births; 26.3% generated ongoing pregnancies and 10.5% produced biochemical pregnancies, while 5.3% had fetal death (16 weeks) ^[4]. In another publication, Zadehmodarres et al. reported that they recruited ten patients with a history of inadequate endometrial growth in frozen-thawed embryo transfer (FET) cycles. In every patient, PRP administration increased endometrial thickness and embryo transfer was performed. After treatment, five patients became pregnant, and in four cases, the pregnancy progressed normally ^[2]. Contrary to those promising results, Tehraninejad et al. published results of PRP infusion into the uterine cavity in 85 patients with normal endometrium thickness (>7 mm) suffering from repeated implantation failure (RIF). In 42 patients 1 mL of PRP was infused into the uterine cavity 2 days before the embryo transfer. The outcomes, including biochemical, clinical and ongoing pregnancy rates were similar between the PRP and control groups and did not reach statistical significance (35.7% vs. 37.2%; 31.0% vs. 37.2%; and 26.8% vs. 25.6%, respectively) ^[4].

The other indication for the administration of PRP is Asherman's syndrome. According to Aghajanova et al. (2021) and Aghajanova et al. (2018), treatment with intrauterine PRP infusion was well tolerated, with no short-term or long-term side effects, and appeared to improve endometrial function—as demonstrated by successful conception and ongoing clinical pregnancies. In conjunction with solid in vitro data on human endometrial cells, these pilot clinical outcomes were very reassuring, but primary results after a pilot study of 30 patients were not very promising compared to standard treatment ^{[5][6]}.

2. Ovaries

In cases of difficulties in becoming pregnant due to ovarian dysfunction, attempts have been made to inject PRP into both ovaries. The effect of its application was an increase in the number of ovarian oocytes ^[7]. Moreover, in women with a poor ovarian reserve and premature menopause, autologous intraovarian PRP therapy increased anti-Mullerian hormone levels and decreased follicle-stimulating hormone (FSH) concentration, with a trend toward increasing clinical and live birth rates ^{[3][8][9]}. In a related study, Farimani et al. published research in which 19 women were enrolled. Therein, the mean numbers of oocytes before and after PRP injection were 0.64 and 2.1, respectively. Two patients experienced spontaneous conceptions. The third case achieved clinical pregnancy and delivered a healthy baby ^[8].

A similar effect was also found in a woman with chronic endometritis and recurrent implantation failure. The case of a 35-year-old woman with premature ovarian insufficiency and a history of six failed donated embryo transfers was described. The patient was referred to the clinic for assisted reproduction and underwent ET of two donated blastocysts graded as 5

BB and 5 BC at the next menstrual cycle, which resulted in a twin pregnancy. Four weeks following a positive β -hCG pregnancy test, clinical pregnancy was confirmed by observing fetal cardiac activity on transvaginal ultrasound. The babies were delivered at the 36th week of gestation and weighed 2.28 kg and 2.18 kg [10].

3. Wound Healing and Tissue Regeneration

Various studies where patients served as their own control ("split-face" studies), investigating whether PRP injections are beneficial for tissue and skin rejuvenation, were undertaken [11]. Platelet rich plasma mode of action is mostly based on stimulating the synthesis of matrix metalloproteinases (MMPs), increasing cutaneous fibroblast growth as well as the production of extracellular matrix (ECM) components including type I collagen and elastin [12]. This was an argument towards applying PRP as a wound healing enhancing factor for various types of wounds, as well as in skin regeneration. The development of the newest type of PRP called lyophilized enhanced PRP (ePRP) is the step toward the standardization of applying a specific, desirable quantity of growth factors by using a defined amount of PRP powder. It was found that ePRP dynamically activates several glycolytic enzymes to modulate and sustain glucose metabolism, mitochondrial biogenesis and respiratory function, to meet energy demands in different wound healing periods. Moreover, multiple antioxidant enzymes are being up-regulated resulting in reactive oxygen species (ROS) decrease thus allowing for proper tissue repair [13]. Those metabolic changes, and many yet unknown, facilitate wound healing and are the driving force for adjunctive treatment of many conditions induced by impaired tissue regenerative capacity.

