Autologous Platelet rich plasma (PRP): A Possibility of becoming a revolutionary therapy in the field of Gynaecology and reproductive Endocrinology and Infertility-A Systematic Review

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ABSTRACT

Platelet rich plasma (PRP) is coming up as a novel therapy that has been utilized in dermatology, dentistry, orthopedics and sports medicine with the view that normally platelets are the inherent blood contents that at the time of injury reach the point of injury and secrete multiple growth factors and induce healing process. With this in mind recently lot of trials are going on in the field of Gynaecology including reproductive medicine regarding its applications in Gynecology and reproductive medicine. Thus, we carried out a systematic search for articles related to PRP in Gynaecology and reproductive medicine till July 2019. In this review we have tried to summarize the beneficial effects of PRP in this field.

Keywords: PRP; Lichen Sclerosis; Prolapse; Genital Urinary Incontinence; Recurrent Implantation Failure; POF/Poor Ovarian Reserve

INTRODUCTION

Platelet rich plasma (PRP) has gained a lot of acceptance, being a non-operative treatment for multiple medical disorders. In orthopedics along with sports medicine it is being used routinely for pain relief via the promotion of natural healing in musculoskeletal diseases like arthritis, tendinitis, ligamentous strains and tears. Especially PRP injections have been used for athletic injuries, resulting in exceptional healing with rapid return to routine activities with complete pain relief [1].

Autologous PRP is derived from an individual’s whole blood, then centrifuged to remove red blood cells. The remaining plasma has a 5-10 times greater concentration of growth factors as compared to whole blood. These growth factors have been found to promote natural healing responses by researchers from varied specialties including dentistry, urology and gynecology [2,3].

The basic mechanism of this healing was proposed as seen in natural healing process in the 1st response of body to tissue injury is to bring platelets to the injured area. Platelets promote healing and attract stem cells
to the site of the injury. Practically, clinically PRP injections have been applied to diseased ligaments, tendons and joints, with great results in relation to repair [4]. With limited experience of use of PRP in Gynaecology and infertility, the aim of this review was to find the use in Gynaecology and infertility relationship.

METHODS

We did a systematic review using the PubMed search engine and google scholar, using the MeSH terms Platelet rich plasma (PRP), preparation techniques; uses in Gynaecology; uses in infertility.

Result-
We came across 90 articles pertaining to this topic out of which we selected 60 articles for this review. No meta-analysis was done.

2) Science of PRP

2.1 PRP preparation

PRP preparation is an OPD procedure which 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 [5,6]. These steps are the ones which represent the routine method of preparing PRP.

1) Venous blood (15-50ml) is drawn from the patient's arm in anticoagulant-containing tubes. 2) the recommended temperature during processing is 21-24°C to prevent platelet activation during centrifugation of the blood. 3) the blood is centrifuged at 1200rpm for 12 minutes. 4) The blood separates into three layers: an upper layer which contains platelets and white blood cells, an intermediate thin (the buffy coat) that is rich in white blood cell, and a bottom layer that contains red blood cells; 5) the upper and intermediate layers are transferred to an empty sterile tube. The plasma is centrifuged again at 3300rpm for 7 minutes to help with the formation of soft pellets (erythrocytes and platelets) at the bottom of the tube; 6) the upper two thirds of the plasma is discarded because it is platelet-poor plasma. 7) pellets are homogenized in the lower third (5ml) of the plasma to create the PRP; 8) The PRP is now ready for injection. Approximately 30ml of venous blood yields 3-5ml of PRP. 9) The affected area is disinfected before the PRP injection. 10) Providing assurance to the patients and discussing the procedure make the injection easier and less painful; 11) PRP stimulates a series of biological responses, and the injection site may become swollen and painful for approximately 3 days.

2.2 Types of PRP preparations

Classification of PRP preparations is as per the method of preparation, the sample content, and the proposed application. Preparations differ in terms of centrifugation speed, centrifugation type, and anticoagulant use, while the content differs based on the predominant constituent (like platelets, leukocytes, or growth factors) [7].

Following centrifugation of whole blood, 4 types of preparations can be obtained (table1) as proposed by Dohan Ehrenfest [8], based on cell content and fibrin density, which got recommended by a multidisciplinary consensus committee [9]. Mishra et al. gave another classification [10] on the basis of presence or absence of WBC's, their activation status, and platelet concentration. Further Magalon et al. added a newer classification of PRP preparations [11] that was called the DEPA (dose of injected platelets, efficiency of production, purity of PRP, activation of PRP) [TABLE2].

