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Mini Review Paper

Platelet Rich Plasma (PRP) Therapy: An Approach in Endometrium Regeneration

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ABSTRACT

PRP is autologous plasma produced from an individual's own blood. The blood is centrifuged and the platelets are separated, concentrated and mixed with some of the plasma and called Platelet Rich Plasma. After the shot of this mixture into the site of injury, the immune system works quickly and holds open the body healthy. Macrophages as a messenger activate local stem cells and begin to breed apparently which build the injured or damaged tissues. Recent days public awareness has been increased in the usage of PRP in the field of orthopedics, ophthalmology, injuries, tendons, surgery healings, and so forth but also behave as an abundant role in gynecology and infertility which takes an increasing order in basic and clinical research. PRP not only brings the solution which will overlay a way to treat endometrium thickness but can put an end to unnecessary medication, economic and emotional load in and among the twosomes.

Keywords: PRP, blood, plasma, endometrium, injuries

INTRODUCTION

A typical blood comprises 93% red blood cells, 6% platelets, and 1% white blood cells. [1] The platelets contain numerous growth factors which are involved in the process of healing and aid in the regeneration of cells. Platelets are small disc shaped cells with a life span of about 7–10 days. Platelets Rich Plasma (PRP) is a growth factor rich component obtained after fractionating the blood constituents and in simple terms can be termed as concentrated plasma component. The concentration of platelets and growth factors can be 5 to 10 times richer in PRP. It is estimated that 600 GFs are present in the PRP [2] which are responsible for attracting macrophages, mesenchymal stem cells, and osteoblasts; they promote the removal of necrotic tissue and enhance differentiation which are also responsible in tissue regeneration and repair [3] and healing mechanism. [4] PRP also includes three major proteins in blood, such as fibrin, fibronectin and vitronectin which act as cell adhesion molecules. [5]

The growth factors and cytokines present in PRP can also influence inflammation, infection, wound, muscle tear and soft tissue healing. [3, 6] The growth factors play a key role in wound healing and regenerative procedures; including chemotaxis, proliferation, differentiation, and angiogenesis. [7] These growth factors also involves in healing and attracting stem cells to restore the damaged area. [8] This plasma derived product is widely used in the treatment of nerve injury, ocular epithelial defects, alopecia, cardiac muscle injury,

osteoarthritis, tendonitis, blood loss, immunological and several metabolic disorders. [9-13] Its efficacies in obstetrics and gynecology are limited. [14-16] In this article we summarize most of the relevant studies conducted with platelet derived growth factors and the endometrium regeneration showing the importance of PRP in reproductive medicine.

Platelet derived growth factors and its role in endometrium repair

Cytokines and growth factors present in PRP include platelet derived epidermal growth factor (PD-EGF), platelet-derived growth factor (PDGF) A and B, transforming growth factor (TGF-β1), insulin-like growth factor (IGF-I, II), vascular endothelial growth factor (VEGF), endothelial cell growth factor (ECGF) and basic fibroblast growth factor (bFGF), connective tissue growth factor (CTGF) and interleukin 8 (IL-8) [16,17] are some of the growth factors present in the PRP. We have summarized the functions of the growth factors secreted by platelets in Table 1.

