ABSTRACT

The purpose of this paper is to review the current clinical uses of platelet-rich plasma (PRP) in the field of Reproductive Medicine. All relevant articles published from January 2000 to December 2019 were reviewed and analysed. The article on PRP in field of Reproductive Medicine were mainly case series, pilot studies, or case reports. PRP is currently considered a new therapeutic modality for some disorders that are refractory to conventional drugs.

The pilot study was to evaluate the effectiveness of intrauterine infusion of Platelet Rich Plasma (PRP) in infertile women undergoing frozen embryo transfer cycles with suboptimal endometrium. Material & methods- Instillation of autologous PRP was done in 20 women between 24 & 38 years over 10 months, with suboptimal endometrial growth. Patients with repeated cycle cancellations in addition to Estradiol valerate. Frozen embryo transfer was performed when the endometrium reached an optimal pattern in terms of thickness, appearance & vascularity. Results- The mean pre-PRP endometrial thickness (ET) was 5 mm which significantly increased to 7 mm post-PRP. There was a significant increase in vascularity, seen by the number of vascular signals seen on Power Doppler, reaching the zones 3 & 4 of endometrium. The positive beta Human Chorionic Gonadotropin (hCG) rate was 70.58% & the clinical pregnancy rate was 58.82%. A total of 2 women are in the second trimester, 8 are in the first trimester with a healthy intrauterine pregnancy, one patient had an ectopic gestation, and one had a biochemical pregnancy.

Conclusion: This study suggests that the use of autologous PRP holds promise in treatment of women with suboptimal ET and vascularity in embryo transfer. It would help to reduce the incidence of cycle cancellations and thus even help reduce the financial & psychological burden of repeated cancelled cycles.

KEYWORDS

platelet rich plasma, reproductive medicine, thin endometrium
4) PRP in Repeated implantation failure

Repeated implantation failure (RIF) is described as a failure to conceive following several embryo transfers in IVF cycles. Numerous factors are involved in implantation process, including embryonic quality, endometrial receptivity, and immunological factors. Several methods have been suggested for RIF management, but little consensus exists on which is most effective. These methods include blastocyst transfer, assisted hatching, hysteroscopy, endometrial scratching, and immune therapy. Recently, intrauterine infusion of PRP has been shown to promote endometrial growth and receptivity.

Nazri et al. enrolled 20 participants with a history of RIF to evaluate the effectiveness of PRP in improving the pregnancy rate in RIF patients. The inclusion criteria were being younger than 40 years and having a BMI below 30 kg/m². They reported that 18 of the 20 participants (90%) became pregnant. Sixteen clinical pregnancies were recorded and their pregnancy were ongoing at the time of the study. They concluded that PRP was effective in improving pregnancy outcomes in RIF patients.

STUDY

Implantation is a complex process involving amultitude of factors and requires a healthy dialogue between the embryo and endometrium. Defining an optimal endometrium prior to embryo transfer has often been a challenge faced by Assisted Reproductive Technology (ART) practitioners, and achieving the parameters apt for ensuring implantation is a task that is worthed with controversies and is poorly defined. For an adequate endometrial growth, diverse therapeutic approaches have been proposed and tested.

The measurement of endometrial volume has been proposed as a predictor of implantation in the recent years. However, in practice, most clinicians empirically prefer endometrial thickness (ET) >7 mm. The available evidence does not support any specific thickness, and pregnancies with similar successes have been described in endometria from 5-15 mm. Similar findings were revealed in a meta-analysis by Kasius et al. published in 2014.

ET is measured by Transvaginal Sonography (TVS) as the maximum distance between the echogenic interfaces of the myometrium and the endometrium in the plane through the central longitudinal axis of the uterine body. Several reports state that more than the thickness or pattern of the endometrium, the vascularity plays an important role in predicting implantation.

Studies have stated that absence of blood flow in the endometrial and subendometrial zones is associated with failure of implantation. The pregnancy rates were doubled when the blood flow reached the zones 3 and 4 of Applebaum's grading, as compared to zones 1 and 2.

In patients who are unable to achieve an optimal endometrial lining, conventionally many therapies have been tried, such as giving higher doses or extended use of Estradiol valerate (Valest 2mg; Walter Bushnell, Mumbai, India), adding low dose aspirin, use of Sildenafil (Silnafil 25 mg; Emcure Pharmaceuticals, Mumbai, India), Human Chorionic Gonadotropin (hCG), intrauterine Granulocyte-colony stimulating factor (G-CSF) instillation, as well as certain unconventional therapies such as electroacupuncture, but they lack consistency in delivering results.

