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Chapter

Autologous Platelet-Rich Plasma Infusion to Improve Pregnancy Outcome in Suboptimal Endometrium: A Review

Casey Zeffiro, Silvina Bocca, Helena Russell and Mitchel C. Schiewe

Abstract

Over the past decade, platelet-rich plasma (PRP) has been used in several fields of medicine to promote cell growth and expedite wound healing for the treatment of arthritis, nerve injury, tendinitis, bone regeneration, cardiac muscle repair, and oral & plastic surgery. Recently, researchers have been applying autologous PRP to bolster the growth of endometrial lining in patients with a history of endometrium-related failed embryo transfers. Evidence reveals that PRP is a rich source of active cytokines and various growth factors, which come from an autologous source that can be easily attained from peripheral blood without risk of disease transmission to the patient. In this review, several studies were analyzed that involved patients 18–42 years of age undergoing hormone replacement therapy (HRT) in preparation for embryo transfer and serial transvaginal ultrasound in conjunction with PRP infusions into the endometrium via an intrauterine insemination (IUI) catheter. Exclusion criteria included patients with endometritis, polyps, or adhesions. Embryo transfers (ET) were performed when the endometrial lining achieved a thickness of >7 mm. The database indicates that PRP infusion therapy is a promising low-cost treatment for HRT patients that significantly increases endometrial thickness and improves pregnancy success in a previous suboptimal ET patient population.

Keywords: cytokines, embryo transfer, endometrial lining, endometrium, growth factors, hormone replacement therapy, infusion, platelet-rich plasma, suboptimal lining

Key Points

Evidence shows that PRP infusion directly into the endometrium enhances lining development in patients suffering from chronically refractive or underdeveloped endometrium. Chemical pregnancy in patients that underwent PRP infusion with frozen embryo transfer was 50% (108/216) in comparison to 17.1% (16/93) in patients that did not receive PRP treatment.

1. Introduction

The overall objective of this review was to determine if platelet-rich plasma (PRP) infusions are viable alternatives to current treatments for thin endometrial lining, and to distinguish if PRP infusions increase endometrial thickness and implantation in patients that underwent treatment in eight different case studies.

Platelet-rich plasma is prepared from autologous whole blood collected from a patient's peripheral vein, mixed with an acid citrate dextrose solution A (ACD-A) anticoagulant, and processed to separate platelets from remaining blood components [1]. Platelet-rich plasma is recognized as plasma from autologous blood with 4–5 times the concentration of normal platelet levels; these high concentrations of PRP contain cytokines and growth factors including: vascular endothelial growth factor (VEGF), transforming growth factor (TGF), platelet-derived growth factor (PDGF) and epidermal growth factor (EGF) [2, 3]. Because of the expression of several regenerative growth factors, PRP is being used in several fields of medicine to promote wound regeneration including: arthritis, nerve injury, tendinitis, bone regeneration, cardiac muscle repair, alopecia, and plastic and oral surgery recovery [4, 5]. When the body is injured, a natural healing process occurs that floods the wound site with activated platelets that instantly promote cell regeneration and proliferation. It is theorized that PRP may be used to promote the same growth and proliferation in endometrium that have previous suboptimal growth patterns. Similar research, such as endometrial scratching, has been studied to promote the generation of growth factors to increase implantation; however, the concentration of platelet levels within direct PRP infusion into the endometrium is vastly superior to the natural, localized endometrial healing process that occurs with the scratching method.

Other treatment strategies for thin endometrial lining have varied throughout recent years, but have been inclusive of extended use of exogenous estradiol, low-dose aspirin, vitamin E supplementation, and use of granulocyte colony stimulation factor (G-CSF), but not all have been proven effective [6–9]. The minimal endometrial thickness suggested for successful implantation at embryo transfer is 7 mm [10], however, there are those that argue endometrial lining is a poor indicator for pregnancy outcomes and therefore should not be heavily considered [11]. During typical HRT cycles, estradiol administration is regulated from day 2 or day 3 of an average 28 day cycle and continues until the endometrial lining reaches optimal thickness for transfer (typically >7 mm) at which time progesterone administration then occurs [12]. This model is utilized in IVF clinics globally; however, patients who fail to reach the recommended endometrial thickness often undergo canceled cycles in which they have wasted valuable time, medications, and expenses without receiving an embryo transfer.

