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REVIEW

A narrative review of platelet-rich plasma (PRP) in reproductive medicine

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Abstract

Purpose Platelet-rich plasma (PRP) has become a novel treatment in various aspects of medicine including orthopedics, cardiothoracic surgery, plastic surgery, dermatology, dentistry, and diabetic wound healing. PRP is now starting to become an area of interest in reproductive medicine more specifically focusing on infertility. Poor ovarian reserve, menopause, premature ovarian failure, and thin endometrium have been the main areas of research. The aim of this article is to review the existing literature on the effects of autologous PRP in reproductive medicine providing a summation of the current studies and assessing the need for additional research.

Methods A literature search is performed using PubMed, MEDLINE, and CINAHL Plus to identify studies focusing on the use of PRP therapy in reproductive medicine. Articles were divided into 3 categories: PRP in thin lining, PRP in poor ovarian reserve, and PRP in recurrent implantation failure.

Results In women with thin endometrium, the literature shows an increase in endometrial thickness and increase in chemical and clinical pregnancy rates following autologous PRP therapy. In women with poor ovarian reserve, autologous intraovarian PRP therapy increased anti-Mullerian hormone (AMH) levels and decreased follicle-stimulating hormone (FSH), with a trend toward increasing clinical and live birth rates. This trend was also noted in women with recurrent implantation failure.

Conclusions Limited literature shows promise in increasing endometrial thickness, increasing AMH, and decreasing FSH levels, as well as increasing chemical and clinical pregnancy rates. The lack of standardization of PRP preparation along with the lack of large randomized controlled trials needs to be addressed in future studies. Until definitive large RCTs are available, PRP use should be considered experimental.

Keywords Platelet-rich plasma · Assisted reproduction · Reproductive endocrinology · Infertility · Gynecology

Introduction

Advancements in reproductive medicine with the introduction of IVF have had a significant impact on the increase in pregnancy rates. Endometrial receptivity is crucial for successful embryo implantation. Endometrial thickness is an indicator for endometrial receptivity as well as a prognostic marker for pregnancy outcome following embryo transfer [1]. However, despite these advancements, the management and treatment of thin endometrium have remained a challenge in infertile patients who struggle with this condition [2, 3]. The incidence rate in women with thin endometrium is 2.4% [4]. A thin endometrium (defined as an endometrial thickness of <7mm) is not optimal for embryo implantation and is associated with poor pregnancy outcomes, increase in recurrent pregnancy loss, and increase in embryo transfer failure [5–9]. There are a number of therapies 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 [2, 3, 5–7]. However, despite these interventions,

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many women with thin or damaged endometrial linings do not respond to these therapies.

Poor ovarian reserve (POR) is one of the main contributing factors of infertility in women of advanced reproductive age. Although these women undergo IVF and other infertility interventions, their pregnancy rates remain low, and they have high rates of recurrent pregnancy loss [10]. Anti-Mullerian hormone (AMH) and antral follicle count (AFC) are the most sensitive markers to assess ovarian reserve. Women suffering from POR have low oocyte yield and may require oocyte donation or adoption; however, the latter two options do not provide genetically related offspring [11].

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 include transforming growth factor-beta, fibroblast growth factor, insulin-like growth factors 1 and 2, vascular endothelial growth factor, and epidermal growth factor [1]. PRP's initial introduction into medical practice was its role in tissue growth and repair in orthopedics, cardiothoracic surgery, plastic surgery, dermatology, dentistry, and diabetic wound healing; however, despite the use of PRP in various fields, there has been little high-quality evidence that demonstrates its efficacy [12–15]. Autologous PRP is obtained through collection of an individual's whole blood via peripheral venipuncture that is then centrifuged to remove red blood cells from the sample [16]. The purpose of this is to have a concentrated sample of platelets that contain a 5- to 10-fold higher concentration of growth factors that get released by activated platelets. The general process of PRP preparation consists of collection of whole blood, an initial centrifugation to separate and remove red blood cells from the sample, then typically one additional centrifugation to concentrate the platelets, and then the addition of a platelet agonist to activate the sample [17, 18].

