Advances of Platelet-Rich Plasma in Female Infertility

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Abstract: As a critical complex of autologous endogenous growth factors, platelet-rich plasma (PRP) has biological functions such as promoting tissue repair, regeneration, angiogenesis, anti-inflammatory, immune regulation and so on. PRP is used in various clinical fields, as its application continues to expand, gradually introduced into the field of female reproduction. In recent years, an enormous number of literatures have been reported at home and abroad that, PRP therapy, serving as a novel assisted reproductive technology, has achieved certain advancements in the treatment of female infertility. Platelet-rich plasma holds definite potential in the realm of infertility treatment. It can promote tissue repair, improve reproductive system function, and bring new hope for infertility patients. To provide a new direction for the studies and therapeutic strategies of female infertility, this review summarizes the functions and related mechanisms of PRP in clinical practice, as well as recent advances of PRP for the treatment of female infertility.

Keywords: Platelet-Rich Plasma; Reproductive Medicine; Assisted Reproductive Technology; Female Infertility; Recurrent Implantation Failure

1. Introduction

Platelet-rich plasma is a blood component separated from one's own whole blood by centrifugation and is a plasma with a high platelet concentration. PRP is rich in a variety of proteins, growth factors and other active substances, which can regulate cell biological activity, promote cell division, proliferation and migration, improve local biological microenvironment, promote wound healing, tissue repair, and form new matrix [1]. PRP technology has attracted extensive attention in clinical application due to its advantages of straightforward operation, safety, minimally invasive and economy. For example, PRP has become an emerging treatment method in reproductive medicine, orthopedics, heart surgery, plastic surgery, dermatology, stomatology, wound treatment and other medical fields [2]. The problem of female infertility is becoming more and more prominent in modern society, which brings great physiological and psychological pressure to many couples. Platelet-rich plasma therapy is to collect the patient's own platelet-rich plasma, after special treatment, perfusion into the ovary or endometrial, in order to promote the recovery of ovarian function and the improvement of the endometrial environment, thereby increasing the chance of conception. After basic theoretical research and clinical application, PRP can effectively help cure related diseases that are not effective with conventional treatment, and introduce a new safe and effective autologous biological material for female infertility treatment.

2 Effects of PRP

In clinical transfusion medicine, platelet transfusion is usually used to treat patients with thrombocytopenia or platelet dysfunction. In the process of natural wound healing, platelets are stimulated by the outside world to play their adhesion and aggregation functions and form primary hemostatic thrombus. Domestic and foreign scholars have found that platelets contain α-particles, which release a variety of growth factors (GFs) when activated and ruptured. Such as transforming GFs (TGFs), epidermal GFs (EGFs), platelet-derived GFs (PDGFs), insulin-like GFs (IGFs), vascular endothelial growth factor (VEGFs), etc. Among them, PDGFs mainly promote cell proliferation by mediating cell mitosis, PDGFs in PRP can stimulate the proliferation of adipose

mesenchymal stem cells in vitro through signal transduction. VEGFs can promote the propagation and translocation of bone marrow-derived mesenchymal stem cells (BM-MSCs), stimulate the differentiation of BM-MSCs into endothelium-like cells, and protect BM-MSCs from endoplasmic reticulum stress-induced apoptosis [3].

These cytokines can coordinate the regulation of cell biological activity, promote cell division, proliferation and migration, improve the local biological microenvironment, and then promote wound healing, tissue repair and formation of new matrix [1]. In addition, the leukocyte components of PRP have anti-inflammatory functions, such as neutrophils have chemotactic, phagocytic and bactericidal effects, which can clear local pathogens and necrotic tissues, help tissue repair and promote wound healing. Fibrinogen also plays an important role in PRP. It is soluble and can be converted into insoluble fibrin under a series of cascade reactions and enzymatic reactions (such as the action of thrombin). After the fibrin is transformed from monomer to polymer, the fibrin network is formed, that is, secondary hemostatic thrombin, which jointly promotes the tissue repair process. Therefore, the collection and preparation of autologous platelets can not only be transfused when needed, but also be widely used and developed in the field of regenerative medicine.