2.3) PRP composition and activation

Platelets are rich in cytokines and growth factors stored within α-granules. These growth factors are Platelet-derived growth factor (PDGF), insulin-like growth factors (IGF), vascular endothelial growth factors (VEGF), platelet derived angiogenic factor, epidermal growth factor (EGF)s, connective tissue growth factor (CTGF), transforming growth factor beta (TGF β), fibroblast growth factors (FGF) and interleukin -8. Besides growth factors, platelets contain other substances, like fibronectin, vitronectin, and sphingosine-1 phosphate which initiate wound healing [12,13].
Activation of Platelets triggers the release of growth factors by different stimuli or substances like thrombin, calcium chloride and collagen. Every method affects both the physical form of PRP and the amount of growth factors released, along with kinetics of release. No evidence is there as per the ideal concentrations of activator needed to trigger the optimum growth factors release during the activation process of PRP, and hence varying concentrations might cause varied results [12].

2.4 Mechanism of Action of PRP
This has not been found completely, but laboratory studies have shown that the high concentration of growth factors in PRP, potentially speeds the healing process [13]. Tissue necrosis resolution, chemotaxis, cell regeneration, cell proliferation and migration, extracellular matrix synthesis, remodeling, angiogenesis and epithelialization are the targets of growth factors to promote wound healing [14]. Superiority of PRP has been observed over recombinant human growth factor since platelet activation => release of multiple growth factors along with differentiation factors. As per Sunita Rajan et al. the fibrin frame work present over platelets was found to support the regenerative matrix, => to rapid attainment of the proper morphological and molecular configurations for wound healing [15].

3. Gynecological Applications of PRP
Tissue repair starts with clot formation and is followed by platelet degranulation with the release of platelet growth factors. These are essential and well-controlled processes to obtain wound healing. Use of PRP in Gynaecology for various diseases is based on its known mechanisms, that involve the wound healing process of the initiation of inflammatory reactions [2].

3.1a Skin Lesions and wound healing –PRP Role
In view of angiogenesis and wound healing with PRP, it is used by dermatologists for treating ulcers, scars and alopecia. Hence Tehranian et al. studied the role of PRP in high risk cases who were for lower segment caesarian section (LSCS). In 70 patients PRP was applied and comparison was done with 71 control cases without PRP application. Patients included were those having a body mass index (BMI>25 kg/m²), previous LSCS, diabetes mellitus (DM), twin pregnancies, use of corticosteroids and anemic patients. A greater decrease in redness, edema, ecchymosis, discharge, approximation score than in the control group(85.5% decrease in PRP group vis a vis 72% in the control group). Thus concluding that one can expect faster wound healing with the use of PRP in view of presence of > platelets and thus growth factors. In another study use of PRP was studied in gynecological surgery in 55 subjects where direct application of PRP was done at the surgical site. They observed that autologous platelet grafts were effective in decreasing pain in major gynecological surgery patients without any adverse effects of PRP [17].

3b Cervical Ectopy and PRP
Use of autologous PRP application with that of laser therapy for benign cervical ectopy was studied by Hua et al. PRP application was done twice on the area of cervical erosion with a week’s interval with PRP in 60 patients, while 60 patients were treated with laser. A complete cure rate was seen in 93.7% of the PRP group while 92.5% in the laser group(p>0.05). Time taken to re-epithelialize was markedly less than that in the laser(P<0.01). Adverse effects were lower in the PRP group like vaginal discharge or vaginal bleeding vis a vis laser group(p<0.01). Thus concluding that autologous PRP application seemed to be a promising therapy for cervical ectopy in symptomatic subjects, in view of shorter tissue healing time and milder side effects in contrast to laser therapy [18].