Autologous PRP has now expanded into the realm of reproductive medicine. Studies on autologous PRP have suggested promising results in women with thin endometrial lining as well as women with diminished ovarian reserve or recurrent implantation failure, possibly resulting in improved outcomes.

Methods

In preparation of this narrative review, a literature search was performed to identify studies focusing on the use of platelet-rich plasma in reproductive medicine from 1995 until February 2021. The search engines used were PubMed, MEDLINE, and CINAHL Plus. The search words were "PRP and fertility," "platelet-rich plasma and fertility," "PRP and infertility," "platelet-rich plasma and infertility," "PRP and thin endometrial lining," "platelet-rich plasma and thin endometrial lining," "PRP and ovaries," "platelet-rich plasma and ovaries," and "poor ovarian reserve." A total of 29 articles were used for this review. Poor ovarian reserve was defined as the reduction in the quality and the quantity of oocytes in reproductive age women. Recurrent implantation failure is defined as failure to achieve clinical pregnancy after at least 3 IVF cycles utilizing high quality. The studies reviewed were randomized controlled trials, case series, case reports, reviews, and pilot studies.

Results

Platelet-rich plasma preparation and standardization

There are numerous methods of preparation for PRP from whole blood collection to commercially made PRP kits. With commercially available PRP kits, concentration and collection time vary greatly depending on the timing and relative centrifugal force (RCF), meaning different concentrations of platelets and leukocytes are obtained which in turn impact the different types of growth factors in the sample [17]. Therefore, the lack of standardization in preparation method can potentially affect the outcomes and reproducibility of a study.

In reviewing the literature, it is clear that the methods of preparation for PRP also lacked consistency. Kamath et al. discuss using 0.5 to 1.0 ml of PRP for intrauterine infusion; however, they do not discuss the method of preparation or if a platelet agonist was used to activate the platelets and if so, which agonist was used [19]. There are different types of platelet agonists used for activation, including calcium chloride, thrombin, and collagen [20]. Chang et al. collected 15ml of whole blood from the participants and then used the two-step centrifugation process, the initial at 300 × *g* for 10 min at 18°C which results in 3 layers consisting of red blood cells at the bottom, buffy coat in the middle, and cellular plasma in the supernatant [21]. The top two layers were placed in a separated tube and centrifuged at 700 × *g* for 15 min at 18°C, and 0.5 to 1.0 ml of PRP was pipetted out for infusion purposes [21]. In contrast Coksuer et al. collected the sample at room temperature and centrifuged at 1500 × *g* for 5 min, the supernatant was then removed from the tube which was then recapped and underwent inversion/resuspension, and the remaining sample (1 ml of PRP) was utilized for infusion [5]. Nazari et al. centrifuged the sample immediately after collection initially at 1200 rpm for 10 min and then centrifuged again at 3300 rpm for 5 min to collect 0.5ml of PRP for infusion [9]. From the few examples discussed above, the importance of standardization in PRP preparation protocols, the need for quality control, and the ability to reproduce consistent results

are critical; otherwise, the interpretation and comparison among studies becomes impossible [17].

PRP in thin lining (summarized in Table 1)

Chang et al. were the first to use PRP in women with thin lining and found an increase in endometrial thickness and improved pregnancy outcome [7]. They analyzed 5 women who had all previously undergone IVF without success with standard hormonal therapy and poor endometrial response. All received estradiol for endometrial preparation, 6mg/day with an increase to 12mg/day if the endometrial lining responded poorly [7]. Despite the increase in the doses of estradiol in all participants, the endometrial lining remained <7mm. These women underwent hysteroscopic lysis of uterine adhesions (if found) and intrauterine autologous PRP infusion [7]. The endometrial lining was remeasured 72 h following PRP infusion, and if the lining was <7mm, another PRP infusion was performed; 2 women received one infusion and 4 received 2 infusions [7]. Chang et al. reported an increase in endometrial thickness 48–72 h after PRP infusion in all 5 women, which reached 7mm by the day of progesterone administration [7]. All underwent embryo transfer with patients 1,2, and 5 undergoing transfer of 2 blastocysts and patient 3 with 1 blastocyst on day 5, whereas patient 4 had two cleavage stage embryos that were transferred on day 3 [7]. This resulted in two twin pregnancies and 3 singleton pregnancies; however, patient 3 had a missed abortion at 9 weeks with chromosomal testing showing 45, XO [7]. In another small study looking at 10 participants with thin endometrium, 4 had history of hysteroscopic resection due to Asherman's syndrome and leiomyomas and underwent intrauterine autologous PRP infusion which resulted in an increase in thickness of the endometrium 48 h following infusion; however, they required a second infusion to reach a thickness of >7mm [23]. Embryo transfer was then performed and 5 of the 10 participants became pregnant, 4 of which had normal progressing pregnancies [23]. It is not reported if these pregnancies resulted in successful live births. Although showing promising results, this study and the aforementioned study have small sample sizes, which affect the strength and validity of these studies.

