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Management of thin endometrium by hysteroscopic instillation of platelet rich plasma: a narrative review

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ABSTRACT

Objective. One of the prerequisites for successful pregnancy outcome is the endometrial thickness. In subfertile patients undergoing IVF treatment, the minimum endometrial thickness is presumed to be approximately 7 mm or more prior to embryo transfer. For the treatment of a refractory endometrium, instillation of platelet rich plasma in the subendometrial region via hysteroscopy is a newer technique. This study is conducted to evaluate the effectiveness of PRP treatment in cases of thin endometrium.

Materials and Methods. Review of various articles on hysteroscopic instillation of platelet rich plasma was undertaken by searching in the data bases like PubMed, Scopus, EMBASE, Web of Science, Science direct, etc. The studies describing platelet rich plasma instillation and its different techniques including efficacy and their role in achieving clinical pregnancy were included in the present study. We searched studies from January 2000 to January 2022.

Results. Here, in the previous studies, we saw promising results with hysteroscopic Platelet rich plasma instillation in infertile women.

Conclusions. Autologous platelet rich plasma instillation is not associated with any side effects as it is derived from patients own blood. Also, it is cost effective, less invasive, easily available as well as feasible for the specialist.

INTRODUCTION AND BACKGROUND

A functional embryo, a receptive endometrium and a synchronized interaction between blastocyst and endometrium are the prerequisite for the successful implantation [1]. Natural endometrial cycle comprises of three sequential phases Proliferative phase, secretory phase and menstrual phase [2]. During the “window of implantation” phase that lasts for few days post-ovulation, the endometrium undergoes proliferation and increases in its thickness and becomes responsive to progesterone, which is essential for the attachment, invasion and finally im-

plantation of the embryo [2]. For embryo transfer the minimum endometrial thickness is presumed to be approximately 7 mm or more [3-5]. An important factor in implantation failure is considered to be a thin endometrium [6-8] due to high blood flow impedance of radial arteries of the uterine vessels, reduced epithelial growth, lower vascular development, and poor expression of vascular endothelial growth factor (VEGF) [9]. Several mechanisms have been proposed to explain the underlying pathophysiology of thin endometrium. Intrauterine adhesions, ovarian stimulation with clomiphene citrate (CC), as well as prolonged use of progesterone [10],

or combined oral contraceptive pills have been associated with thin endometrium [11-13].

Several therapeutic approaches have been studied in the past which includes low-dose aspirin, pentoxifylline, tocopherol, L-arginine, vaginal sildenafil, extended estrogen, gonadotropin therapy, low-dose hCG, tamoxifen, acupuncture and neuromuscular electric stimulation, intrauterine G-CSF, and stem cell therapy [14]. A derivative of fresh whole blood enriched with platelets autologous to plasma is known as Platelet rich plasma (PRP). PRP is considered to increase the receptivity of the endometrium via increasing vascularization, cell proliferation, anti-inflammatory properties and the reduced fibrosis, due to growth factors, peptides, and cytokines present in PRP [15, 16]. For the treatment of a refractory endometrium, instillation of PRP in the subendometrial region via hysteroscopy is a newer technique. In this study we will review various articles on PRP instillation in cases of infertility having thin endometrium. The rationale behind this study is to understand the processes behind thin endometrium and focussing on its management with PRP which is a newer technique so that we can help women having subfertility and IVF failures due to this cause.

AIMS AND OBJECTIVE

First, to study the effect of PRP instillation on endometrial thickness, second, to review the effect on pregnancy outcomes in patients undergoing PRP instillation.

MATERIALS AND METHODS

A non-systematic review of various articles on hysteroscopic instillation of PRP was undertaken by searching in the data bases like PubMed, Scopus, EMBASE, Web of Science, Science direct, etc. The studies describing PRP instillation and its different techniques including efficacy and their role in achieving clinical pregnancy were included in the present study. We searched studies from January 2000 to January 2022. The search strategy included keywords such as Platelet rich plasma, PRP, infertility, gynaecology, endometrium thickness, IVF, Recurrent implantation failure (RIF), hysteroscopic instillation, intrauterine infusion, etc.

DISCUSSION

In most of the studies the patient profile consists of history of repeated implantation failure (RIF), thin endometrium, intra uterine adhesion (IUA) [17] and chronic endometritis (CE), the PRP treatment is tried as no effective treatment is yet available for such cases [18-23]. It is shown that intrauterine PRP infusion gives successful reproductive outcomes, increases the thickness of endometrium and successful pregnancy outcomes thus can be used in various endometrial preparation protocols [18-23]. PRP increases the endometrial receptivity via increasing vascularity, cell proliferation and reduces fibrosis and inflammation due to various growth factors, peptides, and cytokines present in it [15, 16]. PRP is made by taking blood from peripheral veins, it is rich in various growth factors like platelet-derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factor (TGF), VEGF, and cytokines which influences proliferation and growth of the endometrium [24].