One of the publications presents a prospective randomized controlled trial with 200 patients who underwent elective cesarean section. The intervention group received subcutaneous PRP injection into the wound after surgery. The control group received the usual care. Outcome variables included redness, edema, ecchymosis, discharge, approximation scale (REEDA) results, Vancouver scar scale (VSS) outcome and visual analog scale (VAS) determinations. Patients from the PRP group showed a greater reduction in the REEDA score, compared to the control group on day 1 and day 7, and this was continued for the 6 months of the study (1.51 ± 0.90 vs. 2.49 ± 1.12 , $p < 0.001$). Compared to the control group, the PRP group had a significantly greater reduction in the VSS and VAS scores beginning on the seventh day (3.71 ± 0.99 vs. 4.67 ± 1.25 , $p < 0.001$) and (5.06 ± 1.10 vs. 6.02 ± 1.15 , $p < 0.001$), respectively, and this difference was observed for a 6 month period. This study demonstrated that PRP has positive effects on wound healing and pain reduction in high-risk patients undergoing cesarean section in low-resource settings [14].

This was also confirmed in a recently published paper by Starzyńska et al. where PRP was used in patients with surgical removal of impacted mandibular third molars. As this procedure is associated with various postoperative complications mostly concerning impaired healing additional therapies are being developed and one of those is the addition of advanced platelet-rich fibrin (A-PRF) which consists of a three-dimensional fibrin matrix, rich in platelets and leukocytes, containing cytokines, stem cells, and growth factors and namely, it belongs to the second generation of platelet concentrates. The study was conducted within two groups consisting of 50 patients with immediate A-PRF socket filling and a control group of 50 patients without A-PRF socket filling. Several clinical features were postoperatively assessed: pain, analgesics intake, the presence of trismus, edema, hematomas within the surrounding tissues, the prevalence of pyrexia, dry socket, secondary bleeding, presence of hematomas, skin warmth in the post-operative area, and bleeding time observed by the patient were analyzed on the 3rd, 7th, and 14th day after the procedure. There was a significant decrease in pain intensity, analgesics intake, trismus, and edema on the 3rd and the 7th day in patients with A-PRF socket filling ($p < 0.05$). Additionally, the study showed that A-PRF was the most important factor in reducing the incidence of postoperative complications [15].

In order to evaluate the possible utility and efficacy of platelet rich gel after advanced vulvar cancer surgery, Morelli et al. conducted a study on 25 women who had undergone radical surgery. Gel application in 10 out of 25 patients was related to a significant reduction in wound infection, necrosis of vaginal wounds, and wound breakdown rates ($p = 0.032$; $p = 0.096$; $p = 0.048$, respectively). The authors concluded that platelet gel application before vulvar reconstruction represents an effective strategy to prevent wound breakdown after vulvar cancer surgery [16].

A very interesting paper concerning the molecular aspects of radiation induced wound healing and the interaction of endothelial cells and adipose-derived stem cells in conjunction with PRP in the context of radiation effects was published by Reinders et al. The malfunction of wound healing in irradiated tissues is associated with fibrosis, decreased vascularity and impaired tissue remodeling. The study was conducted using cell cultures with human dermal microvascular endothelial cells (HDMEC), adipose-derived stem cells (ASC). Activated PRP was used for cell culture experiments at a final concentration of 5% in the culture medium. The cells were irradiated with doses of 2 (0.7 min irradiation) and 6 Gy (2 min irradiation), respectively. One of the investigated factors was cell viability and it was determined using a colorimetric assay. Human ASC showed no altered viability upon radiation but the treatment of ASC with 5% PRP caused a slight,

although not significant, trend towards increased viability which unfortunately was reversed by irradiation with both tested doses of 2 Gy and 6 Gy. Additionally, endothelial cells showed a trend towards decreased viability upon external radiation, both in the presence and absence of PRP. Interestingly, analysis of co-cultured ASC/HDMEC showed a significant effect for radiation with 6 Gy in both PRP-treated and untreated cells. Furthermore, the effect on PRP treatment of irradiated ASC, HDMEC and the corresponding co-culture was studied using a colorimetric BrdU assay. All cell cultures showed a trend towards decreasing proliferation after irradiation irrespective of PRP. The proliferation of all cells was significantly diminished by radiation with 6 Gy. Remarkably, PRP presence in the cell medium had a pro-proliferating effect on cells after irradiation with 2 Gy. The concluding message of this study is that a combination of treatment with ASC and PRP products might be useful in the care management and adjunctive treatment of chronic radiogenic wounds ^[17].