Thin endometrial lining or suboptimal endometrial growth is a problem that affects up to 5% of the patients undergoing IVF treatment [13]. These patients often experience the emotionally and physically traumatizing effects of canceled cycles or repeated implantation failure (RIF). It is proven that growth factors expressed in the endometrium of women with RIF are less than those expressed in normal fertile women [14]. These growth factors can be stimulated by infusion of autologous PRP into the endometrium in conjunction with HRT prior to embryo transfer. However, many factors are involved in successful embryonic implantation, not limited to embryo quality, but also a synchrony between the embryo and the endometrium in addition to any immunological factors [15]. Without optimal endometrial growth, this synchrony becomes far less likely as the endometrium does not express the adequate genes nor growth factors involved in embryonic implantation [16, 17].

2. PRP collection and infusion

Through multiple studies, PRP processing was performed similarly. On the 10th day of HRT, Chang and coworkers drew 15 ml of autologous blood into a tube with 5 ml of Acid Citrate A Anticoagulant (ACD-A) and centrifuged; separating red blood cells, a gel buffy coat, and cellular plasma. The plasma and buffy coat were then transferred to a second tube and centrifuged again, yielding 0.5–1 ml of PRP [18]. Both Zadehmodarres and Nazari and their colleagues drew 17.5 ml of blood on day 9 or 10 of HRT into 2.5 ml of ACD-A and similarly centrifuged twice to obtain 0.5 ml of PRP [19, 20]. Tandulwadkar et al. used 10 ml of autologous blood into an unspecified amount of ACD-A; which was centrifuged sequentially utilizing first a soft spin for 15 minutes, followed by a hard spin for 6 minutes, again yielding between 0.5 and 0.8 ml of PRP [21]. Eftekhar and others used an alternative approach, collecting PRP on the 13th day of HRT by drawing 8.5 ml of peripheral venous blood into a syringe containing 1.5 ml of ACD-A that was then centrifuged for 10 minutes; following first centrifugation, the buffy coat and plasma layer were then removed and centrifuged again, yielding 1.5 ml of PRP [22]. Meanwhile, Hounyoung et al. collected 18 ml of venous blood in a 30 ml syringe prepared with 2 CC of ACD-A and then centrifuged twice to obtain 0.7–1.0 ml of PRP [23]. Nazari and coworkers performed a follow-up study utilizing a double-blinded trial in which 30 patients underwent PRP infusion, prepared in the same manner as the initial pilot study [19], and 30 patients underwent placebo PRP infusions [24]. Chang et al. performed a secondary study as well, involving a larger cohort of patients compared against a control group, and performed PRP collection as previously reported [18, 25]. All studies transfused the PRP into the endometrium using an IUI catheter, and then repeated intravaginal ultrasound 48 hours later to measure endometrial growth; patients who did not reach the desired lining thickness (>7 mm deemed adequate in all studies) were then treated with a second round of PRP infusion [18–25].

2.1 Hormone replacement therapy

In the past, IVF clinics allowed for natural cycle frozen embryo transfer in which they permitted endometrial lining to develop on its own, but it resulted in many timing issues with need for frequent monitoring and cancelation due to anovulation and poor development of the endometrium. Today, most clinics have moved fully to HRT protocols that allow for artificial stimulation of the endometrium that can be easily tracked utilizing blood serum and ultrasound assessment to time an embryo transfer concordant with a receptive endometrium. In humans, estrogen stimulates endometrial growth and induces progesterone receptors as it moves naturally through the menstrual cycle. After ovulation, the endometrium is exposed to progesterone which induces morphological and biochemical changes that alter the endometrium from the proliferative phase to the secretory phase [17]. In HRT cycles, estradiol administration (typically Estradiol Valerate) occurs until the lining has reached a thickness of greater than 7 mm, at which time progesterone is then administered for the number of days proportional to the embryo being transferred (i.e., a day 6 blastocyst will receive progesterone for 6 days) and then the embryo is transferred to a supposedly receptive endometrium [26, 27]. In these HRT cycles, patients receive estradiol during the follicular phase that inhibits gonadotropin secretion and prevents follicular development and ovulation. The start of the luteal phase can be exactly pinpointed, as it starts when progesterone is added to estradiol dosages.