3c Vulvar Dystrophy –PRP Role
PRP use has been done in multiple dermatological along with autoimmune conditions which are nonresponsive to steroids like lichen sclerosus (LS) and eczema. With LS, vulva is affected along with severe scarring along with labia minora gradually getting lost and sealing of clitoral hood along with clitoris getting buried. Further escalating pruritus, dyspareunia and genital bleeding results due to LS. Thus, quality of life of patients affected is bad with disturbed physical activity, sexual pleasure, and thus a lot of emotional along with psychological problems result [19]. Usually topical and systemic corticosteroids are the first line drugs. Behnia-Willson et al tried PRP application in corticosteroid resistant 28 subjects having LS [20]. PRP was
injected in the vulva in a fanning pattern. PRP treatments were given at a gap of 4-6 weeks and repeated at 12mths. Practically all subjects demonstrated reduction of the size of lesions and in 28.6% of patients there was complete disappearance of the lesion following PRP therapy. No complications besides little pain were observed. Thus concluding that–PRP injections could be used as a treatment for LS efficaciously. Further Esthianghi and Sadownik tried to study effect and safety of adipose derived stem cells (ADSCs) and PRP for the treatment of LS. They reviewed pubmed/medline, ovid, web of science and clinical trials.gov from inception till may 7 2018. 7 Observational studies were identified, with a total of 98 patients. Both ADSCs and PSP were reported to improve symptoms, quality of measures, as well as the clinical and histologic signs of vulvar LS. There is a strong risk of biased estimates of treatment effect. Thus concluding that current evidence is weak for ADSC’s and/or PRP as treatment for vulvar LS. Future research is therefore recommended for this therapy [21].

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3d Reconstructive Surgery for Vulvar Cancer-PRP Role

A retrospective study of patients who underwent radical vulvectomy for Carcinoma Vulva was done by Mortelli et al [22] with the aim of evaluating the effectiveness of platelet gel application following radical surgery. Patients were divided into 2 groups, with group A(n=10), in whom platelet gel was placed on the vaginal breach during reconstructive surgery and group B(n=15), who only had surgery. Significantly lower rates of wound infection (p=0.032), necrosis of vaginal wound (p=0.096) and wound breakdown (p=0.048) in group A vs group B. A decrease in postoperative fever rate, shorter hospital admission, with speedy wound healing in group A was also found. Thus concluding that platelet gel application before vulvar reconstruction was a good move to prevent wound breakdown following surgery to treat locally advanced cancer.

3E. Urogenital Disorders and PRP

i) PRP in Genital Fistulae

Bodner Adler et al [23] presented different methods by which genital fistulae are treated in a systematic review which examined conservative and surgical therapies. Small fistulae could be treated conservatively with different treatments including PRP, with 67–100% success was what they observed. PRP has been tried in vesicovaginal fistulae (VVF) a novel minimally invasive approach for closing these genital fistulae. In a 12 patients series, Shrivan et al [24] injected PRP around the fistula into the tissue and platelet rich fibrin (PRF), glue was interplaced in the tract. On follow up of these cases over 6mths, they found that 11 patients were clinically cured, with normal findings on transvaginal physical examination and cystography. Thus the conclusions drawn was that autologous PRP injection and PRF glue interposition was a safe, efficacious and novel minimally invasive approach for the treatment of VVF which prevented the need for surgery.

A case of complicated low iatrogenic rectovaginal fistula, treated using interposition of buccal mucosa and apposition of PRP was reported by Mongardini et al [25]. In high perianal fistulae Gottgen’s et al [26] injected PRP injections into the fistulous tract following mucosal advancement flap in 10 cases of Crohns disease related high perianal fistulae. Healing of the fistula occurred in 70% of cases (95%CI-3%-89%) at 1 yr. 1 patients had recurrence(10%), and in 2 patients (20%), the fistula persisted following Rx. Thus conclusions drawn were that this method was moderately successful in Crohns disease fistulae having a success rate of 70% with giving suggestion for more future studies.