The healing effect has also been applied to genital rejuvenation. Vaginal rejuvenation involves the management of extrinsic (traumatic) and intrinsic (aging) changes in the vagina and scrotum. Lipofilling, with an additional injection of PRP (with or without hyaluronic acid), has been used to successfully address vaginal atrophy and vaginal laxity ^[18]. In the study, the unexpected resolution of lichen sclerosus in one of the women was a factor that initialized PRP application for the treatment of this condition. Unfortunately, the double-blind placebo-controlled trial that was performed on thirty patients did not prove the efficacy of PRP in managing lichen sclerosus ^[19].

The other indication of the administration of PRP in genital rejuvenation is to improve the quality of sexual life. Sukgen et al. investigated the effect of PRP injection to the lower one-third of the anterior vaginal wall on sexual function, orgasm and genital perception in women with sexual dysfunction. The study revealed that as a minimally invasive method, PRP administration to the distal part of the anterior vaginal wall may improve female sexuality, along with higher satisfaction ^[20]. Another study conducted on 68 women ranging from 32 to 97 years, indicated that O-shot injection, which is PRP administration to the vulvovaginal region, is a satisfactory solution for women having stress incontinence, overactive bladder, lack of lubrication and sexual dysfunction, such as lack of libido, arousal and dyspareunia. The results show that 94% of these patients were satisfied, however, 6% of all patients with overactive bladder did not indicate improvement ^[21].

In one case published to date, PRP was used as a regenerative factor for clitoral reconstruction after female genital mutilation (FGM) in a 35-year-old Guinean woman. After surgical clitoris reconstruction with the Foldès method, an A-PRP was applied. Two months postoperatively, wound healing was complete and the patient reported significant improvement in quality of life ^[22].

4. Urogynecology

PRP has been applied in the treatment of urogynecological disorders and LUTS and there are ongoing observations of the use of PRP as a supporting therapy in addressing recurrent vesicovaginal fistulas. Patients enrolled in this study were injected with PRP around the fistulous canal and underwent the Latzko procedure 6–8 weeks later. In all cases, after a 1–2 months follow-up period, the fistula was healed and the vaginal wall at the site of the procedure healed without any signs of scarring, redness, or granulosa tissue. Moreover, the patients did not complain about any urination difficulties or urinary tract disorders. In addition, post void residuals were lower than 50 mL in all patients ^[23].

There are also published papers describing PRP usage in cystocele treatment (which is the most common vaginal wall prolapse). In a study by Atilgan and Aydin, patients were divided into two groups: (1) cystocele repair only and (2) cystocele repair with platelet-rich plasma injection. Each group consisted of 28 patients. There were no significant differences between the groups in terms of demographic features. At the end of the 48-month follow-up period, the results were compared between the groups. The main outcome was the low recurrence rate with platelet-rich plasma administration. Furthermore, the decrease in prolapse symptoms ascertained with the Pelvic Floor Distress Inventory scale was more significant in group 2. Platelet-rich plasma administration may thus be a good alternative treatment for preventing cystocele recurrence; still, further research is needed to evaluate the safety and efficacy of this treatment ^[24]. On the other hand, Gorlero et al. evaluated the efficacy of PRF in patients with pelvic organ prolapse recurrent surgery. Platelet-rich fibrin was prepared with the use of the Vivostat system in 10 patients and applied on dissected pubourethral fascia before vaginal skin closure. The authors observed an anatomical success rate of 80%, while patients reported a 100% improvement in symptoms. Despite the aforementioned excellent outcomes, the authors did not continue the study on a larger group of women affected with vaginal prolapse ^[25].

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