2.2 Methodology

HRT allows for artificial stimulation of endometrial growth via hormone administration orally, transdermally, intramuscularly, vaginally, subcutaneously, or a combination of both. Most clinics administer estradiol for several days until the endometrial lining has reach a point of optimal growth, at which time they will then administer progesterone to induce the secretory phase of cycle that promotes embryo implantation [21]. Each of the studies examined in this review conducted HRT protocols concordant with physician recommendation as follows:

Chang et al.: In the pilot study, Estradiol Valerate (E_2V) started at 3 mg/d on day 3 of menses and increased every 4 days up to a max of 12 mg/d; and in the cohort study, E_2V started at 6 mg/d and subsequently increased to 12 mg/d [18, 25]. The pilot study included five patients suffering from chronically non-responsive thin endometrium (5.9–6.6 mm) who underwent PRP infusion on the 10th day of HRT and lining was measured via transvaginal ultrasound. In the cohort study, platelet-rich plasma infusion was also performed on the 10th day of HRT, and endometrial thickness was measured in both the control group and study group.

Zadehmodarres et al.: Estradiol Valerate started at 6 mg/d on day 3 of menses, and increased to 8–9 mg/d. Suppository progesterone was started when endometrial thickness reached >7 mm and continued for 2 weeks after ET [19]. PRP infusion was administered on the 11th or 12th day of cycle and assessed 48 hours later.

Nazari et al.: Estradiol Valerate started on day 2 or 3 of menses at 6 mg/d and was increased to 8 mg/d if lining did not reach >7 mm. When thickness reached 7 mm, progesterone suppositories, 4000 mg, were started twice daily [20, 24]. In the pilot study, 0.5 ml of PRP was infused into the endometrium of patients 48 hours prior to frozen embryo transfer in conjunction with an HRT cycle. In the follow-up RCT, PRP infusion or mock infusion was performed on day 11 or 12 of HRT cycle, modified from the initial pilot study, and lining was measured using transvaginal ultrasonography.

Tandulwadkar et al.: Estradiol Valerate started at 6–8 mg/d concordant with baseline endometrial vascularity as measured by Power Doppler on day 1 of menses and increased to 12 mg/d if growth was not seen. Transvaginal ultrasounds were performed starting on day 7/8 [21]. Day of PRP infusion was not given in the initial study.

Eftekhar et al.: In this study, the case group was treated with PRP and increased HRT, and the control group was just treated with increased HRT. For all women, E_2V was started at 6 mg/d, then increased to 10 mg/d [22]. PRP infusion occurred on the 13th day of cycle and endometrial lining was measured transvaginally.

Hounyoung et al.: Patients treated within this study began E_2V administration on the second day of menses, starting at 4-6 mg/d and followed by PRP infusion on cycle day 10 [23]. PRP infusion was administered via IUI catheter and repeated 2–3 times in 3 day intervals until optimal endometrial thickness was achieved (>7 mm).

3. Sample size and selection of samples

Eight clinical trials were selected, all of which were inclusive of a total of 346 patients that underwent HRT in conjunction with PRP infusion. Of 346 patients, 313 underwent embryo transfer at either cleavage or blastocyst stage. The remaining 33 patients dropped out of the studies prior to embryo transfer due to persistently poor endometrial development [18–25].

3.1 Inclusion criteria

Inclusion criteria remained relatively constant through all eight studies. All patients had a history of thin endometrial lining, repeat implantation failure, or two or more canceled cycles due to poor endometrial growth. All patients were between the ages of 18–42 years old and all had a normal BMI of <30%; donor egg cycles were not included due to the potential to skew the results. All patients that underwent embryo transfer post-PRP infusion reached an endometrial thickness of >7 mm, as deemed acceptable by the performing physicians.

3.2 Exclusion criteria

All patients with hematological and immunological disorders, hormonal disorders, chromosomal and genetic abnormalities and uterine abnormalities were excluded from the studies. All patients who did not reach optimal endometrial thickness post-PRP infusion were excluded from embryo transfer. Any patient of advanced maternal age (>42 years old) or increased BMI (>30%) was excluded from the studies.