Tandulwadkar et al. analyzed 68 women between the ages of 20 and 40 years who had a history of thin endometrium despite estradiol therapy, those with more than 2 cycle cancelations due to poor endometrial response, or those with poor endometrial vascularity (defined as <5 vascular signals reaching into zones 3 and 4 of the endometrium) as assessed using power Doppler [24]. Intrauterine autologous PRP was infused in those with poor responding endometrium despite estradiol therapy for 15 to 16 days and poor endometrial vascularity [24]. Following PRP infusion 72 h later, the endometrial lining and vascularity were reassessed. Those with good vascularity and endometrial thickness >7mm underwent embryo transfer, and those who did not meet the criteria repeated the PRP infusion. Results showed a significant increase in the endometrial thickness (p <0.00001), with a chemical pregnancy rate of 60.93% (39 patients) and a clinical pregnancy rate of 45.31%. Of the 39 women with positive HCG, 13 of them were in their second trimester, 13 were in their first trimester, one had an ectopic pregnancy, three had anembryonic gestations, two had missed abortions, and two had biochemical pregnancies [24].

Table 1. Studies evaluating PRP and thin endometrium

Author	Study design	Level of evidence	Control group (n)	Intervention group (n)	Endometrium prior to intervention (mm)	Endometrium post intervention (mm)	p value	p value		
								Clinical	Chemical	Clinical
Chang et al. (2015) [7]	Cohort	3	-	5	5.9–6.6	>7	-	80	-	
Zahedmodarres et al. (2017)	Cohort	3	-	10	4–6	7.1–7.5	-	40	-	
Eftekhar et al. (2018) [6]	RCT	2	33	33	6.09±0.47	8.67±0.64	0.001	32.5	0.091	0.044
Chang et al. (2019) [21]	Prospective cohort	3	30	34	6.32±0.54	7.65±0.22	<0.05	44.12	-	0.036
Kim et al. (2019) [2]	Prospective cohort	3	-	20	4–6.8	4.2–9.1	0.070	30	0.020	
Nazari et al. (2019) [9]	Double-blind RCT	2	30	30	4.92±0.67	7.21±0.18	<0.001	33.3	0.031	0.048
Frantz et al. (2020) [22]	Retrospective case series	4	-	21	<5	-	-	66.7	-	

PRP platelet-rich plasma, *HRT* hormone replacement therapy, *eSF* human endometrial stromal fibroblasts, *eMSC* endometrial mesenchymal stem cells, *BM-MSC* bone marrow–derived mesenchymal stem cells, *IC* Ishikawa endometrial adenocarcinoma cells

Eftekhar et al. conducted the first randomized controlled trial with 66 eligible participants with thin endometrium despite estradiol therapy [6]. They were divided into a control group and PRP group and underwent embryo transfer. A statistical difference in the endometrial thickness was noted in the PRP group after the initial intrauterine autologous PRP infusion compared to that in the control group (p=0.001) as well as a higher implantation rate (p=0.002). They also found a lower cycle cancelation rate and higher pregnancy rate among the PRP group; however, this was not statistically significant [6].

