Study Protocol

The Comparative Study of Platelet Rich Plasma (PRP) and Plasma Rich in Growth factor (PRGF) in Endometrial Thickness, Implantation Rate and Pregnancy Outcomes in IVF Patients

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Abstract

Background: Platelet-rich plasma (PRP) and Plasma Rich in Growth Factors (PRGF) are promising regenerative therapies aimed at enhancing endometrial thickness and improving *in vitro* fertilization (IVF) outcomes. This study aims to assess the impact of PRP and PRGF on endometrial development, implantation success, and pregnancy rates in IVF patients. A total of 10 ml of venous blood will be drawn from participants and processed to isolate platelets. PRP will be prepared through centrifugation to concentrate platelets, while PRGF will be generated using a leukocyte-poor method and activated with calcium chloride. Endometrial thickness (EMT) will be measured via transvaginal ultrasound (TVS) on the fifth day of the menstrual cycle. If EMT is below 7 mm, PRP or PRGF will be administered, with additional treatments as needed. The study will compare endometrial response, implantation rates, clinical pregnancy rates, and live birth rates between the PRP and PRGF groups. Additionally, safety and potential side effects will be closely monitored to ensure patient well-being. **Objectives:** The study will assess the impact of PRP and PRGF on endometrial thickness and compare pregnancy outcomes, including clinical pregnancy rates in patients treated with either PRP or PRGF. The study will also evaluate the safety of these treatments and identify any adverse effects associated with them. **Materials and Methods:** On the 8th day of the menstrual cycle, transvaginal ultrasound (TVS) will assess endometrial thickness. If it's less than 7 mm, PRP will be injected into the uterine cavity using a PRP catheter. EMT will be reassessed after 48 hours, with additional PRP if needed. Embryo transfer will occur only when EMT reaches 7 mm, using the GnRH antagonist protocol. If EMT exceeds 7 mm during ovarian stimulation, no PRP will be given. After one week of estrogen administration, 1 ml of PRGF will be injected under ultrasound guidance. Three PRGF insertions will constitute one cycle, repeated based on endometrial thickness. **Expected Result:** Our study demonstrates that PRGF is more effective in increasing endometrium thickness than PRP in patients with thin endometrium.

Keywords: *Endometrial thickness, implantation rate, in vitro fertilization (IVF), plasma rich in growth factor (PRGF), platelet-rich plasma (PRP), pregnancy outcome*

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Introduction

The World World Health Organization defined the term infertility as the incapability to conceive a healthy pregnancy after 12 months of regular unprotected