3f) Genital Prolapse and Urinary Incontinence

Absorbable and nonabsorbable vaginal implants used in pelvic floor reconstruction procedures possess multiple side effects. PRF is a mixture of platelets, leukocytes, cytokines and circulating stem cells that is optimal for stimulating fibroblast migration and proliferation. The mixture => rapid remodeling and CTGF following vaginal surgery.
In 10 consecutive women who needed surgery for prolapse recurrence (stage II or greater) a prospective observational study was carried out by Gorleo et al [27]. After operating on cases PRP injections were given. A success rate of 80% with complete symptomatic relief was obtained. Increase in sexual activity by 20% without dyspareunia occurred. Thus concluding that use of PRF for site specific prolapsed repair was associated with good functional results. Attachment of fibroblasts to vaginal meshes increased in a significant way following coating the meshes with PRP in vitro was demonstrated by Mendel et al [28]. The animal experimental and clinical studies that have proved regarding potential of PRP in treating genital prolapse was summarized by Christianopoulos et al [29]. Concluding that PRP restores anatomy and function of pelvic ligaments, but no evidence has yet emerged to support or oppose PRP use in women suffering from genital prolapse. In the same way Nikopoulos et al [30] gave a summary of studies which advised the use of PRP in urinary incontinence resulting from damage of the pubourethral ligament strength. It was observed that PRP helped in controlling tissue reconstruction and the restoration of pubourethral ligament but the studies could not give enough proof to justify its use. On the other hand in another study that used to study if autologous PRP gel application during anterior colporrhaphy raised the collagen content of the pubocervical fascia,=> greater duration of repair. The authors applied autologous PRP gel to the surgical site during anterior colporrhaphy in 9 patients. They collected biopsy samples from anterior vaginal wall both at the time of surgery along with 3mths postsurgery. No significant increase in collagen was found at 3mth following the surgery and thus concluded that autologous PRP gel did not increase collagen levels or improve durability of the repair [31].

3i) PRP IN DUB

Turan et al evaluated the efficacy of intracavitary PRP therapy in patients diagnosed as having abnormal uterine bleeding (DUB). A total of 149 patients with AUB were included in this. Seventy four of these patients were included in the study group and 75 in control group. All patients were evaluated using transvaginal sonography (TVS). Endometrial curettage was done to exclude underlying organic pathologies. This study group underwent intracavitary PRP therapy. Both patient groups were called for follow up at the end of 3rd month. Their Endometrial thickness (EMT) and amount of bleeding (pictogram and pads/day) were evaluated using TVS. No statistical difference between the study and control group in terms of the increase of EMT was seen. Thus concluding that it was seen that intracavitary PRP Therapy did not make a statistical difference in the reduction of bleeding and in the increase of EMT, between the study and control groups [32].

4. Reproductive Medicine and PRP

4A) Premature Ovarian failure (POF)

POF implies loss of ovarian function prior to the age of 40 years which is accompanied with loss of fertility. Research team from Harvard University injected murine ovaries with growth factors and mature eggs appeared to develop from ovarian stem cells. They stated that introduction of isolated growth factors bearing platelets directly into the ovaries might stimulate the resurgence on production of oocytes [33]. Investigation of PRP treatment in women with POF, women over35 years with infertility and in those with low ovarian reserve. Treatment with PRP is called ovarian rejuvenation, where PRP is injected into the ovary under USG.
guidance, just like oocyte retrieval in IVF. Still trials are going on in this method. At ESHRE conference held in Helsinki, Finland, Pantos et al [34] introduced ovarian rejuvenation. They used PRP injections in 8 perimenopausal/POF women with poor ovarian reserve. Successful ovarian rejuvenation was found in 1-3 mths following PRP therapy. All patients underwent natural IVF cycles of 15.20±.205mm in diameter r and resulting oocytes were inseminated using ICSI and all embryos were cryopreserved. Further sills et al tried autologous PRP In 4 cases having diminished ovarian reserve, as was found by at least one previous IVF cycle cancelled for poor follicular recruitment response or determined by serum AMH and or FSH, with no menses for>=1yr. Once PRP was isolated and activated with calcium gluconate, roughly 5ml of autologous PRP was injected in each ovary under direct transvaginal USG guidance. AMH, FSH, and serum E2 data were recorded at 2wks interval post PRP, and compared to prePRP values. The mean age was 42+.4yrs in this pilot study with infertility duration 60+.25mths. An increase in serum AMH(P=0.17), reduction in FSH(P<0.01), or both were seen in all cases enough to allow retrieval of 5.3±1.3 MI oocytes. IVF took place 78+.22(range 59-110)days following activated PRP injection, with results appearing independent of age, infertility duration, baseline platelet concentration or pretreatment antral follicle count AFC. Each patients had at least one blastocyst suitable for cryopreservation. This was the first description of direct injection of activated PRP into the human ovary of poor prognosis IVF patients. Evidence of improved ovarian function was noted in all who received intra ovarian PRP, probably as early as 2mths following treatment. Thus concluding more research is needed to clarify and enhance which PRP components are responsible for altered ovarian function and to identify predictive characteristics for patients most likely to benefit from this intervention[35]. Further Sfakianoudis et al [36] treated 3 poor responder patients with the common denominator of failed IVF attempts, poor oocyte yield, and poor embryo quality, after donor oocyte option was rejected. Autologous PRP ovarian infusion following written consent was done. Within a 3mth interval, FSH reduced by 67.33%, while AMH increased by 75.18%. These impressive results on the biochemical infertility markers alone are classified as a complete biological paradox, coupled by improved embryo quality. Results report a natural conception at 24 weeks, an uncomplicated healthy pregnancy at 17 weeks and a successful live birth. The authors, reported this was the 1st time that such an approach and results were reported, where PRP treatment on poor responder lead to overcoming their challenging reproductive barrier [36].