3. Preparation Requirements of PRP

For patients, PRP is a blood product used directly for treatment, and its safety must be strictly guaranteed. The preparation technology of PRP has the characteristics of strong professionalism, high risk and high safety requirements, and has extremely high requirements for the qualification of relevant personnel, medical devices and consumables, collection and preparation environment, and product quality control. There are many methods to prepare PRP, from the early stage to the present stage through test tube method, set method, blood bag method, monopexy method. In terms of ensuring patient safety, different collection methods have differences that cannot be ignored. In 2017, the International Cellular Medicine Society (ICMS) published guidelines for the application of PRP, which clearly stated that PRP should be obtained by an independent, autologous blood dedicated separation device, with a closed system preferred to prevent blood exposure to air. In the years that followed, several international experts pointed out that PRP collection using a blood component separator was the only way in order to obtain repeatable PRP, to ensure that PRP products possess standardized platelet and white blood cell concentrations could only be obtained with apheresis [4]. Therefore, PRP collection by blood component separator is the preferred preparation method, disposable plastic blood bags and PRP special separation kits are alternative methods, and test-tube collection is not recommended.

4. Clinical Application of PRP

With the rapid development of PRP research by domestic and foreign scholars, the application of PRP covers many clinical disciplines, such as orthopedics, surgery, reproductive medicine, wound treatment, cosmetic plastic surgery and other fields, providing new and effective treatment methods for diseases that are difficult to cure by traditional drugs.

4.1 Orthopedics

There have been reports regarding the treatment of diseases like osteoarthritis, cartilage tissue lesions, and ligament repair using PRP in recent years. Bone healing and remodeling is a process in which multiple cell factors such as bone morphogenetic proteins (BMPs), PDGFs, VEGFs, TGFs, IGFs and fibroblast growth factors (FGFs) participate synergistically [5]. PRP rich in these factors can accelerate the healing of bones and surrounding tissues. After injecting PRP into damaged cartilage, ligaments, tendons, muscles, and joints, it not only repairs and regenerates cells, improves the local inflammatory response, relieves joint pain, but also improves joint function. Compared with traditional therapies such as corticosteroids, PRP has the advantages of low side effects, good effectiveness, and high safety, which greatly improves the satisfaction rate of patients.

4.2 Wound Healing

PRP also shows strong efficacy in the problem of wound healing and regeneration. Wound healing has always been the focal point and a major challenge in the field of tissue repair and regenerative medicine, and is a biological activity in which multiple cells, extracellular matrix, growth factors, and cytokines participate synergistically. Hemostasis, inflammation,

proliferation, and remodeling, these four stages develop gradually and overlap with each other. With the rapid development of regenerative medicine in recent years, the application of cells and their derived products for wound treatment has achieved remarkable results [6]. Owing to its high concentration of platelets, leukocytes, and fibrinogen, PRP meets the conditions required for the wound repair process. For example, for common diabetic ulcers in clinical practice, many studies and randomized controlled trials have shown that PRP holds the potential to facilitate the healing of diabetic ulcers and enhance the quality of life of patients [7].

4.3 Cosmetic Plastic Surgery

In recent years, due to the outstanding tissue repair and cell regeneration ability of PRP, it has become one of the research hotspots in plastic surgery. After injecting PRP into aging tissues, various GFs and cytokines secreted by PRP combine with their respective receptors to promote the proliferation of skin fibroblasts, promote angiogenesis, cell migration, extracellular matrix remodeling, and thereby promote the generation of new collagen, hyaluronic acid, etc. Hyaluronic acid absorbs water and causes the matrix to swell, enhancing skin elasticity and reducing tissue edema, thereby achieving the purpose of tissue regeneration and anti-aging [8]. Injecting PRP intradermally or subcutaneously into the skin around the hair follicle, a variety of autologous growth factors possess the ability to stimulate the proliferation and differentiation of dermal papilla cells and the formation of hair follicles. Many research results show that PRP is also very safe and effective in the treatment of alopecia areata and hair loss [9].

5. Clinical Application of Platelet-Rich Plasma in the Management of Female Infertility

5.1 Improving Ovarian Function

Some women are infertile due to accelerated ovarian senescence. These women exhibit suboptimal ovarian reserve function and produce very few oocytes after stimulation with gonadotropins (Gn), so they are diagnosed with poor ovarian response (POR). POR is more prevalent among women over 40 years old, mainly manifested as fewer follicles developing during the ovarian stimulation cycle, a low peak estrogen level in blood, a high dosage of Gn, a high cycle cancellation rate coupled with a low clinical pregnancy rate, etc. [10]. For the purpose of more effectively promoting follicle activation, augmenting the number of eggs, and enhancing the result of in vitro fertilization, the minimally invasive therapy of intraovarian perfusion of PRP shows good efficacy. A considerable number of studies have demonstrated that platelet-rich plasma therapy can improve the ovarian responsiveness and the quality of follicular development, thereby increasing the chance of conception. Yigit's team included 510 POR patients in the study. After injecting PRP into the ovaries, 22 of them conceived naturally, and 367 (77.5%) of the 474 who underwent in vitro fertilization (IVF) obtained at least one mature oocyte [11]. PRP treatment can improve the hormone level of POR patients, promote the maturation of oocytes, increase the yield of oocytes, promote the development and discharge of follicles, augment the quantity of embryos in both the cleavage stage and blastocyst stage, thereby improving the poor ovarian reserve status and poor pregnancy outcome of POR women, and achieving ovarian rejuvenation [12].

