

Is Platelet-rich plasma (PRP) the new wonder therapy for infertility?

Platelet-rich plasma (PRP) is an autologous blood-derived product with an increased concentration of platelets in plasma relative to whole blood, supporting its therapeutic effects¹. It has been integrated into numerous treatment regimens in various aspects of medicine, including orthopedics, cardiothoracic surgery, dermatology, dentistry and diabetic wound healing². While some of these uses are well established, many need to be reported more in the literature. Given the rise in the popularity of PRP, multiple clinical trials have been conducted to assess its application in various medical and surgical conditions. In addition, PRP is now becoming an area of interest in reproductive medicine, explicitly focusing on infertility². The term PRP was first used in the 1970s to describe plasma with an increased concentration of platelets than in peripheral blood³. In 1974, Kohler and Lipton, in studying fibroblast physiology, found that platelets could have significance as growth stimulants⁴. In the following years, further research indicated that platelets are a source of growth factors that stimulate fibroblast activity⁵. To obtain a clinical effect, platelets should be activated first by external factors and/or by the exposed collagen fibres of damaged tissues. The main advantage of using PRP is the autologous nature of the preparation; therefore, there is no risk of immune reaction and transmission of microorganisms from other donors⁶. Another significant advantage lies in its simple and fast practice (about 30 min from blood withdrawal to its application), and the preparation cost is low⁶.

Infertility is a global public health issue; about 13% of couples suffer from infertility. Implantation failure occurs, despite fertility clinics' efforts in assisted reproductive technology (ART); therefore, high-quality embryos and

adequate receptive endometrial growth are required for successful implantation⁷. Pregnancy rates can be increased by increasing the endometrial thickness (ET); the minimum thickness needed for implantation is seven mm⁸.

Advancements in reproductive medicine with the introduction of IVF have significantly impacted the increase in pregnancy rates. Endometrial receptivity is crucial for successful embryo implantation. Endometrial thickness indicates endometrial receptivity and is a prognostic marker for pregnancy outcome following embryo transfer⁹. However, despite these advancements, the management and treatment of thin endometrium have remained challenging in infertile patients who struggle with this condition^{10,11}. The incidence rate in women with thin endometrium is 2.4%¹². A thin endometrium (defined as an endometrial thickness of <7mm) is not optimal for embryo implantation and is associated with poor pregnancy outcomes, an increase in recurrent pregnancy loss, and an increase in embryo transfer failure¹³. Several therapies are currently being used to improve chances of implantation, such as extended estrogen therapy, low-dose aspirin, vitamin E, vaginal sildenafil, pentoxifylline, GCSF, and stem cell therapy^{10,11,13}. However, despite these interventions, many women with thin or damaged endometrial linings do not respond to these therapies. Several studies have evaluated autologous platelet-rich plasma (PRP) and its effects on infertility. PRP has been shown to play a role in tissue regeneration, angiogenesis, cell migration, differentiation, and proliferation, which are mediated by the numerous growth factors and cytokines PRP releases once activated. Specific growth factors and cytokines including transforming growth factor-beta, fibroblast growth factor, insulin-like growth factors 1 and 2,

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vascular endothelial growth factor, and epidermal growth factor⁹.

Autologous PRP is obtained by collecting an individual's whole blood via peripheral venipuncture that is then centrifuged to remove red blood cells from the sample¹⁴. This is to have a concentrated sample of platelets containing a 5- to 10-fold higher concentration of growth factors released by activated platelets. The general process of PRP preparation consists of collecting whole blood, initial centrifugation to separate and remove red blood cells from the sample, then use of one additional centrifugation to concentrate the platelets, and then adding a platelet agonist to activate the sample^{15,16}. Autologous PRP is a novel alternative to treating and managing specific infertility etiologies, especially in women refractory to standard therapy. It offers a low-cost, easily obtained therapeutic option to these patients. Although studies suggest that PRP has the potential to be promising in reproductive medicine through the demonstration of endometrial regeneration, restoration of the menstrual cycle, improving folliculogenesis, increasing endometrial receptivity, and increasing clinical pregnancy and live birth rate, there is a need for prospective randomized controlled trials with large sample sizes¹⁶. There are currently few ongoing RCTs worldwide evaluating the role of PRP in poor ovarian reserve, recurrent implantation failure, and thin endometrium in ART. In the current issue, an excellent prospective cohort study was conducted at Maltepe University, Center for Reproductive Medicine. The authors aim to investigate the efficacy of intrauterine administration of platelet-rich plasma (PRP) in a frozen-thawed embryo transfer (FET) cycle with a thin endometrium.

Intrauterine PRP administration was performed after hormonal therapy in patients whose cycles were previously cancelled due to thin endometrium. A total of 41 women participated in the study. Eighteen of them were in the PRP group (n: 18), and 23 of them formed the control group (n: 23). On the 11th day of hormone replacement therapy (HRT), intrauterine autologous PRP infusion was applied. At the beginning of the menstrual cycle, the control group's mean endometrial thickness (EMT) was 6.3 ± 0.5 mm, and the mean EMT of the PRP group was 6.2 ± 0.6 mm. Following the HRT, the mean EMT in control and PRP groups were 7.4 ± 0.8 mm and 8.4 ± 0.9 mm, respectively.

EMT increased by 1.1 ± 0.7 mm in the control group and 2.2 ± 0.8 mm in the PRP group. The increase in the EMT of the PRP group was statistically significant compared to the control group ($p < 0.05$). This study showed that intrauterine PRP administration significantly increases EMT. Moreover, PRP application increases the pregnancy rates in patients with thin endometrium, although this was not statistically confirmed.

Chang et al. were the first to use PRP in women with thin lining and found an increase in endometrial thickness and improved pregnancy outcome⁷. They analyzed five women who had all previously undergone IVF without success with standard hormonal therapy and poor endometrial response. Despite the increase in the doses of estradiol in all participants, the endometrial lining remained < 7 mm. Chang et al. reported an increase in endometrial thickness 4872 h after PRP infusion in all five women, which reached 7 mm by the day of progesterone administration. Many other studies were performed after Chang to determine PRP's utility in increasing endometrial thickness. Frantz et al. performed a retrospective analysis on 21 patients with a history of endometrium refracting from standard hormone therapy (endometrial lining not rising above 5 mm)¹⁷. If the endometrium did not reach 7 mm or above after 14 to 17 days of estradiol, they underwent intrauterine PRP infusion every second day for three infusions. Following the third PRP infusion, the patients were started on 800 mg per day of vaginal progesterone, and after the 5th day, their embryos were thawed and transferred¹⁷. There were 16 clinical pregnancies (66.7%), of which 13 resulted in ongoing pregnancies or live births (54%), and three ended in a miscarriage. The authors suggest that PRP improves intrauterine receptivity to embryo implantation, regardless of whether the endometrium reaches the appropriate growth for embryo transfer.

Although studies suggest that PRP has the potential to be promising in reproductive medicine through the demonstration of endometrial regeneration and an increase in endometrial thickness, there is a need for prospective randomized controlled trials with large sample sizes. In addition, there currently needs to be more ongoing RCTs worldwide evaluating the role of PRP in reproductive medicine. A standardized PRP preparation protocol is crucial to reproduce consistent and accurate results in all

future studies. Only when definitive large RCTs are available PRP use may gain popularity.

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