

# *Regenerative Therapy in Gynecological Disorders*

## *Review*

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**Abstract** – Platelet-rich plasma (PRP) could be perceived as a unique planning of plasma in which concentration of platelet is tremendously high. This reasoning for plasma use has been in the clinically broadly utilized in medical sciences. All along, yet in the beyond couple of years its utilization has been stretched out to different fields, like obstetrics and gynecology. From the actual beginning of the presentation of platelet-rich plasma in gynecology, there had been consistent research being done to demonstrate and affirm its accurate role in the management of gynecological problems. Regenerative medication in gynecology was among the principal regions where the platelet-rich plasma was executed and has significantly given extraordinary outcomes, which urged further broad studies to be done in different spectrums of gynecology. The implications of such extraordinary battles at last gave method for proving proposing the significance of platelet-rich plasma in managing gynecological problems like Asherman's disorder, urinary incontinence, genital fistulas, and thin endometrium. This article by sums up the different utilization of platelet-rich plasma in gynecology.

**Keywords** – Platelet Rich Plasma (PRP), Platelet Rich Fibrin, Vesicovaginal Fistula, Asherman's Syndrome, Premature Ovarian Failure, Urogynecology

### I. Introduction

The use of PRP in gynecology is as yet a creating cycle. In spite of simple admittance to PRP, moderately straightforward planning and the sufficiently known system of activity, it is utilized somewhat in this field. Up to this point its largest application is in regenerative medication, particularly in instances of thin endometrium, Asherman's syndrome, or premature ovarian failure (POF) yet in addition in wound healing and lower urinary tract symptoms (LUTS), like urinary incontinence or genitourinary fistula treatment.

Table 1. Dohan- Ehrenfest 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

## **1. Endometrium**

Endometrium status is one of the fundamental elements of pregnancy implantation failure. In women with a thin endometrium, PRP was utilized as an intrauterine failure to prompt endometrial growth and increment clinical rates of pregnancies [1,2,3]. This was portrayed in several cases. Molina et al., for instance, portrayed 19 patients who had gone through in vitro preparation, matured somewhere in the range of 33 and 45 years, with refractory endometrium, to whom PRP was implanted with a catheter into the uterine cavity. PRP was utilized two times, after the tenth day of the hormonal replacement treatment, and afterward 72 h after the first administration. Endometrial thicknesses >7.0 mm was accounted for with the principal use, and in all cases, endometrial thickness > 9.0 mm was clear after the subsequent administration. The whole review group equipped for embryo transfer at the blastocyst stage. There were 73.7% of positive pregnancy tests, of which 26.3% yielded live births; 26.3% created ongoing pregnancies and 10.5% produced biochemical pregnancies, while 5.3% had fetal demise (16 weeks) [1]. In another publication, Zadehmodarres et al., revealed that they enlisted ten patients with a background marked by inadequate endometrial development in frozen-thawed embryo transfer (FET) cycles. In each patient, PRP administration expanded endometrial thickness and embryo transfer was performed. After treatment, five patients became pregnant, and in four cases, the pregnancy advanced typically [2]. In opposition to those promising outcomes, Tehraninejad et al., published results of PRP infusion into the uterine cavity in 85 patients with normal endometrium thickness (>7 mm) experiencing repeated implantation failure (RIF). In 42 cases 1 mL of PRP was infused into the uterine cavity 2 days before the embryo transfer. The results, including biochemical, clinical and progressing pregnancy rates were comparable between the PRP and control gatherings and didn't arrive at statistical significance (35.7% versus 37.2%; 31.0% versus 37.2%; and 26.8% versus 25.6%, respectively) [4]. The other indication for the infusion of PRP is Asherman's syndrome. As per Aghajanova et al. (2021) and Aghajanova et al. (2018), treatment with intrauterine PRP infusion was well endured, with no present moment or long term side effects, and seemed to improve endometrial capability, as exhibited by effective conception and continuous clinical pregnancies. Related to strong in vitro information on human endometrial cells, these pilot clinical results were exceptionally consoling, yet essential outcomes after a pilot investigation of 30 patients were not extremely encouraging contrasted with standard treatment [5,6].