Coksuer et al. performed a retrospective study evaluating 70 women with history of recurrent implantation failure [5]. Women with suboptimal endometrial linings (<7mm) underwent PRP and FET (34 women), and those with optimal linings who had undergone FET only consisted the control group (36 women). Endometrial preparation was performed using estradiol 6mg daily on cycle day 1 and was increased to 12mg daily if the endometrium was <7mm. Once the endometrial thickness reached 8mm or above, vaginal progesterone 400mg twice a day was started and continued until 12 weeks' gestation if the patient became pregnant [5]. Women whose endometrium was refractory to 20 days of the preparation regimen received autologous PRP 48 h prior to FET. The endometrial thickness in the PRP group was significantly higher after PRP treatment, (10mm (range 8–14mm)) compared to pre-PRP treatment 6.25mm (range 4.3–6.9mm), p<0.001. The biochemical pregnancy rate was 61.8%, clinical pregnancy rate was 50%, and the live birth rate was 41.2%, with the latter two being statistically significant (0.042 and 0.045, respectively) [5].

In a follow-up study to their initial report, Chang et al. conducted a prospective cohort study analyzing a larger population (64 patients) [25]. All participants were under the age of 40 with FSH levels < 10 and have 2 good-quality frozen blastocysts [25]. Estradiol was used for endometrial preparation on day 2 or 3 of the menstrual cycle at 6mg/day with a maximum of 12mg/day if the endometrium was <7mm, and if it remained <7mm, patients chose to undergo intrauterine autologous PRP infusion and, if they declined, were placed in the control group [25]. For those in the PRP group (n=34) it is unclear how long after the PRP infusion the transfer occurred. Eight participants in the PRP group had repeated cycles due to cancelation of their cycle secondary to refractory thin endometrium compared to 21 cancelations in the control group [25]. The cancelation rate in the PRP group compared to the control was 19.05 and 41.18%, respectively (p =0.022) [25]. They also found a significant increase in the endometrial thickness in the PRP group compared to that in the control (p =0.013), as well as an increase in the clinical pregnancy rate (44.12% vs 20%, p =0.036) and the implantation rate (27.94% vs 11.67%, p =0.018). The study did not provide follow-up regarding progression of the pregnancies and if this led to successful live births.

In the second double-blind RCT, Nazari et al. analyzed 60 women who were randomly assigned to the PRP group (30) or the sham-catheter group (30) [26]. All participants received estradiol 6mg/day on day 2 or 3 of the menstrual cycle for endometrial preparation, and it was increased to 8mg/day on days 9–10 due to inadequate endometrial thickness. On days 11–12, intrauterine PRP infusion or the sham-catheter was performed due to persistently thin endometrial lining. Once the endometrial lining was ≥ 7mm, 400-mg progesterone was administered vaginally twice daily, and embryo transfer was performed on embryonic day 3. The endometrial thickness was 7.21 ± 0.18 mm in the PRP group and 5.76 ± 0.97 mm in the sham-catheter group (p<0.001). There were 12 chemical pregnancies in the PRP group and 2 in the sham-catheter group (40% vs 6.7%, p=0.031), with 10 clinical pregnancies noted in the PRP group compared to one in the sham-catheter group (33.3% vs 3.3%, p=0.048).

Most recently Frantz et al. performed a retrospective analysis on 21 patients with a history of their endometrium being refractory to standard hormone therapy (endometrial lining not increasing above 5mm) as well as having day 5 or day 6 good-quality blastocysts that were graded 3BB or greater [22]. These patients underwent endometrial preparation with 6mg of oral estradiol starting on the last day of the menstrual cycle. They all underwent ultrasounds on day 7 or 10, and if the endometrial thickness was still below 7mm, the estradiol was increased to 8mg per day [22]. If the endometrium did not reach 7mm or above after 14 to 17 days of estradiol, they underwent intrauterine PRP infusion every second day for a total of three infusions [22]. 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 transferred [22]. There were 16 clinical pregnancies (66.7%), of which 13 resulted in ongoing pregnancies or live births (54%) and 3 ended in a miscarriage. Of note, the authors suggest that PRP improves intrauterine receptivity to embryo implantation, regardless of whether the endometrium reached the appropriate growth for embryo transfer [22].

Based on the above literature, intrauterine autologous PRP in women with thin lining seems to show promise. The increase in endometrial regeneration, implantation rate, and chemical and clinical pregnancy rates associated with PRP therapy suggests a promising alternative for women struggling with this problem, even in those whose endometrial thickness does not reach 7 mm. However, additional research needs to be done using larger-scale randomized controlled trials with larger sample sizes to demonstrate the utility of autologous PRP in clinical practice.