Table 1: Growth factors present in PRP and its functions

Growth factors in PRP	Functions
Platelet-derived growth factor (PDGF)	1. PDGF plays a role in blood vessel formation and also it regulates cell growth and division. [18] 2. PDGF helps in tissue remodeling and cellular differentiation. [18-20] PDGF helps in mesenchymal proliferation and directs the migration and differentiation. [20]
Transforming growth factor beta (TGF-β)	1. TGF-β controls proliferation and also plays an important role in embryonic development, cell growth, cellular differentiation, hormone secretion and immune function. [21] 2. It is an inducer of extracellular matrix proteins and has a potential use in female reproduction and development [22] 3. TGF-β1 shows expression levels in the uterus during embryo implantation [22] 4. TGF-β contributes in the reproductive process by enhancing endometrial proimplantatory Leukemia Inhibitory Factor (LIF). [23]
Vascular endothelial growth factor (VEGF)	1. VEGF stimulates angiogenesis and vasculogenesis and assists in the production of fallopian tube luminal epithelium, and may increase vascular permeability and modulate tubal luminal secretions [24] 2. It stimulates endothelial degradation and it helps in underlying basement membrane, migration into the surrounding tissue, proliferation and tube formation. [25] 3. VEGF is involved in the physiological processes of follicular development, corpus luteum formation, and uterine endometrial proliferation during the ovarian cycle. [26-28]
Interleukin 8 (IL-8)	1. Interleukin (IL) 8 attracts neutrophils, basophils, and T-cells during the inflammatory process and binds to specific cell surface receptors [29] 2. IL-8 plays a major part in infertility and is involved in mitogenesis, inhibition of angiogenesis, inflammation, chemotaxis, neutrophil degranulation, leukocyte activation and calcium homeostasis. [30]
Fibroblast Growth Factor (FGF)	1. FGF is involved in angiogenesis, wound healing, embryonic development, and various endocrine signaling pathways [31] 2. FGFs helps in the regulation of many developmental processes, including morphogenesis, differentiation, cell proliferation and migration during embryonic development [32, 33]
Insulin-Like Growth Factor 1 (IGF-1)	1. IGF-1 is found in plasma, tissue fluids and has an important role in steroidogenesis, metabolism, cell proliferation, differentiation and peripheral blood circulation. [34] 2. IGFs are produced in the liver; it bears on various reproductive processes and receives an essential role in the regulation of spermatogenesis. [35] 3. IGF-1 in the seminal fluid was found to possess a positive correlation with the number of motile cells and with progressive spermatozoa [36] 4. IGF-1 increase sperm motility by stimulating the production of spermatozoa in a paracrine/autocrine. [37]
Insulin-Like Growth Factor 2 (IGF-2)	1. IGF-2 is a growth promoting hormone during gestation and plays a central function in embryonic and fetal development. [38] 2. IGF2 promotes granulosa cell proliferation during the follicular stage of the menstrual cycle with follicle stimulating hormone (FSH) and helps in progesterone secretion during the luteal stage of the menstrual cycle after the ovulation along with luteinizing hormone (LH) [39]
Epidermal Growth Factor (EGF)	1. Epidermal growth factor is widely present in urine, saliva, milk, and plasma. It is also stimulated by testosterone. [40] This factor also accumulates in the follicle at the time of ovulation. [41] 2. EGF is identified in male reproductive tissues and fluids and plays a substantial part in the maintenance of spermatogenesis. [42]
Connective Tissue Growth Factor (CTGF)	1. CTGF plays an important role in cell adhesion, migration, proliferation, angiogenesis, skeletal development and tissue repair. [43] 2. CTGF is important for pancreatic beta cell development and ovarian follicle development. [44, 45] It helps in the development of corpus luteum development and follicle wall degradation which is essential for normal fertility. [45, 46]

Thin Endometrium and role in pregnancy

The endometrium is soft and spongy that is present inside of the uterus or womb. The ovary releases estrogen and thickens the

endometrium. In addition, the ovaries also secrete progesterone and support the embryo which leads to pregnancy. The endometrium will become thick when it is ready for pregnancy. The endometrium varies its thickness as part of the menstrual cycle, which frequently strikes out every month for women as a termination. If pregnancy did not go on, the hormonal level decreases and the stratum of the endometrium is shed as menstrual fluid. During the menstrual cycle, the endometrium undergoes changes at the structural, biochemical, and molecular levels. It is a significant factor in implantation and pregnancy therefore the rate of gestation is increased by the endometrial thickness. [46]

Several cases reported that the endometrial thickness below 6-9 mm had no success in their pregnancy. [47, 48] For a pregnancy or embryo transfer, the minimum endometrial thickness was reported to be 7 mm. [49] Endometrial thickness of less than 7 mm, the cycle will be canceled and this is associated with lower probability of clinical pregnancy for patients opting for assisted reproductive technology. [49] Low estradiol levels and poor vascularity may also contribute to poor endometrial growth. [50] The routine medical practice for assessing the endometrial thickness is high-resolution ultrasonography. Figure 1 demonstrates the methodology for PRP preparations and its applications in various fields.