4B) Ovarian Torsion and PRP

60 Adult female rats were subjected to ischemia and bilateral adnexal torsion for 3hrs. Intraperitoneal PRP was given 30 minutes before ischemia in one group, while in the other group PRP was not used. Then detorsion was done and oxidative stress levels, histopathological changes and reperfusion injuries were lower in the PRP group as compared to non PRP group.

Thus the workers concluded that PRP was effective for the prevention of ischemia and reperfusion damage in rat ovary [37].

4c) Refractory Endometrium and PRP

For obtaining success in ART role of Endometrium is of great value. Following inadequate ovarian stimulation might result in inadequate Endometrial growth, resulting in poor IVF/ICSI results. Different strategies have been suggested to improve Endometrial thickness (EMT), like low dose aspirin, pentoxifylline, vitamin E, Sildenafil, granulocyte–colony stimulating factor (G-CSF) are being used for endometrial expansion[38]. PRP being a novel therapy has been tried in such patients [39]. 8 Patients were included who underwent PRP treatment by Colombo et al [40]. Inclusion of patients was based on previous 3 cancelled cryo transfers in view of poor endometrial growth (<6mm), women with a negative hysteroscopy screening for Endometrial pathology and women with negative bacteriologic screening. Following PRP application, the ET was satisfactory in various cases. A positive test for β-HCG was found in 6 women. Thus, concluding that the multiple implantation failures were secondary to inefficient adhesion molecules expression, that could probably be improved by PRP application.

In the same way in a pilot study Zadehmodadarres et al [41] studied 10 patients with a history of cancelled cycles in view of inadequate endometrial growth (<7mm). An increase in ET was observed 48h following the first PRP application and reached >7mm following the 2nd PRP application in all patients. Then embryo transfer was done in all patients. Five patients got pregnant (50%), of which pregnancy progressed normally
in 4 of them. Thus concluding that PRP was effective for endometrial growth in patients having a thin endometrium.

Eftekhar et al [42] conducted a RCT, where 83 women with poor endometrial response to standard hormone therapy (HRT)(ET<7mm) on the 13th day of the cycle in a frozen thawed embryo transfer (FET) were entered in 2 groups. In PRP group (n=40), besides HRT, 0.5cc of PRP was infused into the uterine cavity on the 13th day of the HRT cycle. The control group (n=43) only received HRT. If ET did not increase 48h later, a repeat PRP infusion was repeated in the same cycle. Once ET reached >7mm embryo transfer was done. Finally the EMT, chemical, clinical, and ongoing pregnancy rates were compared between the two groups. EMT increased significantly to 8.67±.64 in PRP group than in controls (p=0.0001). This rise was >in women who conceived in PRP group (p=0.031). Implantation rate and per cycle clinical pregnancy rate were significantly higher in PRP group as compared to controls (p=0.001). This increase was higher in women conceiving following PRP group (p=0.031). The implantation rate and per cycle clinical pregnancy rates were significantly >in PRP group (p=0.002 and p=0.44), respectively. Thus concluding that PRP effectively improves endometrial growth and possibly pregnancy outcomes with a thin endometrium [42].