PRP in women with diminished ovarian reserve (summarized in Table 2)

Intraovarian PRP therapy is a novel alternative for women with POR. Active PRP collected as discussed earlier is then injected under ultrasound guidance into the ovarian cortex. Typically, following intraovarian PRP injection on day 2 or 3 of the subsequent menstrual cycle, FSH and AMH levels, along with AFC, were repeated to evaluate the effects of PRP [11, 27, 33].

Sills et al. were the first to use intraovarian PRP in this context [27]. They conducted a study with 4 patients with history of POR undergoing intraovarian autologous PRP with controlled ovarian stimulation using gonadotropin and found a decrease in FSH levels and an increase in AMH levels after this intervention; however, only the FSH finding was clinically significant ($p<0.01$), whereas the increase in AMH was not ($p=0.17$). Following autologous PRP injection, all women had an oocyte yield ranging from 4 to 7 eggs per patient. All underwent intracytoplasmic sperm injection (ICSI) which resulted in each patient having at least one day 5 blastocysts to undergo cryopreservation with a plan for future frozen embryo transfer with the exception of one patient who opted for embryo thaw transfer which progressed to a pregnancy at 9 weeks' gestation [27].

Pantos et al. were the first to use intraovarian PRP in menopausal women [11]. In their case series of 3 women, two were diagnosed with POF ages 40 and 27, and one woman was diagnosed with menopause age 46. In this study, each woman had normal hysteroscopic evaluation, elevated FSH and low AMH levels, and an AFC that was essentially zero. Following intraovarian autologous PRP injection, on day 2 of the subsequent menstrual cycle, their FSH levels had significantly decreased (patient 1 119->27, patient 2 65->10, and patient 3 46.5-> 20), AMH levels increased (patient 1 0.16->0.22, patient 2 0.06->0.13 , patient 3 0.17->0.25), and the AFC showed 2 follicles in each ovary for patient 1 (age 46) and 2 follicles in the right ovary in both patients 2 and 3. Patient 1 had spontaneous restoration of her menstrual cycle 1 month following PRP treatment and opted out of IVF to attempt natural conception. At the time of publication, she had a spontaneous healthy pregnancy and was at 37 weeks' gestation [11]. Patient 2 also had restoration of her menstrual cycle and conceived naturally and at the time of publication was at 37 weeks' gestation with a healthy pregnancy [11]. Patient 3 had a healthy pregnancy at 26 weeks' gestation; however, it was not disclosed whether this pregnancy was from natural conception or IVF.

Sfakianoudis et al.'s case series included 3 women diagnosed as poor responders who had previously undergone IVF and were unsuccessful, had poor oocyte yield, as well as had poor embryo quality [28]. Three months after undergoing intraovarian autologous PRP injection, there was an overall decrease in FSH by 67.33% and an increase in AMH by 75.18% (patient 1 FSH 27. 8->11.1, AMH 0.65-> 1.1; patient 2 FSH 18.3-> 4.1, AMH 0.54->0.93; patient 3 FSH 24.1-> 8.6, AMH 0.44->0.81). Following autologous PRP therapy one patient underwent six natural cycles which resulted in 3 excellent quality blastocysts, as per Gardner's criteria [28]. All 3 blastocysts were transferred, and she had a successful live birth via cesarean section [28]. Patient 2, following autologous PRP injection, underwent 2 natural cycles which resulted in 2 good-quality oocytes and 2 zygotes which were cryopreserved for future cycles; however, she spontaneously conceived and was at 24 weeks' gestation. Patient 3 had 2 excellent quality blastocysts that were transferred and was at 17 weeks' gestation at the time of publication [28].