4. Results and data analysis

Five patients were included in the initial pilot study by Chang et al. [18]. 48–72 hours post PRP, all five patients reached a minimum lining of 7 mm (7.0–8.0). All patients underwent frozen embryo transfer, and all five patients were pregnant (5/5) with an ongoing pregnancy rate of 80% (4/5).

Zadehmodarres and colleagues [19] performed their study on 10 patients with previous canceled cycles due to thin endometrial development, four of which were diagnosed with Asherman's Syndrome. All 10 patients reached adequate lining thickness for embryo transfer (7.0–7.5). All patients underwent frozen embryo transfer resulting in chemical pregnancy in 50% of patients (5/10) with an ongoing pregnancy rate of 40% (4/10).

The pilot study by Nazari and coworkers [20] was based upon a study group of 20 patients suffering from RIF due to thin endometrial lining. All patients received a blastocyst stage transfer of one to two embryos that were graded morphologically normal. Chemical pregnancy was reported in 90% of patients (18/20) with an ongoing pregnancy rate of 80% (16/20).

Tandulwadkar et al. [21] assessed not only endometrial thickness, but endometrial vascularity as well post PRP infusion as measured by serial transvaginal ultrasound. Of the 68 patients included in the study, 64 went on to achieve optimal lining thickness for frozen embryo transfer. Average mean lining thickness before PRP infusion was 5 mm, and 7.22 mm after PRP infusion. Of the 64 patients that received a frozen embryo transfer, endometrial vascularity increased in all patients. 60.1% (39/64) reported chemical pregnancy with an ongoing pregnancy rate of 45.3% (26/64).

A randomized control trial was performed by Eftekhar and others [22] in which 83 women participated; 40 were allocated to the study group and received PRP infusion, while 43 were placed in the control group and did not receive PRP. Prior to PRP infusion on the 13th day of cycle, there were no significant differences in endometrial lining as measured between the two groups; however, after PRP infusion, significant differences were noted (8.80 vs. 8.04 mm). Of the 40 women in the study group, 7 did not receive an embryo transfer due to persistently thin

endometrium, whereas 10 women in the control group were excluded from frozen embryo transfer for the same reason. Thirty-three women in the study group and 33 women in the control group underwent cleavage stage frozen embryo transfer. In the study group, chemical pregnancy was reported in 42.2% (14/33) in comparison to the control group, which recorded chemical pregnancy in only 24.2% (8/33) of patients. Ongoing pregnancy rates were 33.3% (11/33) versus 18.2% (6/33), respectively.

Hounyoung and colleagues [23] performed a pilot study on 24 patients with a history of refractory endometrium. Of the 24 patients initially included in the study, two patients were canceled, and two were lost to follow-up. Data was collected for the remaining 20 patients, all of whom received a frozen embryo transfer of 2–3 day 3 cleavage stage embryos. Among the study group, a chemical pregnancy rate of 30% (6/20) was reported with an ongoing pregnancy rate of 20% (4/20).

After an initial pilot study, Nazari et al. [24] performed a follow-up double blinded randomized control trial to validate their previous findings. Sixty patients were selected for inclusion in the study; 30 were randomly assigned to the study group to receive PRP infusion, and 30 were aliquoted to the control group in which a sham-catheter was utilized for mock PRP infusion. In the PRP group, lining increased to 7.21 ± 0.18 mm respectively, and in the mock infusion group, lining reached 5.76 ± 0.97 mm. Of the 30 patients in the study group, all patients received a frozen embryo transfer in comparison to just 6 that reached optimal lining (>7 mm) for frozen embryo transfer in the control group. Chemical pregnancy was recorded in 40% (12/30) of cases in the study group, and in 6.7% (2/30) in the control group. Ongoing pregnancy rate was 33.3% (10/30) in the PRP group, and 3.3% (1/30) in the control group.