There is a need to evaluate other modalities in this regard, since a suboptimal endometrial growth or vascularity might lead to repeated cycle cancellations or recurrent implantation failure, thus causing not just a psychological but also financial impact on the patient. This drives the patients toward surrogacy as an option, which, considering the medical/legal implications, might not be a viable option now.

The primary objective of the study was to evaluate the role of intrauterine infusion of autologous platelet rich plasma (PRP) on the ET and vascularity of women undergoing frozen embryo transfer cycles with suboptimal endometrial pattern as assessed by transvaginal ultrasound and Power Doppler.

Secondary objectives were to study the implantation rate, clinical pregnancy rate, and outcome of pregnancy, studied up to the second trimester.

We included 20 women between 24 and 38 years of age undergoing frozen embryo transfer cycles over a period of 8 months from January to October 2019, with a suboptimal endometrial pattern, as identified by ET < 7 mm despite standard dose of Estradiol valerate (up to 16 mg/day), or suboptimal endometrial vascularity, defined as <5 vascular signals reaching the central zone (zones 3 and 4 as per Applebaum grading) of the endometrium, as measured by Power Doppler by the same observer. Women with more than two cancelled cycles or recurrent implantation failure due to poor endometrial lining were also included in the study.

Women with any other known cause of implantation failure, such as poor embryo quality, Ashermann syndrome, or congenital uterine anomalies, were excluded.

The women were started on Estradiol valerate from day 1 of their menses in a dose of 6 to 8 mg/day, which was gradually increased up to 12 mg/day in divided doses as needed. Serial transvaginal ultrasound examinations were done using transvaginal probe of 5 to 9 MHz, on Samsung R5, starting from day 7/8, and repeated as required.

RESULTS

The age group of women included in the study was 24 to 38 years. A total of 20 women were included in the study, of which, frozen embryo transfer was performed in 17. Cycles were cancelled in three women—two due to suboptimal endometrial lining, one due to bleeding 2 days prior to embryo transfer, and one due to viral fever a day before the embryo transfer.

A total of 15 women required a single sitting, whereas 5 women required two sittings of intrauterine PRP infusion. The mean pre-PRP ET was 5 mm and the post-PRP ET was 7 mm (P < 0.00001 at 95% confidence interval) [Figure 1].

8 patients displaying sparse to modest vascularity pre-PRP instillation had an excellent vascularity pattern [Figure 2], whereas, in 10 patients, the vascularity pattern improved to modest from sparse. Only 2 patients persisted to have a sparse vascularity pattern [Figure 3].

Positive beta hCG values were observed in 12 patients (70.58%) after frozen embryo transfer and the clinical pregnancy rate, as defined by the observation of a gestational sac with fetal cardiac activity at 6 weeks gestation by transvaginal ultrasound, was 58.82% [Figure 4].

Among the 12 women with a positive beta hCG value, 2 have crossed into the second trimester of pregnancy, whereas another 8 are in the first trimester with a healthy intrauterine pregnancy. One patient had an ectopic gestation, and biochemical pregnancies (Figure 5).

![Fig-2 Sonography Of Patients Displaying Sparse To Modest Vascularity Pre-prp Instillation](image-url)
Aghajanova et al. evaluates an in vitro model of activated PRP for endometrial regeneration. Activated PRP promoted the migration of all the cells studies, namely human primary endometrial epithelial cells, endometrial stromal fibroblasts, endometrial mesenchymal stem cells (MSC), bone marrow-derived MSC, and Ishikawa endometrial adenocarcinoma cells. These data provide an initial ex vivo proof of principle for the use of autologous PRP to promote endometrial regeneration in Asherman’s syndrome and a thin endometrial lining and warrant preclinical studies in animal models and subsequently in the clinical setting.16

Endometrial vascularity is an important parameter to assess the implantation potential of the endometrium as cited by several studies. A retrospective study of 500 ovum donation-embryo transfer cycles published by Nagori and Panchal in 2012 demonstrated that conception rates were almost doubled when vascularity was seen in zone 3 and 4 of the endometrium than when it reached only zones 1 and 2, with low abortion rates.14 Another recent study in 2014 by Sardana et al. also evaluated 165 women undergoing frozen embryo transfer cycles and concluded that the presence of endometrial vascularity significantly improves the outcome in frozen embryo transfer cycles.15 Autologous PRP is a safe, easily available, and inexpensive treatment modality for women with refractory endometrium.

If performed under strict asepsis, the adverse effects are virtually none. This procedure, if used routinely in practice, would reduce not just the physical, but also the financial and psychological burden faced by such patients, who would otherwise face the risk of repeated cycle cancelations or recurrent implantation failures. However, further research in the form of large scale randomized controlled trials is needed, which would help to strengthen our observations and enable practitioners to use this modality clinically to optimize their success rates.

Beta hCG values after frozen embryo transfer.

REFERENCES