Stojkovska et al. reported on 40 patients (35 to 42 years of age) [34]. They were divided into group A and group B, where group A (20 patients) received intraovarian injection of autologous PRP prior to IVF. Ovarian stimulation in all patients consisted of 100mg/day of clomiphene citrate on days 2–6 of the cycle. When a leading follicle was 14mm or greater, low-dose human menopausal gonadotropin and Cetrotide 0.25mg daily were initiated [34]. HCG trigger was administered once the leading follicles reached 18mm or greater and the estradiol level was 200pg/ml or above, followed by oocyte retrieval. Embryo transfers were performed 3–5 days later. Results showed an implantation rate of 33.33 ±44.99%, clinical pregnancy rate of 33.33±44.99%, and a live birth rate of 40.00 ±50.71% in the PRP group, compared to an implantation rate of 10.71 $\pm$ 28.95% ($p=$ 0.70), a clinical pregnancy rate of 10.71 $\pm$ 28.95% ($p=$ 0.69), and a live birth rate of 14.29 $\pm$ 36.31% ($p=$ 0.71) in the control group [34]. There were no differences in outcome between the two groups.

Cakiroglu et al. treated 311 women who had previously been diagnosed with primary ovarian insufficiency [29]. They received intraovarian PRP injection, and of these 311 women, 23 were able to achieve spontaneous pregnancy (7.4%), and 82 (26.3%) developed at least one cleavage stage embryo after undergoing ovarian hyperstimulation for IVF [29]. Of the 23 women who had conceived spontaneously, 7 ended in miscarriages, 5 were still ongoing between 24th and 35th weeks' gestation, and 11 continued to full-term pregnancies and were delivered between 37 and 40 weeks' gestation. Prior to treatment with intraovarian PRP injection, 186 of the 311 women had an AFC of 0, and following treatment only 87 had an AFC of zero. For the rest, there was a statistically significant increase in AFC (1.7± 1.4 vs 0.5 ± 0.5; $p<0.01$). There was also an increase in AMH following intraovarian PRP treatment (0.18 ± 0.18 ng/ml vs 0.13 ± 0.16; $p<0.01$); however, FSH was not statistically significantly different (41.6 ± 24.7 vs 41.9 ± 24.7, $p=0.87$). Of the 311 participants, 201 underwent IVF with at least one antral follicle following PRP treatment; however, only 130 underwent oocyte retrieval, and of those 82 had at least one cleavage stage embryo, and

Table 2. Studies evaluating PRP and ovarian insufficiency/menopause

Author	Study design	Level of evidence	PRP group (*n*)	Labs prior to intervention		Labs post intervention		*p* value		Embryos/oocytes post intervention	Restoration of menstrual	Pregnancy rate (%)	*p* value
				AMH	FSH	AMH	FSH	AMH	FSH				
Sills et al. (2018) [27]	Cohort	3	4	0.38 (0.03–0.78)	13.6 (10.8–14.9)	0.61 (0.03–0.92)	7.7 (3.3–11.8)	0.17	<0.01	4–7	-	-	-
Sfakianoudis et al. (2018) [28]	Case series	4	3	0.65/0.54/0.44*	27.8/18.3/24.1*	1.1/0.93/0.81*	11.1/4.1/8.6*	-		3/2/3*	-	100	-
Pantos et al. (2019) [11]	Case series	4	3	0.16/0.06/0.17*	119/65/46.5*	0.22/0.13/0.25	27/10/20*	-		**	Yes	100	-
Stojkavska et al. (2019)	Prospective	3	20	-		0.35±0.19	19.27±2.29	0.03	0.97	1.87±1.13***	-	33.33 ±44.99	0.69
Cakiroglu et al. (2020) [29]	Cohort	3	311	0.01–0.82	25–155	0.18±0.18***	41.6±24.7	<0.01	0.87	1.81±1.3***	-	8	-
Hsu et al. (2020) [30]	Case report	-	1	0.23	63.65	-	17.84	-		6	Yes	100	-
Melo et al. (2020) [31]	Prospective non--randomized	3	46	0.62 (0.47–0.76)	13.6 (12.9–17.5)	1.01 (0.9–1.3)	9.07 (8.3–10.5)	<0.001	<0.001	2.0–9.0	-	23.9	0.03
Sills et al. (2020) [32]	Prospective non--randomized	3	182	0.21 ± 0.5 0.17 ± 0.03	43.1 ± 5.9 63.4 ± 6.2	0.32 ± 0.08 0.21 ± 0.04	54.3 ± 7.3 68.4 ± 4.7	0.030 0.009	NS	-	-	-	-