Chang and others [25] performed a follow-up randomized control trial to their initial pilot study as well, assigning 34 patients to the PRP infusion group and 30 patients to the control group, which received only HRT without PRP. In the study group, endometrial thickness reached an average of 7.65 ± 0.22 mm versus 6.52 ± 0.31 mm in the control group. The cycle cancelation rate was 19.0% in the study group, and 41.2% in the control group, which was statistically significant. All patients that reached optimal endometrial thickness received a frozen blastocyst transfer of one or two morphologically good blastocyst stage embryos. In the PRP group, clinical pregnancy was reported as 44.1% (15/34), and 20% (6/30) in the control group.

All patients within study groups that underwent embryo transfer reached optimal lining thickness (>7 mm) after one or multiple rounds of PRP infusion. Patients that underwent PRP infusion in the study groups reached an average endometrial thickness of 7.36 mm with an average increase of 1.68 mm post PRP infusion. In the control groups presented by studies performing RCT, the control patients reached an average endometrial thickness of 6.77 mm with an average increase of 0.91 mm after HRT. Among patients within study groups, the overall chemical pregnancy rate was 50% (108/216) in contrast to 17.1% (16/93) following conventional HRT without PRP infusion.

5. Discussion

Platelet-rich plasma infusion is a novel approach to endometrium enhancement. This autologous therapy strives to increase endometrial thickness among patients with histories of canceled cycles and repeat implantation failure due to chronically refractive endometrium. While there is no universally agreed upon treatment for this patient population, the search to find an effective solution for non-reactive

STUDY	Type of Study	Participants	Age	Day of PRP	Average EMT Before PRP (Study Group)	Average EMT Before PRP (Control Group)	Average EMT After PRP (Study Group)	Average EMT After HRT (Control Group)	Clinical Pregnancy Rate
Chang et al. 2015	Pilot	5	35.0 ± 4.0	10	6.22mm	N/A	7.52mm	N/A	5/5
Zadehmodarres et al. 2017	Pilot	10	35.0 ± 5.0	11 - 12	5.82mm	N/A	7.25mm	N/A	5/10
Nazari et al. 2016	Pilot	20	36.0 ± 3.0	16 - 18	N/A	N/A	N/A	N/A	18/20
Tandulwadkar et al. 2017	Pilot	64	31.0 ± 9.0	15 - 16	5.0mm	N/A	7.22mm	N/A	39/64
Eftekhar et al. 2018	RCT	66	32.5 ± 2.0	13	6.09mm ± .47mm	6.15mm ± 0.37mm	8.67mm + 0.64mm	8.04mm + 0.27mm	14/33 (s) vs. 8/33 (c)
Hounyoung et al. 2019	Pilot	20	37.5 ± 7.5	12, 15, 18	5.4mm ± 0.8mm	N/A	6.0mm + 1.1mm	N/A	6/20
Nazari et al. 2019	RCT	60	33.11 ± 3.77	11 - 12	4.92mm	5.06 mm	7.21mm	5.76mm	12/30 (s) vs. 2/30 (c)
Chang et al. 2019	RCT	64	33.5 ± 1.5	10	6.32mm + 0.54mm	6.39mm + 0.72mm	7.65mm + 0.22mm	6.52mm + 0.31mm	15/34 (s) vs. 6/30 (c)

* (s) denotes study group

** (c) denotes control group

Table 1.
Eight studies were compared for the measurement of endometrial thickness before and after PRP infusion in study groups vs. control groups. Clinical pregnancy outcomes are included following PRP treatment.

endometrial lining should be at the forefront of clinical researchers within the ART industry. Platelet-rich plasma is easily attained, cost-effective, minimally invasive, rich in cytokines and growth factors, and carries very little risk of disease or infection transmission as the patient uses their own blood to attain PRP. Infusion into the endometrium takes place in conjunction with traditional HRT and therefore can be administered during the average cycle while patients are already present for serial ultrasounds and serum hormone level measurements.