Similarly Chang et al [43] investigated the effects of PRP in women with thin endometrium in FET program. 64 patients with thin endometrium (<7mm) were recruited. PRP intrauterine infusion was given in PRP group during HRT cycles in FET cycles. Following PRP infusion, the EMT in PRP group was 7.65±.22mm, that was significantly thicker than the control group (6.52±.31) (p<0.05). Further cancellation rate of PRP cycles was lesser in contrast to control group (19.05% vs 41.18%, p<0.01). The implantation rate and clinical pregnancy rate in PRP group were significantly greater than those in the control group (27.94% vs 11.67%; p=0.05; 44.12% vs 20%p<0.05 respectively). PRP blood contained 4 fold higher transforming growth factor β(TGF-β), than peripheral blood (p=0.01). Thus concluding that PRP plays a positive role in promoting endometrium proliferation, improving embryo implantation rate and clinical pregnancy rate in women presenting with thin endometrium in FET cycles [43].

Jang et al [44] used an animal model, where investigation of role of PRP in the regeneration of the endometrium, along with reducing fibrosis was done in a murine model of endometrial damage, and the endometrium was damaged with the use of ethanol. Intrauterine delivery of autologous PRP stimulated and accelerated regeneration of the endometrium, along with reducing fibrosis, in this murine model of endometrial damage.

4D Repeated Implantation Failure(RIF) – Role of PRP

RIF by definition is a failure to conceive following several embryo transfers in IVF-ET cycles. Implantation involves multiple factors like embryo quality, endometrial receptivity, and immunological factors [45]. Various modalities have been suggested for the management of RIF, but little consensus is there regarding which is more efficacious. These include blastocyst transfer, assisted hatching, hysteroscopy, endometrium scratching along with immune therapy. Intrauterine infusion of PRP has been shown as a method by which endometrial growth and receptivity can be improved [34,46]. Nazari et al [47] enrolled 20 cases of RIF for examining the effectiveness of PRP in improving pregnancy rate. Inclusion criteria being age <40yrs, BMI<30kg/m². 6/20 cases (90%) became pregnant. 16 clinical pregnancies were recorded, and their pregnancies were ongoing at the time of this report. Thus a conclusion was drawn that PRP was effective in improving pregnancy outcomes in RIF patients. Kim et al [48] carried out a prospective interventional study where women giving a history of 2 or more failed IVF cycles and refractory thin endometrium were enrolled in their study. The main inclusion criteria were EMT <7mm after more than 2 cycles of previous medical therapy for increasing EMT, 24 women got enrolled in this study. The cases were treated with intrauterine infusion of autologous PRP 2 or 3 times from menstrual cycle day 10 of their FET cycle and ET was performed 3 days after the final autologous PRP infusion. 22 patients underwent FET and 2 patients were lost to follow up. The ongoing pregnancy rate and LBR were both 20%. The implantation rate and clinical pregnancy rate were 12.7% and 30% respectively and the difference was statistically significant. Average increase of EMT was 0.6mm compared with the EMT of the previous cycle. However the difference was not statistically significant. Further ET of 12 patients increased (mean difference 1.3 mm) while that of 7 patients decreased (mean difference-0.7mm). EMT of 1 patient did not change. No adverse effects were reported by patients treated with autologous PRP. They said that in all previous 4 studies published the
information on the type and concentration of PRP was not revealed. In their study platelet concentration of PRP ranged from \(717 \times 10^3\) to \(1565 \times 10^3/\mu\text{L}\) and the WBC concentration varied from \(24,000\) to \(37,000/\mu\text{L}\). Thus concluding that use of autologous PRP improved the implantation, pregnancy and live birth rates of the patients with refractory thin endometrium. They assumed that the ability of autologous PRP to restore the endometrial receptivity of damaged endometrium has some aspects other than increasing the EMT. The molecular basis of the treatment needs to be revealed in future studies [48].