## **2. Ovaries**

In instances of troubles in becoming pregnant because of ovarian dysfunction, endeavors have been made to infuse PRP into the two ovaries. The impact of its application was an expansion in the quantity of ovarian oocytes [7]. Besides, in women with a poor ovarian reserve and premature menopause, autologous intra-ovarian PRP treatment expanded anti-Mullerian hormone levels and diminished follicle-stimulating hormone (FSH) concentration, with a trend toward expanding clinical and live rates of birth [3,8,9]. In a related report, Farimani et al., distributed research in which 19 women were enlisted. In that, the mean quantities of oocytes when PRP injection were 0.64 and 2.1, respectively. Two patients experienced spontaneous conceptions. The third case accomplished clinical pregnancy and delivered a healthy baby [8]. A comparable impact was likewise tracked down in a woman with ongoing endometritis and recurrent implantation failure. The instance of a 35-year-elderly person with premature ovarian insufficiency and a background marked by six failed donated embryo transfers was depicted. The patient was alluded to the center for assisted reproduction and went through ET of two donated blastocysts reviewed as 5 BB and 5 BC at the following menstrual cycle, which brought about a twin pregnancy. Four weeks following a positive  $\beta$ -hCG pregnancy test, clinical pregnancy was affirmed by noticing fetal cardiac activity on trans-vaginal ultrasound. The infants were delivered at the 36th week of gestation and weighed 2.28 kg and 2.18 kg [10].

## **3. Wound Recuperating and Tissue Recovery**

Different studies where patients served in as their own control ("split-face" studies), researching whether PRP infusions are advantageous for tissue and skin restoration, were attempted [11]. Platelet rich plasma mode of activity is for the most part founded on stimulating the synthesis of matrix metalloproteinases (MMPs), expanding cutaneous fibroblast development as well as the creation of extracellular framework (ECM) components including type I collagen and elastin [12]. This was a contention towards applying PRP as a wound recuperating improving element for different kinds of wounds, as well as in skin regeneration. The improvement of the most up to date kind of PRP called lyophilized enhanced PRP (ePRP) is the move toward the standerization of applying a particular, helpful amount of growth factors by utilizing a characterized measure of PRP powder. It was found that ePRP dynamically enacts a several glycolytic enzymes to modulate and support glucose metabolism, mitochondrial biogenesis and respiratory capability, to fulfil energy needs in various wound recuperating periods. Also, numerous anti-oxidants enzymes are being up-regulated bringing about receptive oxygen species (ROS) decline consequently taking into

consideration appropriate tissue repair [13]. Those metabolic changes, and numerous yet obscure, work with wound recuperating and are the main force for adjunctive treatment of many circumstances prompted by impaired tissue regenerative capacity.

One of the publications gives a forthcoming randomized controlled preliminary 200 patients who went through elective cesarean section. The intervention group got subcutaneous PRP infusion into the wound after surgery. The control group got the standard care. Result factors included redness, edema, ecchymosis, release, approximation scale (REEDA) results, Vancouver scar scale (VSS) result and visual simple scale (VAS) determinations. Patients from the PRP group showed a more prominent decrease in the REEDA score, compared with the control group on day 1 and day 7, and this was gone on for the a half year of the review ( $1.51 \pm 0.90$  versus  $2.49 \pm 1.12$ ,  $p < 0.001$ ). Compared with the control group, the PRP group had a fundamentally more noteworthy decrease in the VSS and VAS scores starting on the seventh day ( $3.71 \pm 0.99$  versus  $4.67 \pm 1.25$ ,  $p < 0.001$ ) and ( $5.06 \pm 1.10$  versus  $6.02 \pm 1.15$ ,  $p < 0.001$ ), separately, and this distinction was noticed for a 6 months time span. This study exhibited that PRP a positive affects wound recuperating and pain decrease in high-risk patients going through cesarean segment in low-resource settings [14].