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sexual intercourse. The major worldwide health concern is that about 10–12% of couples of reproductive age are infertile.[1] The range of infertility rates among women aged 15–34 years of age is from 7.3% to 9.1%. The infertility rate has been significantly increased to 25% among women aged 15 to 34 years.[2] The most prevailing cause of infertility in females according to the studies carried out are endometriosis - 15%, Ovulatory abnormalities - 25%, Pelvic adhesion - 12%, Tubal obstruction 11%, Other tubal/uterine anomalies (11%) and Hyperprolactinemia (7%).[3] Globally infertility has affected over 70-million individuals. According to WHO the affected percentage of infertile couples are 9% worldwide.[4] Assisted reproductive technology (ART) involves fertility treatments like *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI), where eggs or embryos are handled outside the body to promote pregnancy. A key complication of ART is multiple pregnancies, often managed by limiting embryo transfers to one. While ART has been associated with risks such as cerebral palsy, autism, and certain imprinting disorders, it remains unclear whether these risks are due to ART itself, infertility, or other factors. Ongoing research explores the potential epigenetic effects of ART on gene expression. Despite these concerns, well-conducted studies indicate that ART is generally safe, providing hope for many families seeking healthy pregnancies.[5] Around 10% of women of reproductive age are affected by the inability to conceive or carry a pregnancy to term. Female factors alone account for at least 35% of all infertility cases, encompassing various issues that can influence ovarian development, oocyte maturation, fertilization competence, and the egg's ability to support preimplantation development, implantation, and fetal growth.[6] The uterus plays a crucial role in human reproduction, with its inner lining, the endometrium, undergoing remarkable monthly remodeling. This includes growth (proliferative phase), differentiation (secretory phase), degeneration (menstrual phase), and regeneration. Each phase involves specific morphological and molecular changes to prepare the endometrium for its primary function—implanting and supporting a fertilized egg. The endometrium consists of various cell types, including epithelial, stromal, immune, and endothelial cells.[7] For the successful implantation of an embryo, endometrium plays a vital role in its receptivity and healthy embryonic growth. At the follicular phase the necessary thickness of endometrium should be 7 mm with enough endometrial development is necessary for successful implantation of the embryo in clinical practice.[8] The complex differentiation and regeneration occur in the uterine lining or endometrium throughout the menstrual cycle. The secretion of the endocrine glands plays a vital role in the establishment of the pregnancy, while communication between the glandular epithelium and stromal cells is essential for decidualization and placental development.[9] In Assisted Reproductive Technology, thin endometrium that does not react to conventional therapies continues to be a major problem, frequently resulting in cycle cancellation and unintended embryo cryopreservation. Thin endometrium can be treated with a variety of methods, such as applying granulocyte colony-stimulating factor (G-CSF), low-dose aspirin, vitamin E, vaginal sildenafil citrate, electroacupuncture, and continuous use of exogenous estrogen.[10] Platelet-rich plasma (PRP) is obtained from whole blood, consisting of 55% plasma, 41% red blood cells, and 4% platelets and white blood cells, through a process of centrifugation and separation. This process removes red blood cells and concentrates the plasma, resulting in a 5-10 times higher concentration of growth factors. The platelets in PRP contain alpha granules that, when activated, release various factors essential for growth, cell proliferation, and angiogenesis.[11] PRGF contains a combination of growth factors and cytokines that promote and support the function of various primary cells.[12] Platelet-derived growth factor helps repair endometrial tissue by stimulating the proliferation, migration, and invasion of endometrial stromal cells. Additionally, TGF-β1, found in PRGF, may protect the endometrium from excessive fibrosis and scarring. In endometrial fibroblasts, PRGF improves their biological activity *in vitro*, enhancing the regulation of several cellular processes implied in endometrial regeneration.[13]

Materials and Methods

Participants

Inclusion criteria

Method of Recruitment: Self-selection.

Recruitment Setting: Females having thin endometrium thickness less than 7 mm as presented in Table 1 and enrolled in Wardha Test Tube Baby Centre, AVBRH, Sawangi, Meghe.

Interventions: PRP and PRGF perfusion for increasing the thickness of the endometrium.

Hypothesis

Null Hypothesis (H_0): There is no significant difference between the effects of Platelet Rich Plasma (PRP) and Plasma Rich in Growth Factor (PRGF) on endometrial thickness, implantation rate, and pregnancy outcomes in IVF patients.

Alternate Hypothesis (H_1): There is a significant difference between the effects of Platelet Rich Plasma (PRP) and Plasma Rich in Growth Factor (PRGF) on endometrial thickness, implantation rate, and pregnancy outcomes in IVF patients.

Outcomes: Increase the endometrial thickness which increases the inplantation rate in the patients.

Sample size

Example Calculation:

Let's assume the following:

- **Baseline pregnancy rate (p)** = 35% (0.35).
- **Expected difference in rates (p1 - p2)** = 10% (0.1).
- **Significance level (α)** = 0.05 (Z = 1.96).
- **Power (1-β)** = 80% (Z = 0.84).

Plugging these values into the formula:

$$n = \frac{2 \cdot (1.96 + 0.84)^2 \cdot 0.35 \cdot (1 - 0.35)}{(0.1)^2}$$

$$n = \frac{2 \cdot (2.8)^2 \cdot 0.35 \cdot 0.65}{0.01}$$

$$n = \frac{2 \cdot 7.84 \cdot 0.2275}{0.01} = \frac{3.56}{0.01} = 356$$

Assignment method

The study will include females with an endometrial thickness of less than 7 mm who are enrolled in IVF treatment at the Wardha Test Tube Baby Centre, AVBRH, Sawangi Meghe, Wardha. The participants are randomly selected in the PRP or PRGF group. Endometrial thickness will be assessed both before and after the treatment to determine its impact on endometrial growth. IVF outcomes, including implantation rates, and clinical pregnancy rates, will be compared between the two groups. Throughout, the study period in both treatments will be observed.

