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Analysis of the Application Value and Safety of Intrauterine PRP in RIF

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Abstract

Recurrent Implantation Failure (RIF) affects approximately 10% of *in vitro* fertilization-embryo transfer (IVF-ET) patients worldwide, posing a significant challenge for reproductive physicians globally. Its etiology is complex and diverse, with maternal factors being paramount, particularly endometrial receptivity (ER). Platelet-rich plasma (PRP), an emerging regenerative medicine therapy, is rich in growth factors and cytokines. Studies have shown that intrauterine PRP infusion can improve endometrial condition and increase embryo implantation rates. This article systematically reviews the application value and safety of intrauterine PRP in RIF patients.

Keywords

Platelet-Rich Plasma, Assisted Reproductive Technology, Recurrent Implantation Failure, Endometrial Receptivity, Controversy

1. Introduction

Recurrent implantation failure (RIF) typically refers to the failure to achieve clinical pregnancy despite undergoing multiple embryo transfer cycles and having transferred a cumulative number of high-quality embryos. Due to its complex nature, there is currently no unified definition or diagnostic criteria for RIF both domestically and internationally. However, it is generally accepted that RIF is defined as the inability to achieve clinical pregnancy after transferring at least three high-quality embryos across three fresh or frozen cycles [1]. In 2023, the European Society of Human Reproduction and Embryology (ESHRE) proposed defining RIF as the failure to obtain a positive pregnancy result after transferring a sufficient number of viable embryos in specific patients, necessitating further examination and/or intervention measures. ESHRE also recommended setting different

cumulative embryo transfer threshold values for patients with various conditions, such as different ages and embryo chromosomal statuses [2]. RIF affects approximately 10% of patients undergoing *In Vitro* Fertilization and Embryo Transfer (IVF-ET) [1]. The etiology of RIF is complex, encompassing maternal factors, male factors, and embryonic factors, with the primary contributors being embryo quality and maternal endometrial receptivity. Studies have shown that poor endometrial receptivity can lead to implantation failure in approximately two-thirds of transferred embryos [3]. Intrauterine perfusion is a procedure that involves inserting a transfer catheter through the vagina into the cervix to infuse contents into the patient's uterine cavity. Recent clinical studies have demonstrated that intrauterine perfusion of medicinal solutions can enhance endometrial receptivity by increasing endometrial thickness and regulating the endometrial microenvironment [4]. Platelet-rich plasma (PRP), derived from autologous blood, is rich in platelet-derived growth factors, vascular endothelial growth factors, epidermal growth factors, and other substances [5]. It possesses functions such as promoting cell proliferation, angiogenesis, and tissue repair, and has been widely used in clinical departments such as wound repair, orthopedics, and ophthalmology, as well as in the field of reproductive medicine. This article analyzes the application value and safety of intrauterine perfusion of PRP in RIF.

2. The Application Value of PRP Intrauterine Perfusion in RIF

2.1. Improving Endometrial Receptivity

Endometrial thickness is an important indicator commonly used to evaluate endometrial receptivity [6]. PRP enhances the proliferation and migration of endometrial-related cells, regulates the expression of matrix metalloproteinases, inflammatory factors, chemokines, and growth factor receptors, thereby providing support for endometrial regeneration [7]. Single growth factors in PRP do not exert effects independently; instead, the synergistic or antagonistic interactions among multiple growth factors collectively act on target cells to produce the overall effect. For example, factors such as platelet-derived growth factor-BB (PDGF-BB), epidermal growth factor (EGF), and fibroblast growth factor-2 (FGF-2) can bind to receptors on the surface of endometrial stromal cells, rapidly activating signaling pathways such as ERK1/2 and PI3K/Akt that are essential for inducing migration, thereby promoting cell migration and rapid proliferation [8]. Uterine angiogenesis can also influence endometrial receptivity. PRP promotes endometrial regeneration and remodeling in mice by upregulating the expression of multiple pro-angiogenic factors (such as Hif1α and Hif2α) in the uterus, inducing the expression of vascular endothelial growth factor, and modulating angiogenesis switches, vascular permeability, as well as endothelial cell migration and proliferation [9]. Some studies have shown that PRP intracavitary infusion can promote the formation of endometrial spiral arteries, accelerate endometrial growth and synchronization with embryo development, and improve endometrial receptivity