Coksuer et al [49] aimed to evaluate the effect of intrauterine PRP treatment on FET cycles in patients with history of RIF and endometrium was unable to achieve optimal lining in cases of unexplained infertility. A retrospective analysis of charts of a total of 302 cycles performed in 273 patients attending Diyar Life Centre between January 2014 till January 2017. After excluding 232 cycles, they compared pregnancy outcomes of 34 patients who had suboptimal endometrial lining and only underwent FET. They found that EMT, was higher 48hrs following PRP as compared to EMT before PRP (10mm vs 6.25mm, \(p<0.001\)). Clinical pregnancy rate, and importantly LBR were also significantly higher in PRP group than the control group. Based on this, they demonstrated that intrauterine autologous PRP infusion is a safe, inexpensive adjuvant treatment for optimizing endometrium especially in patients with RIF history and besides improving lining autologous PRP infusion also improved success rates of IVF along with pregnancy outcomes [48]. Mehratza et al presented a retrospective cohort study that included 123 patients with history of more than 2 repeated failed ET’s. Cycles were divided into 2 groups of intrauterine infusion of PRP(n=67) and systemic administration of GCSF(n=56). Pregnancy outcome were compared between the 2 groups. The \(p\) value \(<0.05\) was considered statistically significant. The Clinical pregnancy rate was significantly higher in PRP group than the GCSF group(40.3\% vs 214\%, \(p=0.025\)). The crud and adjusted odds ratio (95\%CI were 2.5 and 2.6(\(p=0.025\), CI:1.11-5.53) and \(P=0.03\), CI:1.10-6.15 respectively. Thus concluding that intrauterine infusion of PRP can positively affect pregnancy outcome in RIF patients in comparison with systemic administration of GCSF and greater studies need to be designed to conclude the effectiveness of this method [50].

### 4E Role of PRP in human menstrual blood stem cells.

Haining Lv et al [51] reviewed how human menstrual blood can be used as a valuable source of menstrual blood derived stem cells (Men SC). Since Men SC come from body discharge as compared to SC’s from bone marrow and adipose tissue, hence obtaining them is noninvasive to the body, easy to collect, with no ethical concerns [50]. Thus Zhang et al [52] used Men SC’s cultured with 10\% activated PRP and compared these with 10\% fetal bovine serum(FBS). Differences in cell proliferation, differentiation, and endometrial receptivity-related gene expression were evaluated. 10\% activated PRP significantly promoted Men SC’s proliferation and adipogenic/osteogenic differentiation while suppressing apoptosis. Expression of the mesenchymal SC’s (MSC) marker CD 105 and the perivascular markers SUSD2 and CD146 were increased following PRP therapy. Furthermore, short term PRP Stimulation activated the phosphorylation of Akt and signal transducer and activator of transcription 3(STAT3) Pathways, upregulated expression of FoxO1, LIF, and IL-1β and downregulated IL-6. Thus concluding that PRP could promote Men SC proliferation, markedly increase stemness and evaluate Men SC function by enhancing the expression of angiogenesis and endometrial receptivity markers, suggesting its potential use as a promising supplement for Men SCs in endometrial regenerative medicine. There results give a theoretical ground for the clinical application of cotransplantation of PRP combined with Men SC [52].

Further Zhang et al [53] used rat IUI models, where they caused intrauterine mechanical injury. Nine days later, all rats were randomly assigned to 4 groups who received different treatment protocols: placebo; Men SC transplantation, PRP transplantation and Men SC + PRP transplantation. The traces of Men SCs were tracked with GFP label. Endometrial morphology and pathology, tissue proliferation, inflammation, pregnancy outcomes and the mechanism of Men SCs in the regeneration of endometrium were investigated. At day 9 and 18 post treatment Men SC transplantation, significantly improved Endometrial proliferation, angiogenesis and morphology recovery and reduced collagen fibres and inflammation in the uterus. Men SCs had lesion chemotaxis, colonized around the Endometrial glands. Gene expression of human derived secretory protein IGF1, SDF1, and TSP1 was detected in the uterus that received Men SCs on day 18. The 3 treatments can all improve fertility in IUI rats. Furthermore the Gene expression of cell proliferation, developmental processes and other biological processes were induced in Men SCs transplantation group. Hippo signaling pathway was the most significantly changed pathway and the downstream factors CTGF,
Wnt5a and Gdf5 were significantly regulated in treatment groups. PRP enhanced these parameters through a synergistic effect. Thus concluding Men SCs could effectively improve uterine proliferation, markedly accelerate endometrial damage reparations and promote fertility restoration in IUA rats, suggesting a paracrine restorative effect of Hippo signaling pathway stimulation. Their results indicated Men SCs, a valuable source of cells for transplantation in the treatment of intrauterine adhesion. Combined with PRP, this cell therapy was more effective [53].