For women suffering from premature ovarian insufficiency (POI) or premature ovarian failure, PRP treatment is beneficial in promoting the restoration of ovarian function and ameliorating infertility [13]. POI is a symptom of gonadal dysfunction in women under 40 years old, manifested as secondary amenorrhea, uterine atrophy, and infertility, often accompanied by night sweats, insomnia, memory loss and other perimenopausal symptoms. At present, there are many treatment methods for POI, but the effect is not good. PRP is capable of releasing a diverse array of cytokines and growth factors for the purpose of regulating cell proliferation, differentiation, stimulate the regeneration and repair of ovarian tissue, induce the expression of estrogen receptor genes, and increase the hormone secretion level of the ovaries. Hsu et al. reported a case of a 37-year-old patient with POI, who had secondary amenorrhea for six months, who was treated with intraovarian injection of PRP and Gn. After two menstrual cycles, a sum total of six oocytes were retrieved, and finally fertilized by intracytoplasmic sperm injection (ICSI) and successfully gave birth to a pair of twins [14]. Murat et al. used intraperitoneal perfusion of PRP to treat a mouse model of

ovarian ischemia injury and found that PRP has a certain preventive and protective effect on the damage caused by ovarian ischemia-reperfusion [15].

5.2 Improving the Endometrial Environment

Successful embryo implantation is contingent upon several factors, not only high-quality embryos, but also a healthy uterus. In assisted reproductive technology (ART), the endometrium is a research object of great concern. The endometrium is an important membranous layer that constitutes the inner wall of the uterus. It is highly sensitive to estrogen and progesterone and can undergo significant changes with the fluctuation of the sexual cycle. The microenvironment formed by endometrial cytokines can affect endometrial receptivity, regulate decidualization, embryo adhesion, trophoblast infiltration, vascular remodeling, etc., and is an important determinant of embryo implantation and later survival [16]. Therefore, in clinical practice, the endometrial environment needs to be monitored daily before embryo implantation to meet the requirements for implantation. The potential of PRP in improving the endometrial environment, and the repairing effect of PRP on the endometrium is mainly reflected in the following aspects.

For women with thin endometrium, combined with previous studies, PRP uterine perfusion is considered to be the newest and most effective treatment plan to improve endometrial thickness [17]. This is because PRP treatment can improve the hemodynamic parameters and vascular density of the endometrium, stimulate angiogenesis, improve the blood supply to the endometrium, increase the thickness and nutrition of the endometrium, thereby improving the success rate of embryo implantation. Colombo's team implemented PRP treatment on 8 patients with thin endometrium (less than 6mm), multiple transplant failures with traditional therapies, and negative endometrial pathology and bacterial screening. After the treatment, the endometrial thickness of 7 patients exceeded 6.5mm (average 6.9mm), meeting the transplantation requirements, and 6 patients had positive β-HCG after transplantation [18]. Kim et al. proposed that autologous PRP treatment has the potential to enhance the implantation rate, pregnancy rate and embryo survival rate of patients with refractory thin endometrium [19]. Their study included 24 patients suffering from refractory thin endometrium who had failed IVF more than 2 times. PRP was infused into the uterus two to three times according to the transplantation cycle, and frozen embryo transfer (FET) was carried out on the third day after the last PRP infusion. After the injection, the average endometrial thickness of the patients increased by 0.6mm, 12 of them thickened by 1.2mm, and the final clinical pregnancy rate increased to 30% without adverse reactions throughout the process [19]. Lusine's team showed through in vitro experiments that PRP participates in the regeneration of endometrial cells, such as human endometrial stromal fibroblasts (eSF), endometrial mesenchymal stem cells (eMSC), BM-MSC, and the proliferation and differentiation of endometrial adenocarcinoma cells, explaining why PRP can effectively improve the poor growth of the endometrium and promote the healing of intrauterine scars [20].