[10]. In a clinical controlled study conducted by Chang Yajie *et al.* [11], the endometrial thickness on the day of progesterone administration in patients receiving PRP intracavitary infusion reached 7.56 ± 0.38 mm, which was significantly higher than the 6.41 ± 0.36 mm in the control group. Additionally, the biochemical pregnancy rate, embryo implantation rate, and clinical pregnancy rate were markedly elevated compared to the control group. The most valuable reference to date is the meta-analysis published by Arezoo Maleki-Hagiagha *et al.* [12]. Compared to the control group, patients receiving PRP intracavitary infusion exhibited a significant increase in endometrial thickness (SMD: 1.79, 95% CI: 1.13 to 2.44; $P < 0.001$, $I^2 = 64\%$), with a mean difference of 0.94 mm (MD: 0.94 mm, 95% CI: 0.44 to 1.44; $P < 0.001$, $I^2 = 88\%$). Both the embryo implantation rate and clinical pregnancy rate were significantly improved.

2.2. Improve the Endometrial Immune Environment

Chronic endometritis is a long-standing mild inflammation of the endometrium. It often presents without symptoms or with only mild discomfort, making diagnosis challenging and resulting in a low diagnostic rate for endometritis [13] [14]. Chronic endometritis can lead to a decline in endometrial receptivity and is associated with reduced pregnancy rates and recurrent implantation failure in women undergoing assisted reproductive technology [14] [15]. Studies have shown that PRP releases several anti-inflammatory factors, such as VEGF, TGF-β, PDGF, and IL-8, which can effectively reduce uterine inflammatory responses through immune modulation mechanisms, including inhibiting inflammatory reactions and protecting cells from damage [16] [17]. In one study, PRP intrauterine perfusion was performed on five infertile women with chronic endometritis, and all cases achieved clinical pregnancy after embryo transfer [18].

The endometrium contains abundant immune cells, primarily natural killer cells (uNK), T cells, macrophages, and dendritic cells (DCs). In patients with recurrent implantation failure (RIF), the proportion of Th cells producing TNF-α and the Th1/Th2 cell ratio are significantly elevated [19]. Studies have shown that PRP improves the Th1/Th2 cytokine imbalance by upregulating Th2-type cytokine levels, shifting the overall balance toward Th2-type cytokines, and increasing endometrial thickness, which facilitates embryo implantation and thereby enhances pregnancy outcomes in RIF patients [20].

2.3. Improve Pregnancy Outcomes

In a small-scale study conducted by Nazari *et al.* in 2016 [21], 0.5 mL of PRP was intrauterinely perfused into 20 women with a history of RIF 48 hours prior to frozen embryo transfer. The results showed that 18 out of the 20 women conceived, achieving a remarkable pregnancy rate of 90%. In 2018, Nazari *et al.* expanded their research scope [22] and studied 97 cases of recurrent implantation failure. The results indicated that the clinical pregnancy rate in the PRP group was significantly higher than that in the control group (44.89% vs. 16.66%, P-value =

0.003). In 2021, Nazari *et al.* further expanded their research scope once again [23]. This study involved a controlled trial and data analysis of 393 patients with recurrent implantation failure, and the results also demonstrated that the clinical pregnancy rate in the PRP group was higher than that in the control group. Research findings from Kim, Zamaniyan, Hagiagha, Chen Zeyang, and others all suggest that the biochemical pregnancy rate and clinical pregnancy rate in the group receiving PRP intrauterine perfusion were significantly higher than those in the control group [12] [24] [25].