5) Aesthetic Gynaecology –Role of PRP

5A) Breast Reconstruction
In the field of Aesthetic and plastic surgery, although all were pilot studies had small samples, or used animal models. Use of PRP along with adipose tissue has been used in breast reconstruction [54]. 100 Patients between the age of 19-60 yrs who were affected by breast soft tissue defects were included by Gentile et al [55]. Patients were divided into 2 equally sized groups. The study group were treated with fat grafting and PRP, while the control group received fat grafting injections only. The study group where autologous PRP was used to treat fat grafting, displayed a 69% maintenance rate of the restored contour and of 3 dimensional volume after 1 year, while a proportion of patients in the control group i.e.39% only demonstrated maintenance rate. Thus a conclusion drawn was that PRP mixed with fat grafts caused improvement in the maintenance of breast volume in patients affected by breast soft tissue defects. Similar findings were shown by Salgarello et al [56].

5B) Female Sexual Dysfunction –Role of PRP
Around 35 growth factors are released from platelets which promote tissue regrowth, healing and regeneration. This property has been utilized by Aesthetic Gynecologists like in vaginal rejuvenation and O-shot therapy [57].

i) O-shot therapy-Utilization of PRP in sexual dysfunction has been considered a revolutionary new nonsurgical OPD therapy which helps in improvement of both urinary incontinence and sexual dysfunction through using a woman’s own growth factors. Specific areas of vagina are injected with the help of a local anaesthetic cream. This method is known as ‘O-shot’. PRP activates tissue regeneration immediately, with dramatic enhancement of sexual response. The response expected is improved arousal, stronger orgasm, reduced dyspareunia along with natural lubrication [58].

11 women presenting with dyspareunia were recruited by Runals et al [59]. PRP was injected into the clitoris and observed that intravaginal and intraclitoral injection might be an efficacious modality for treating sexual dysfunction, especially in the areas of desire, arousal, lubrication and orgasm.

ii) Vaginal rejuvenation.
Aesthetic gynecologists have utilized PRP for the rejuvenation of vaginal mucosa, muscles, and skin. Following PRP injection, increase in vaginal vascularity is improved, with a dramatic increase in sensitivity. Additionally the skin becomes thicker and firmer, making the vagina look more youthful. Furthermore, the ligaments and muscles supporting the urethra become firmer, alleviating urinary incontinence [60]. Further Kim et al [61] published the use of PRP for the rejuvenation of vagina. Their conclusions were that application of autologous lipofilling mixed with PRP in patients with vaginal atrophy induced relief of symptoms and contour restoration. The appearance of rejuvenated external genitalia provided a pleasing cosmetic result for the patients.

6. PROM-Role of PRP.
PROM results secondary to damage and tears in the fetal membranes, resulting in congenital infections along with poor neonatal outcomes. In an in vitromodel for examining the ability of PRP for sealing iatrogenic fetal membrane defects PRP was tried by Lewi et al [62]. They used single and double layer animal models. PRP plug was found to be stable and attached firmly to the tear in amnion. Thus, the researchers concluded that they found experimental evidence that a PRP plug persisted for practically 2 mths in an amniotic fluid environment. It also gave a waterproof sealing of iatrogenic defects in the amnion and chorion. Furthermore PRP stimulates cell growth and proliferation, and may thus enhance the membrane healing response.
CONCLUSIONS

Thus autologous PRP has become an attractive nonsurgical option for a broad spectrum of medical disorders including gynecology in view of it being a noninvasive, affordable, simple, easy to perform and being effective with the idea that platelets are the normal products of blood involved in achieving haemostasis at the time of bleeding with their ability to release multiple growth factors and other substances. This review has reviewed how we can utilize it for wound healing like in LSCS, refractory cases of lichen sclerosus, recurrent implantation failures (RIF) with or without thin endometrium. It seems to be giving a new ray of hope for those who have very poor ovarian reserve or in cases of POF although in budding stage, it might become an alternative for those who do not want to undergo donor ivf. Further this might also obviate the need for an IVF with natural conceptions reported following this in those where previous >= 3 ivf had failed in view of poor ovarian reserve. Patients having endometrium destroyed secondary to tuberculosis or other causes of severe resistant Asherman’s syndrome where along with menstrual stem cells combined with PRP might help in regaining natural endometrial growth and subsequent pregnancy. The risks of PRP with regard to infection bleeding and nerve damage seemed to be minimal. Only till now most studies have been case studies, pilot studies and thus large randomized trials are needed for it to become a permanent therapy for these refractory cases.

REFERENCES

et al


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