This was likewise affirmed in a recently published paper by Starzyńska et al. where PRP was utilized in patients with careful expulsion of affected mandibular third molars. As this methodology is related with different postoperative complications for the most part concerning impaired recuperating extra treatments are being created and one of those is the addition of advance platelet-rich fibrin (A-PRF) which comprises of a three-layered fibrin matrix, rich in platelets and leukocytes, containing cytokines, stem cells, and growth factors and specifically, it has a place with the second era of platelet concentrates. The review was directed inside two groups comprising of 50 patients with prompt A-PRF socket filling and a benchmark group of 50 patients without A-PRF socket filling. A several clinical highlights were postoperatively surveyed: pain, analgesics consumption, the presence of trismus, edema, hematomas inside the encompassing tissues, the predominance of pyrexia, dry socket, secondary bleeding, presence of hematomas, skin warmth in the post-usable region, and bleeding time observed by the patient were analyzed on the third, seventh, and fourteenth day after the procedure. There was a large reduction in pain intensity, analgesics intake, trismus, and edema on the third and the seventh day in patients with A-PRF socket filling ( $p < 0.05$ ). Moreover, the review showed that A-PRF was the main factor lessening the frequency of postoperative complications [15].

To assess the conceivable utility and efficacy of platelet rich gel after advanced vulvar disease surgery, Morelli et al., led a study on 25 women who had gone through a radical surgery. Gel application in 10 out of 25 patients was related with a significant decrease in wound infection, necrosis of vaginal wounds, and wound breakdown rates ( $p = 0.032$ ;  $p = 0.096$ ;  $p = 0.048$ , separately). The authors reasoned that platelet gel application before vulvar reconstruction addresses a powerful methodology to prevent wound breakdown after vulvar malignant surgery [16]. An exceptionally interesting paper concerning the molecular parts of radiation induced wound healing and the interaction of endothelial cells and adipose derived stem cells related to PRP with regards to radiation impacts was published by Reinders et al. The malfunction of wound healing in irradiated tissues is related with fibrosis, diminished vascularity and impaired tissue remodelling. The review was directed utilizing cell cultures with human dermal microvascular endothelial cells (HDMEC), adipose derived stem cells (ASC). Activated PRP was utilized for cell culture tests at a final concentration of 5% in the culture medium. The cells were irradiated with doses of 2Gy (0.7 min irradiation) and 6 Gy (2 min irradiation), respectively. One of the researched factors was cell suitability and it was resolved utilizing a colorimetric assay. Human ASC showed no modified viability upon radiation except for the therapy of ASC with 5% PRP caused a slight, albeit not critical, pattern towards expanded viability which tragically was switched by irradiation with both tried dosages of 2 Gy and 6 Gy.

Moreover, endothelial cells showed a pattern towards diminished viability upon external radiation, both in the presence and absence of PRP. Analysis of co-cultured ASC/HDMEC showed a massive impact for radiation with 6 Gy in both PRP-treated and untreated cells. Besides, the impact on PRP therapy of irradiated ASC, HDMEC and the relating co-culture was studied on utilizing a colorimetric BrdU assay. All cell cultures showed a pattern towards diminishing multiplication after irradiation regardless of PRP. The multiplication of all cells was fundamentally lessened by radiation with 6 Gy. Surprisingly, PRP presence in the cell medium affected cells after irradiation with 2 Gy. The concluding message of this study is that a combination of therapy with ASC and PRP products may be helpful in the consideration the management and adjunctive therapy of chronic radiogenic wounds [17]. The recuperating impact has additionally been applied to genital restoration. Vaginal rejuvenation includes the management of extrinsic (traumatic) and intrinsic (aging) changes in the vagina and scrotum. Lipofilling, with an extra infusion of PRP (with or without hyaluronic acid), has been utilized to effectively address vaginal atrophy and vaginal laxity [18]. In the

review, the surprising goal of lichen sclerosis in one of the women was an element that initialized PRP application for the treatment of this condition. Unfortunately, the double-blind placebo controlled preliminary that was performed on thirty patients didn't demonstrate the adequacy of PRP in managing lichen sclerosis [19]. The other indication of the administration of PRP in genital rejuvenation is to work on the quality of life. Sukgen et al. explored the impact of PRP infusion to the lower third of the anterior vaginal wall on capability, orgasm and genital perception in women with sexual dysfunction. The review uncovered that as a negligibly invasive method, PRP administration to the distal part of the anterior vaginal wall might improve female sexuality, alongside higher fulfillment [20]. One more review directed on 68 women ranging from 32 to 97 years, showed that O-shot injection, which is PRP administration to the vulvovaginal region, is a satisfactory answer for women having stress incontinence, overactive bladder, absence of lubrication and sexual dysfunction, like absence of libido, excitement and dyspareunia. The outcomes show that 94% of these patients were fulfilled, in any case, 6% of all patients with overactive bladder didn't demonstrate improvement [21]. In one case published to date, PRP was utilized as a regenerative element for clitoral reconstruction after female genital mutilation (FGM) in a 35-year-old Guinean woman. After surgical clitoris reconstruction with the Foldès technique, A-PRP was applied. Two months postoperatively, wound recuperating was finished and the patient announced significant improvement in personal satisfaction [22].