In the eight studies discussed above, PRP infusion into the endometrium proved effective when administered on various days of an HRT cycle as well as in variable quantities. While the majority of studies reviewed were clinical applications, which presents a weakness in the data as there was no comparative control group, the randomized controlled trials that were performed offered arguably conclusive, supportive evidence of PRP effectiveness. All the patients that underwent PRP infusion experienced a significantly marked increase in endometrial thickness, allowing for frozen embryo transfer. In the studies that did utilize a study population versus a control population, results among the study participants were significantly improved with greater cycle completion. Although most studies utilized frozen blastocyst transfers, there were some that elected to use frozen cleavage stage embryo transfers, which can also be considered a limiting factor among the data. The studies here agreed upon 7 mm as the minimal lining thickness for embryo implantation success, but some physicians argue that endometrial thickness is a poor marker for transfer outcome. While this argument can be made and supported, as it was by Griesinger and colleagues [11], there is a wide consensus that endometrial thickness does play a vital role in receptivity (**Table 1**).

The patient populations presented in these studies, including those among the study group and those in the control group, were all patients that had suffered two or more failed previous cycles due to poor lining development. The inclusion criteria for these studies were consistent through all eight trials and provided an unbiased patient group in order to obtain reliable results. The data conclusively shows that endometrial thickness among patients with chronically poor endometrial development is greatly increased with PRP infusion therapy in comparison to traditional HRT alone. The primary outcome of each study was satisfied by the significant increase in endometrial lining development with the secondary satisfaction of improved clinical pregnancy outcomes in the PRP group versus the control group.

Another diagnostic tool to be considered in patients with a history of suboptimal endometrial development and repeat implantation failure is the use of the Endometrial Receptivity Array (ERA). The ERA is a customized array that allows to test for 248 different genes expressed during the endometrial cycle and works concordantly with a computational algorithm that identifies the receptivity status of an endometrial biopsy to diagnose a personalized window of implantation [28]. ERA is performed with a mock embryo transfer cycle. Utilizing the ERA, Ruiz-Alonso and colleagues were able to validate conclusively that 25% of RIF patients had a displaced window of implantation and went on to coin the phrase "personalized embryo transfer" (pET) to increase the chance of a successful pregnancy in women suffering from mistimed endometrial receptivity [29]. Potentially, ERA can be utilized in conjunction with PRP infusion to determine receptivity of the endometrium in PRP patients. In the study by Tandulwadkar et al. [21], not only was lining thickness assessed, but endometrial vascularity was observed as well utilizing 3D Doppler ultrasound. Blood flow to the endometrium as well as the uterine biophysical profile can be measured via a combination between abdominal and transvaginal ultrasound. Greater blood flow to the uterus has been associated with higher implantation rates and can be seen in color utilizing Doppler ultrasound methods [27]. PRP infusion has the potential to increase lining development as well

as endometrial vascularity as proven by Tandulwadkar, and future studies should observe an increase in vascularity concordant with lining and uterine biophysical profile. Utilizing the ERA and 3D Doppler system in conjunction with PRP in future studies can be therefore linked to the immune, genetic, and biophysical pathways of the endometrium.

While the use of PRP infusion into the endometrium to increase lining growth and vascularity is a relatively new area of research, the initial trials show encouraging results. The patients that were included within these studies are patients who had suffered from multiple failed or canceled cycles and would not have received embryo transfers otherwise. In a patient population that has had multiple failures, PRP infusion into the endometrium provides a suitable solution that effectively allows for embryo transfer, giving these patients a chance at pregnancy that they otherwise would not have had utilizing traditional HRT alone. Although the data is still new and there is need for additional research and much larger randomized controlled trials, the initial use of PRP as a universal means of treating poor responders to HRT shows a promising treatment method for the future.

6. Conclusion

The review of the initial data presented in these eight early studies of PRP infusion into the endometrium in conjunction with traditional HRT reveals statistically significant outcomes. Patients with previous failures that did not reach the minimal lining thickness needed to perform embryo transfer (>7 mm) underwent PRP infusion into the endometrium and reached an average endometrial thickness of 7.36 mm in comparison to the control group, which reached an average of only 6.77 mm. Clinical pregnancy rates within the study group were also significantly higher than the control group, 50% (108/216) versus 17.1% (16/93), respectively. For patients that have had multiple failures and canceled cycles, offering an absolute solution that at minimum guarantees them an embryo transfer can potentially increase the success of frozen embryo transfers in clinics globally, while decreasing patient stress and costs, and reducing the potential for embryo wastage.

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Conflict of interests

The author declares no conflict of interest.

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