Platelet-rich plasma therapy can effectively alleviate the pain symptoms of patients with endometriosis. The growth factors in PRP have anti-inflammatory and repairing effects, can alleviate the inflammatory response caused by endometriosis, improve the pathological state of endometriotic foci, and increase the chance of conception [21]. PRP treatment can also effectively improve the endometrial receptivity of patients with intra-uterine adhesions (IUA). Chang's team included 6 IUA patients in a self-controlled study to compare the differences before and after PRP uterine perfusion. The study found that after PRP treatment, the levels of endometrial uNK cells, CD8+ T cells, and Th1 cells (the increase in the number of these immune cells often leads to pregnancy failure) were markedly lower than those prior to treatment, and the microbial components were also improved, proving that PRP is beneficial to regulating the immune environment of the endometrium and enhancing endometrial receptivity [22]. For IUA patients after hysteroscopic adhesiolysis, PRP intervention can effectively reduce the IUA grade, improve the duration of menstruation and the amount of menstruation [23]. Ebraheem et al. included 260 patients (132 participants in the PRP treatment group and 128 participants in the control group) in a randomized controlled trial, and after meta-analysis. It was found that in the group treated with platelet-rich plasma (PRP), there

was a significant reduction in IUA grade. Additionally, the number of menstrual days was prolonged and the amount of menstruation was increased. This significantly improves the prognosis of IUA patients and promotes the recovery of the intrauterine pregnancy environment for such patients [23].

Assisted reproductive technology has been developed for more than 40 years, which has improved the rate of clinical pregnancy of infertile women, but there are still some patients who have not become pregnant after multiple transfers of high-quality embryos. Today, 20% of patients those who undergo IVF encounter recurrent implantation failure (RIF) and recurrent abortion. [24]. RIF has become a bottleneck problem that hinders the further improvement of pregnancy rate, and is a difficult point and research focus in the field of reproductive medicine.

The causes of RIF are complex and diverse, including but not limited to embryo defects, physiological or pathological disorders of hormone levels during implantation and pregnancy, decreased endometrial tolerance, abnormal uterine anatomy, and uterine immune environment disorders [25]. Studies have shown that platelet-rich plasma can serve as an adjunctive therapy during IVF-FET to improve embryo quality and implantation rate and reduce the risk of embryo implantation failure [26]. Mustapha's team systematically reviewed a variety of treatment strategies for RIF and found that deploying activated peripheral blood mononuclear cells (PBMCs) or activating PRP represents a promising alternative. Because the immune system is the key to establish uterine tolerance and promote pregnancy, both of which can effectively improve the endometrial immune dysfunction after implantation [24]. Other studies have shown that one of the reasons for repeated planting failure is the low expression of cell adhesion molecules (CAM), and the application of PRP can improve the level of CAM molecules [17]. The Leila team indicated that PRP could significantly improve the pregnancy outcome of RIF patients. In this study, 20 RIF patients were recruited as candidates for frozen embryo transfer, and intrauterine PRP treatment was given 48 hours before implantation. 18 of them were successfully implanted, and 16 of them obtained clinical pregnancy [27]. Kong et al. carried out a horizontal comparison of the effectiveness of four types of intrauterine infusion drugs for patients with RIF [28]. The four drugs include human chorionic gonadotropin (HCG), granulocyte colony-stimulating factor (G-CSF), PBMCs, and PRP. This study used meta-analysis to analyze the rate of clinical pregnancy and live birth of RIF patients with a statistical sample size of 2917 cases. The study showed that all four drugs increased pregnancy rates, but only PRP significantly increased live birth rates, followed by PBMCs. Results indicated that the four intrauterine infusion drugs could enhance the pregnancy outcome of patients with RIF to different extents. Among them, PRP had the most optimal effect [28].

6. Summary and Prospect

Female infertility is a common health problem, which brings great economic burden to the patient's family and physical and mental trauma to the couple, so it has been paid more and more attention by the academic circle. As a self-derived preparation, platelet-rich plasma has the advantages of simple operation, non-trauma and no side effects, which can effectively improve the fertility outcome of infertile women, but also avoid the risk of infection and allergic reaction. As a new assisted reproductive technology, PRP treatment brings new hope to the majority of infertility patients. It should be emphasized that although PRP treatment shows some potential in addressing female infertility issues, it is currently in the stage of research and practice. More clinical studies are required to confirm its safety and efficacy and to determine the optimal treatment options and indications. In addition, platelet-rich plasma therapy is not suitable for all infertility patients, and it is necessary to evaluate and select the appropriate treatment method on an individual basis. Although PRP has made remarkable progress in more and more infertility treatments, its exact molecular mechanism is still unknown for researchers to explore. Since Platelet-rich Plasma (PRP) is abundant in active cells and cytokines, it is significantly influenced by external factors such as anticoagulants, activators, storage time, temperature, and storage solution. To enable PRP to play its role to the fullest extent possible, strict control should be exercised in its preparation, storage, and injection processes. Moreover, the standardization and normalization of PRP technology should be strengthened. This will

make the application of PRP more scientific and ensure its more sustainable development.

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