Table 1 shows various studies done on PRP treatment in infertile cases and their outcomes. Zamaniyan *et al.* conducted a study in Iran in a group of 98 women with RIF which showed positive clinical pregnancy outcomes with intrauterine infusion of PRP; significant higher clinical pregnancy rate in PRP infusion group (48.3%) as compared with control group (23%) [18]. Similar results were shown in RCT done by Nazari *et al.* [19], where increased clinical and chemical pregnancy rates were observed in PRP group in comparison to control group (PRP infusion group vs control group: 45% vs 17% and 53% vs 27%, respectively). Mehrafza *et al.* [20] in their study done on group of 123 women showed comparison between the outcome of PRP infusion with granulocyte colony stimulating factor(G-CSF) systemic injection and they showed significantly increased pregnancy outcomes with intrauterine infusion of PRP in contrast to systemic administration of G-CSF.

Eftekhari *et al.* [21], in their study on a group of 83 women, which included 40 cases and 43 controls, to the case group were given PRP infusion and in the control group the embryo transfer was done without PRP infusion. The endometrial lining of the patients with PRP treatment increased significantly as compared to the controls ($p = 0.001$). The per-cycle clinical pregnancy rate was higher in the PRP group (32.5%) as compared to the control group (14%), but was not significant ($p = 0.044$) [14]. Zadehmodarres *et al.*, in their study on

Table 1. Various studies on PRP instillation and their outcomes.

Study	Type of study	Number of patients	Method	Outcome
Zamaniyan <i>et al.</i> [18]	Case control study	98 women with RIF	0.5 ml intrauterine PRP infusion 48 hours prior to embryo transfer	Significant higher clinical pregnancy rate in PRP infusion group (48.3%)
Nazari <i>et al.</i> [19]	RCT	138	Intrauterine PRP infusion group vs control group	Increased clinical and chemical pregnancy rate in PRP group compared to controls
Mehrafza <i>et al.</i> [20]	Retrospective cohort study	123	Compared the effect of intrauterine infusion of PRP with systemic administration of granulocyte colony stimulating factor (G-CSF)	PRP more effective as compared to G-CSF in RIF patients
Eftekhari <i>et al.</i> [21]	RCT	83 (40 patient, 43 control)	0.5-1.0 ml intrauterine PRP infusion on the 13 th day of HRT cycle	ET increased in patients as compared to control Clinical pregnancy: same in 2 groups
Zadehmodarres <i>et al.</i> [22]	Prospective cohort study	10	Intrauterine infusion of 0.5 ml of PRP with the IUI catheter	Clinical pregnancy: 4
Agarwal <i>et al.</i> [23]	Cross sectional	32 Secondary infertility: 8 Primary infertility: 24	Under hysteroscopic guidance 4 ml of PRP was injected into the subendometrial region using ovum pickup needle (1.0 ml in each wall)	Improved ET 24 patients Clinical pregnancy: 10 Chemical pregnancy: 2

10 patients infused 0.5 ml of PRP with IUI catheter, showed 40% clinical pregnancy rate [22]. Another cross sectional study conducted by Agarwal *et al.* [23], where they injected 4 ml PRP under hysteroscopic guidance in subendometrial junction using ovum pickup needle, among 32 primary and secondary infertility women showed improved ET in 24 patients and clinical pregnancy in 10 women and chemical pregnancy in 2 women. The studies conducted by Wang X *et al.* [25], Tandulwadkar *et al.* [26] and Molina *et al.* [20] stated that the use of autologous PRP shows promising outcomes in the form of endometrium thickness and diverse pregnancy tests [25-27]. A meta-analysis done by Maleki *et al.* stated that the administered PRP at a dose range of 0.5-1 ml was more efficacious than those delivered PRP at the doses deviated from this range (≤ 0.5 ml and ≥ 1 ml) [28].

Kaur *et al.* in their study on 98 patients with history of one previous FET failure with endometrium 7 mm or more in thickness and divided them into the control group and the intervention group (intrauterine infusion of 0.3-0.4 ml of PRP). There was no increased pregnancy rate in the intervention group [29]. Therefore, the dose of the PRP used may have an important role to play in the outcomes.

CONCLUSIONS

The thin endometrium is a nightmare for an ART specialist as it poses challenges in embryo transfer and successful pregnancy outcome. Here, in the previous studies, we saw promising results with hysteroscopic

PRP instillation in infertile women. Autologous PRP instillation is not associated with any side effects as PRP is derived from patients own blood. Also, it is cost effective, less invasive, easily available as well as feasible for the specialist. Further randomised trials are needed for creating guidelines for the clinicians around the world. Additionally, we need standardised PRP preparation technique and also the precise indication of the PRP treatment needs to be published for its utility.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

R.M.: Supervision. T.Y.: Conceptualization. A.D.: Writing – original draft, writing – review & editing.

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Disclosure of interests

The authors declare that they have no conflict of interests.

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