3. Controversy Surrounds the Application of PRP Intrauterine Perfusion in Recurrent Uterine Lavage (RIF)

Numerous clinical controlled studies and meta-analyses have demonstrated that intrauterine perfusion of PRP has a beneficial effect on improving uterine pregnancy outcomes in cases of RIF. However, some studies have yielded contradictory results. For instance, a randomized controlled study conducted by Allahveisi *et al.* [26] on 50 patients with RIF revealed no significant difference in pregnancy rates between the group receiving PRP intrauterine perfusion and the group receiving Lactated Ringer's solution intrauterine perfusion (all P-values > 0.05). The study concluded that the injection of platelet-rich plasma before frozen-thawed embryo transfer in women with recurrent implantation failure had no significant impact on pregnancy outcomes. Therefore, the use of intrauterine PRP perfusion remains controversial, and the possible reasons for this are discussed below.

3.1. Non-Uniform Definition of RIF

The definitions of RIF vary across studies (e.g., the number of embryos transferred, patient age), leading to differences in the enrolled populations. Although the European Society of Human Reproduction and Embryology (ESHRE) proposed new recommendations in 2023, the concept remains relatively broad. Given that most research findings were published prior to this, extensive in-depth studies and follow-up statistics, combined with clinical practice, are necessary to summarize and unify the concept of RIF.

3.2. PRP Preparation Methods and Component Concentrations

There are numerous methods for preparing PRP, but most studies provide insufficient details on the preparation protocols, including whole blood volume, whole blood platelet concentration, processing equipment, centrifugation parameters, and other aspects. Different preparation methods can lead to substantial variations in the concentrations of platelets, leukocytes, and growth factors in PRP [27]. Currently, there is a lack of standardization in PRP preparation methods [28], and most studies rarely mention the preparation protocols or component concentrations [29]. For instance, varying platelet concentrations may adversely affect cell growth [5], and excessive leukocytes can trigger inflammatory responses. At present, the double-centrifugation method is considered more advantageous for pre-

paring both autologous and allogeneic PRP, as it yields higher platelet quantities and recovery rates with reduced cellular contamination [30]. Nevertheless, further in-depth research into the molecular mechanisms of PRP is required to precisely determine its platelet concentrations and growth factor content, and to standardize the preparation process and component concentrations.

4. Safety Analysis of PRP Intracavitary Infusion Application in RIF

The preparation of PRP utilizes the patient's own blood, making it easy to obtain the raw materials, with extremely low risks of pregnancy complications, allogeneic immune rejection, and transmission of blood-borne diseases [31]. During the process of intracavitary infusion of PRP for treating recurrent implantation failure, there have been no reports of adverse events such as abdominal pain, fever, or pelvic inflammation to date.

5. Summary and Outlook

As a form of regenerative medicine, PRP is derived from autologous peripheral blood, offering high safety in terms of immune rejection and blood-borne disease transmission. It holds promising applications and research prospects in the reproductive field, providing a novel adjuvant therapeutic approach for treating RIF. By improving endometrial receptivity and modulating the endometrial immune environment, it effectively enhances pregnancy rates in RIF patients. However, factors such as the lack of a unified definition for RIF and the absence of standardization in PRP preparation methods and component concentrations have led to contradictory results in some studies.

In alignment with the 2023 ESHRE new recommendations, future research should prioritize the following directions: 1) Adopt standardized diagnostic criteria for RIF and establish stratified enrollment standards based on patient age, embryo chromosome status, and other factors to enhance study comparability; 2) Develop unified PRP preparation protocols, specifying centrifugation parameters for efficient methods like double centrifugation, platelet concentration thresholds, leukocyte control ranges, and concentrations of various growth factors to achieve component standardization; 3) Strengthen long-term safety follow-up by systematically monitoring the prolonged effects of adverse events such as infection and bleeding.

Through these measures, it is anticipated that the application value of PRP in RIF can be further clarified, promoting the standardization of its clinical use and improving pregnancy outcomes for more RIF patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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