#### **4. Urogynecology**

PRP has been applied in the treatment of urogynecological disorders and LUTS and there are continuous perceptions of the utilization of PRP as a supporting treatment in addressing recurrent vesicovaginal fistulas. Patients enrolled in this study were injected with PRP around the fistulous canal and went through the Latzko procedure 6-8 weeks later. In all cases, following a 1-2 months follow-up period, the fistula was mended and the vaginal wall at the site of the methodology recuperated with practically no signs of scarring, redness, or granulosa tissue. In addition, the patients griped about no urination hardships or urinary tract problems. Furthermore, post voidal residuals were lower than 50 mL in all patients [23]. There are additionally published papers portraying PRP utilization in cystocele treatment (which is the most widely recognized vaginal wall prolapse). In a study by Atilgan and Aydin, patients were divided into two gatherings: (1) cystocele repair only and (2) cystocele repair with platelet-rich plasma infusion. Each gathering comprised of 28 patients. There were no significant differences between the gatherings with regards to demographic differences. Toward the end of the 48 weeks follow-up period, the outcomes were thought about between the gatherings. The principal result was the low recurrences rate with platelet-rich plasma administration. Besides, the decline in prolapse symptoms found out with the Pelvic Floor Distress inventory scale was more significant in group 2. Platelet-rich plasma administration may subsequently be a good alternative treatment for preventing cystocele recurrent; actually, further studies are expected to assess the safety and efficacy of this treatment [24]. Then again, Gorlero et al. assessed the efficacy of PRF in patients with pelvic organ prolapse recurrent surgical procedure. Platelet-rich fibrin was ready with the utilization of the Vivo stat framework in 10 patients and applied on dissected pubourethral fascia before vaginal skin closure. The authors noticed an anatomical achievement rate of 80%, while patients detailed a 100 percent improvement in symptoms. Regardless of the previously mentioned superb results, the authors didn't proceed with the research on a bigger gathering of women affected with vaginal prolapse [25].

Stress urinary incontinence (SUI) is a significant medical condition, which crumbles the nature of one's life. As per the basic hypothesis, the main element engaged with female stress urinary incontinence occurrence is a pubourethral ligament (PUL) deformity [26]. This ligament anchors the anterior wall of the bladder and proximal urethral descending like a fan from the lower part of the pubic bone forming a hammock under the mid-urethra. Studies on in animal trial models have shown that the transaction of the PUL is related with long-term SUI [27]. Platelet rich plasma contains a several growth factors that add to the pathophysiology of ligament reconstruction including vascular endothelial development factor (VEGF), insulin development factor I (IGF-I), platelet determined growth factor (PDGF), hepatocyte growth factor (HGF), transforming growth factor beta (TGF- $\beta$ ) and fibroblast growth factor (FGF). Considering this information, a pilot study was directed to research in the event that PRP prompts the resolution of SUI. In 20 women, PRP was infused into the anterior vaginal mucosa around the patient's mid-urethra, which was roughly 1 cm beneath the urethra meatus with a depth of around 1.5 cm. 2 mL under mid-urethra and 1.5 mL for each side of the urethra. The injection was injected 3 times one month separated. The review result is confirmed by various self-reported questionnaire previously, 1 month and a 6 months after the treatment and all revealed significant and enduring effectiveness in 12 out of 20 patients (60%). Besides, women 40 years old or younger, have better treatment results compared with the older ones. A disadvantage of this study is the absence of a control group infused with saline to eliminate the bulking

agent impact and the small sample size. Nonetheless, further research could reveal more insight into the PRP impact on SUI. Notwithstanding, this innovative intervention could be an elective treatment for SUI [19]. In one more pilot study, likewise founded on results after infusing PRP two times in 20 consecutive women at 4-to 6-week intervals, a critical improvement in SUI side effects was noticed 3 months after treatment with a further improvement at 6months. A mean decrease of 50.2% in urine loss was seen in the 1-h pad test. At the 6 months follow-up, 80.0% of women detailed improvement. No adverse impacts were noticed. All in all, platelet-rich plasma infusions appear to be both compelling and protected temporarily and could be presented as an elective short term strategy for the treatment of SUI, particularly in more younger women [28].