*Patient 1/patient 2/patient 3

**Did not undergo retrieval. Had spontaneous pregnancies

***Mean ± SD

cryopreservation or fresh embryo transfer was performed [29]. Of the 82 women who underwent IVF, 25 stored the embryos for later transfer. For those who underwent transfer, 28 (49.1%) were fresh and 29 (50.9%) were frozen-thawed transfers. Of the fresh transfers, 3 miscarried during the first trimester (42.9%); 3 were ongoing pregnancies at 24 weeks', 30 weeks', and 31 weeks' gestation; and 1 transfer resulted in delivery at 34 weeks' gestation. Among the frozen-thawed transfers, one resulted in a miscarriage during the first trimester (16.7%); 3 were ongoing pregnancies at 17 weeks', 22 weeks', and 36 weeks' gestation (50.0%); and 2 resulted in term pregnancies (33.3%). Of the women who underwent embryo transfer following intraovarian PRP treatment, 13/57 (22.8%) achieved pregnancy and 9/57 (15.8%) achieved sustained implantation or live birth.

Hsu et al. presented a case report of a 37-year-old woman with POI and secondary amenorrhea for 6 months [30]. Her AMH was <0.02 ng/ml, FSH was 63.65 mIU/ml, and LH was 44.91 mIU/ml. She underwent intraovarian injection of autologous PRP as well as gonadotropin consisting of 150IU rFSH and 75IU rLH. Following PRP treatment, on day 4, a 4-mm follicle was detected which continued to grow to 10mm by day 8, and she underwent spontaneous ovulation. She underwent controlled ovarian stimulation in the two following menstrual cycles using Gonal-F 300IU and Menopur 375IU on days 2 and 5. Mature follicles developed, and she underwent oocyte retrieval on day 11 in both cycles. A total of 6 oocytes were obtained from both cycles and were fertilized using ICSI and cultured until day 3. Two 8-cell and one 5-cell good embryos were transferred back into the uterus and resulted in a successful twin pregnancy which were delivered preterm at 30 weeks' gestation of a male (1300g) and female (1258g) infants. Following treatment, FSH decreased to 17.34 mIU/ml; however, AMH level was not reported.

Melo et al. conducted a prospective non-randomized comparative pilot study of 83 women undergoing IVF who were 38 years of age or above, had a baseline FSH on day 3 of their menstrual cycle of 12mIU/ml or greater, had AMH of <0.8 ng/ml, and had a normal uterine cavity that was assessed using hysteroscopy that were eligible to participate in this study [31]. Of the 83 women, 46 underwent intraovarian PRP therapy and 37 had no intervention. Those treated with PRP were found to have a 63% increase in their AMH levels compared to those without intervention (Table 2). FSH levels decreased by 33% in the PRP group compared to those in the control [31]. Notably, 75% more antral follicles were present in the autologous PRP group compared to those in the control at the 3-month follow-up (p<0.001). Those who underwent PRP therapy also had a higher biochemical rate (p=0.02) and a clinical pregnancy rate (p=0.03). The live birth rate in the PRP group was 8.7% compared to 2.7% in the control group; however, this was not statistically significant (p=0.38).

Most recently, Sills et al. reported on 182 women who underwent ovarian PRP injection, all having menopausal levels of FSH and AMH, regardless of age (mean age 45.4 ± 6.1 years) [32]. They showed a statistically increased AMH and higher FSH levels, with FSH levels actually increasing post PRP from 43.1 ± 5.9 to 54.3 ± 7.3 in women < 42 and from 56.1 ± 4.1 to 68.4 ± 4.7 in women > 42. AMH increased from 0.21 ± 0.5 to 0.32 ± 0.08 in women < 42 and 0.17 ± 0.03 to 0.21 ± 0.04 in women > 42. None of these levels are clinically different even if statistically so in the case of AMH [32]. The biggest deficiency in this study is whether any of these women underwent subsequent ovarian stimulation. If anything, this study shows the futility to using PRP in menopausal women.