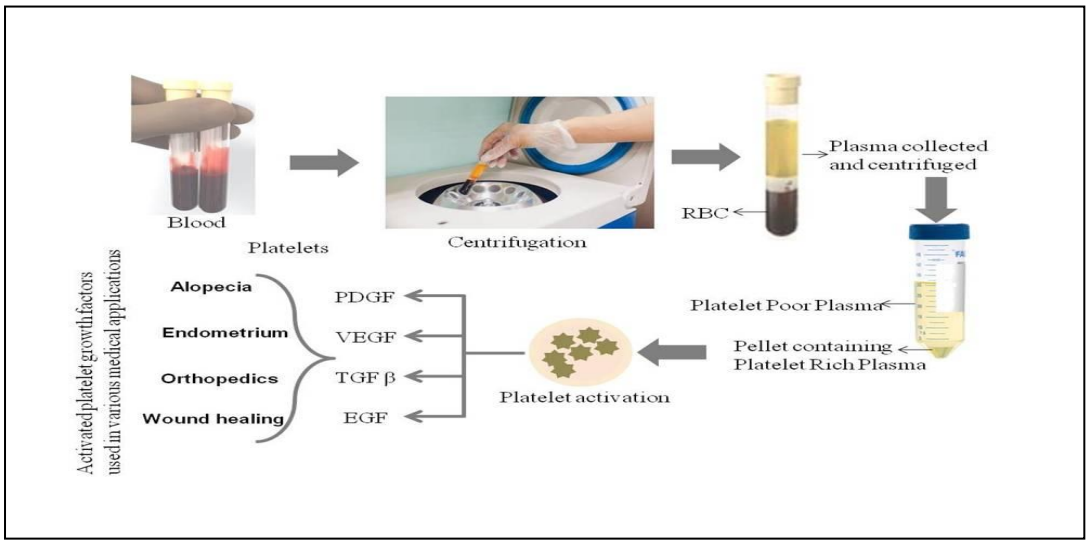

Figure 1 Protocol of Platelet Rich Plasma Preparation: Small amount of blood drawn from the patient and centrifuged to separate the Platelet Rich Plasma fractions. The separated PRP fractions on activation release various growth factors which are widely used in many medical applications like alopecia, endometrium regeneration, osteoarthritis and wound healing.

Studies on PRP and Endometrium thickness

Chang and team (2015) studied by infusing PRP, prepared from patient's own blood in 5 women (<7 mm) into the uterine cavity. Later after the application of PRP, the endometrial thickness was increased to >7 mm in all the patients, all became pregnant after successful Embryo Transfer (ET), out of one had missed abortion. [14]

In another independent study conducted by Zadehmodarres and team (2017), a total of 10 patients with a history of Frozen Embryo Transfer (FET) cancellation due to thin endometrium (<7 mm) was recruited into the study and resulted in adequate endometrial growth (>7 mm) after two PRP infusions, Embryo Transfer (ET) was done for all of them and five were pregnant. [46]

Tandulwadkar and team (2017) conducted a pilot study of PRP in 68 women. The study includes 68 women between 22 to 40 years, with sub optimal

endometrial growth and repeated cycle cancellations. As a result of administering autologous PRP, the endometrium had significant increment from 5 mm to 7.22 mm. As an outcome of ET, thirteen women passed second trimester, thirteen passed first trimester with healthy IUI pregnancy, and one had ectopic gestation, three with blighted ova, two missed abortions and two biochemical pregnancies. [51]

Chang and his team (2017) from Reproductive Medicine Center, China conducted a study with 34 patients in PRP group and 30 patients in control group during July 2015 to July 2016. After PRP infusion, the endometrium thickness increased in PRP group (7.65±0.22mm) compared to the control group (6.52±0.31mm). However, PRP group had less ET cancellation rate. [52]

Hounyoung Kim and his colleagues (2019) conducted a clinical trial with twenty four women with history of two or more failed IVF with thin endometrium. They were treated with autologous PRP, 2 or 3 times after their menstrual cycle and 22 out of 24 went frozen embryo transfer. As a result of ET, 12 patients had increase in endometrium thickness, while 7 patients had a decrease and the endometrium thickness of 1 patient did not change. However, the clinical pregnancy rate was reported as 30%. [53]

CONCLUSION

PRP therapy is widely applied in dissimilar fields of medicine including infertility. In that respect there is no exact mechanism showing how PRP works, but laboratory studies have indicated that the increased concentration of growth factors in PRP can accelerate up the healing procedure. But there is a need to study the efficacy of PRP which improves the pregnancy outcomes. The complex relationship among the multiple growth factors must be clearly studied and understood. The above studies suggest that PRP is effective for endometrial growth and also it could be a replacement for G-CSF, hormonal or hormonal therapies. PRP is produced from an autologous blood sample; it is more accessible and affordable with minimal risks of infectious diseases and immunological reactions. This treatment towards endometrial inadequateness will definitely pave a pathway for infertility caused by endometrial thinning. Therefore, a future research is mandatory to understand the mechanism of PRP and its effectiveness which can remodel the damaged tissue to a healthier state. However, there are several reports for improving endometrium thickness, a large clinical trial data will help us understand better on PRP and its regeneration mechanism.

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