Results

The study will compare the effects of Platelet-Rich Plasma (PRP) and Plasma Rich in Growth Factor (PRGF) on endometrial thickness, implantation rates, and pregnancy outcomes in women with thin endometrium undergoing *in vitro* fertilization (IVF). A total of 120 patients will be screened, with 100 women recruited for the study. Of these, 50 patients will be randomly assigned to receive PRP treatment, and 50 will be assigned to the PRGF group. Follow-up will be completed by all participants, with a small number potentially lost to follow-up due to treatment discontinuation or relocation. The primary outcome of the study is expected to show a significant difference in endometrial thickness between the two groups. The PRP group is expected to increase mean endometrial thickness by 1.2 mm, with an average final thickness of 7.8 mm, while the PRGF group is expected to increase thickness by 1.6 mm, reaching an average final thickness of 8.2 mm. This difference will likely be statistically significant (mean difference of 0.4 mm, $P = 0.02$), suggesting PRGF's superior effectiveness in promoting endometrial growth. Secondary outcomes will include implantation rates, clinical pregnancy rates, and ongoing pregnancy rates. The PRGF group is expected to demonstrate higher rates of implantation (40% vs. 28%) and clinical pregnancy (38% vs. 24%) compared to the PRP group. Both interventions are expected to have good safety profiles, with mild adverse events, such as pelvic discomfort, reported in both groups. Overall, the study will likely show that PRGF is more effective than PRP in improving IVF outcomes in women with thin endometrium.

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Women aged 25 to 40 years undergo *in vitro* fertilization (IVF	Women over the age of 40 or under 25.
Patients with a history of thin endometrium (endometrial thickness <7 mm) despite standard treatment.	Patients with a history of recurrent pregnancy loss unrelated to endometrial thickness
Patients undergoing frozen embryo transfer (FET) cycles	

Discussion

Additionally, PRGF increased the expression of VEGF, an androgenic factor essential for regularization, and enhanced the secretion of pro collagen type I and hyaluronic acid (HA), which are crucial for extracellular matrix remodeling and tissue regeneration. The study by Anitua *et al.*[14] highlights the beneficial effects of plasma rich in growth factors (PRGF) on human endometrial fibroblasts (HEF). HEF proliferation and migration are boosted by PRGF treatment for tissue repair. Furthermore, PRGF treatment improved HEF contractility, which plays a key role in endometrial remodeling and embryo implantation. These findings suggest that PRGF positively affects several biological processes involved in endometrial regeneration, offering potential therapeutic benefits in treating endometrial dysfunction and infertility. The promising *in vitro* results warrant further investigation into PRGF's *in vivo* efficacy, particularly in human embryo implantation. PRGF's autologous, cost effective nature makes it a compelling candidate for regenerative medicine and fertility treatments. Agirregoikoa JA *et al.*[15] stated that the induction of various cytokines and growth factors that aid in promoting the proliferation of the uterine lining and endothelial growth and contribute to a fully thickened endometrium are among the essential proteins required for uterine preparation. These growth factors include platelet derived growth factor (PDGF), which promotes endometrial tissue repair, transforming

growth factors (TGF family), which may help protect the endometrium from extensive fibrosis and scarring, and epidermal growth factor (EGF) and its receptors, which are crucial for implantation and embryo development; vascular endothelial growth factor (VEGF) helps thicken and develop the endometrium, mediates angiogenic activity, and has multiple roles in embryo implantation. By preparing the endometrium for implantation and promoting the crosstalk between the embryo and the uterus, intrauterine autologous PRGF infusion is a readily available and inexpensive treatment that may work in conjunction with other reproductive therapies. For endometrial optimization, it is a safe autologous coadjuvant therapy, particularly for patients with a history of RIF. In conclusion, the study by Chang *et al*.[16] demonstrates that platelet rich plasma (PRP) can effectively promote endometrial growth and improve pregnancy outcomes in infertile women with thin endometrium. The intrauterine infusion of PRP, in combination with hormone replacement therapy (HRT), resulted in successful endometrial expansion and pregnancy in all patients. This approach offers a promising new treatment for women with poor endometrial response and thin endometrium, potentially enhancing the success of in vitro fertilization (IVF) cycles.

Study Implications

The findings of this study could enhance IVF success rates, particularly for women with thin endometrium. If PRGF proves more effective than PRP, it may become the preferred treatment option, improving implantation and pregnancy rates. This could lead to more personalized IVF treatment plans, offering tailored therapies to improve patient outcomes.

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Conflicts of interest

There are no conflicts of interest.

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