One more condition that can be analyzed by the gynecologist is interstitial cystitis/painful bladder syndrome (IC/PBS), an ongoing disease with side effects like overactive bladder (OAB) which is expanded urination frequency, urgency, urgency urinary incontinence joined by repeating occasions of pelvic pain. Its occurrence is thought to be pretty much as high as 52-67 for every 100,000 cases in the US [29]. In spite of the fact that OAB and IC/PBS are viewed as discrete neurotic circumstances there is developing logical proof that both are connected with underlying, synaptic, and complex flagging pathway changes that trigger altered bladder sensation [30]. As of late, the efficacy of intra-vesical instillation with PRP and hyaluronic acid for cyclophosphamide-prompted acute IC/PBS was researched in a rodent model. The review was directed on thirty virgin female rodents which were randomized into five gatherings. One gathering comprised of rodents instilled CYP in addition to PRP and showed the main prolongation of voiding spans compared with different gatherings. Besides, The statement of cell junction related protein zonula occludens-2 (ZO-2) and inflammatory cytokine interleukin 6 (IL-6) was likewise estimated through histological staining and was observed that the outflow of ZO-2 was expanded and IL-6 was diminished in the CYP in addition to PRP group compared and the CYP-activated acute IC/PBS group. These discoveries brought about a review embraced by Jhang and collaborators on 19 patients with IC/BPS who went through 4 months intra-vesical PRP infusions with platelet concentration of roughly 5 times that of the prephiral blood. Seven to ten days after the last infusion patient satisfaction was estimated. Functional bladder capacity and maximum flow rate expanded as well as the visual simple scale (VAS) of pain, IC symptom index, IC symptom score, O'Leary-Sant symptom score, and global response assessment worked on in all patients. Moreover, they additionally researched histological features of PRP instillation and found that ZO-1 and different proteins associated with bladder barrier function, for example, E-cadherin and TGF- $\beta$  expression, expanded altogether after repeated PRP infusions [31]. Those results show that Intra-vesical repeated PRP infusions might can possibly improve urothelial health and result in symptoms improvement in patients with IC/BPS. Nevertheless, further studies should be led, additionally on patients with OAB to explain the genuine function of PRP in decreasing those debilitating symptoms.

## **II. Conclusion**

Subsequent to having a careful review of the different research deals with the utilization of platelet-rich plasma in gynecology, published on globally perceived scientific stages, different significant insights of knowledge were gotten, which can possibly achieve an extraordinary revolution in obstetrics and gynecology. Beginning from extremely minor diseases and crossing to probably the most persistent types of gynecological issues, platelet-rich plasma is without a doubt a commendable candidate for the managment of these issues. The wide range of its utilization has made different gynecological issues like thin endometrium, recurrent genital fistulas, ovarian abnormalities, Asherman's syndrome, urinary stress incontinence, and so on, really made due. Platelet-rich plasma has been experimentally demonstrated to build the thickness of the endometrium. In this way helping implantation in women as implantation could never have been generally conceivable in these females in view of their thin endometrium. Those women who were experiencing ovary-related issues benefited when platelet-rich plasma was directed to them. The role of platelet-rich plasma in the management of urinary complaints is exceptional, and in this manner the implementation of PRP considerably works on the symptoms in these women. From the analysis of the impacts of platelet-rich plasma in gynecology which is presently accessible, there is no question that more research would support finding the hidden potentials of platelet-rich plasma in the managment of many more amount of the issues experienced in gynecology.

### **Conflict of Interest**

All authors declare no conflicts of interest.

### **Author Contribution**

Authors have equally participated and shared every item of the work.



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