PRP in recurrent implantation failure (summarized in Table 3)

The first report regarding the use of PRP in recurrent implantation failure was a case report by Farimani et al. in a 45-year-old woman diagnosed with RIF, having normal ovarian reserve, and who underwent 2 IVF cycles without success [8]. She proceeded with donor oocytes but still had "multiple" failed cycles (unknown number of attempts). She then received intrauterine autologous PRP 24 h prior to frozen-thawed embryo transfer using 3 embryos from donor oocytes. This resulted in a successful live birth of a male infant via cesarean section [8].

In a retrospective cohort study, Mehrafza et al. compared the impact of autologous PRP and GCSF on pregnancy outcome in patients who suffered from recurrent implantation failure [35]. A total of 123 patients were included in a PRP group (n=67) or a GCSF group (n=56). In the GCSF group, a single dose of 300μg of systemic recombinant GCSF was administered 2 h prior to embryo transfer. Both groups underwent endometrial preparation with 4mg/day of oral estradiol, and progesterone was started when the endometrium was 7mm or above. The PRP group received PRP infusion 48 h prior to embryo transfer [35]. The clinical pregnancy rate was higher in the PRP group compared to the GCSF group (40.3 and 21.4%, respectively), with p values of 0.025. However, the implantation rates were not statistically significant (17.2% vs 10.5%, p= 0.14) [35].

In the first randomized controlled trial (RCT), Nazari et al. evaluated 97 participants with prior history of failed implantation who were randomly assigned to either the control group who underwent FET or the autologous PRP plus FET group [26]. All participants received estradiol 6mg/day starting day 2 or 3 of the menstrual cycle for endometrial preparation, with an increase to 8mg/day if endometrial thickness (ET) did not reach 7mm or greater. When this occurred, vaginal progesterone therapy 400mg twice daily was initiated [26]. All participants had good-quality embryos that were transferred. For

Table 3. Studies evaluating PRP and recurrent implantation failure

Author	Study design	Level of evidence	Intervention group (*n*)	Endometrial thickness pre-PRP	Endometrial thickness post PRP	Implantation rate (%)	*p* value	Clinical pregnancy rate (%)	*p* value
Farimani et al. (2017) [8]	Case report	-	1	-	-	-	-	100	-
Mehrafza et al. (2019) [35]	Retrospective cohort	3	67	-	-	17.2	0.057	40.3	0.025
Coksuer et al. (2019) [5]	Retrospective cohort	3	34	<7	10 (8–14)	-	-	50	0.042
Nazari et al. (2019) [9]	RCT	2	97	-	-	-	0.009	44.89	0.003
Sfakianoudis et al. (2019) [36]	Case report	-	1	-	-	-	-	100	-
Aghajanzadeh et al. (2020) [37]	Cohort	3	30	<7	7.79±1.05	6.7	0.12	3.3	1
Zargar et al. (2021) [38]	Prospective randomized	3	40	-	-	-	-	12.5	NS

those in the PRP group, intrauterine autologous PRP was infused 48 h prior to embryo transfer. The chemical pregnancy rate was significantly higher in the PRP group than the control group (53.06% vs 27.08%, p=0.009) [26]. The clinical pregnancy rate was also significantly higher in the PRP group than the standard group (44.89% vs 16.66%, p=0.003) [26]. Just like Coksuer at al.'s results [5], the benefit could be in the increased endometrial thickness in the PRP group.

Sfakianoudis et al. presented a case report of a 35-year-old woman with a history of premature ovarian insufficiency and 6 failed donor oocyte embryo transfers who underwent diagnostic hysteroscopy and found to have endometritis [36]. Following treatment, she underwent hormonal treatment and embryo transfer with two donor oocyte blastocysts which was unsuccessful. Another hysteroscopy was performed with endometrial sampling, and she was again diagnosed with endometritis [36]. The patient was again treated and received autologous intrauterine PRP infusion (2.5 cc) in the follicular phase (no exact timing was given) and underwent a third hysteroscopy with endometrial sampling, which showed no signs of endometritis [36]. A frozen embryo transfer with two donor oocyte blastocysts (5BB and 5 BC) was performed in the next menstrual cycle (no data given on how many days after the initial PRP administration the ET was done), which resulted in a twin pregnancy that was delivered at 36 weeks' gestation [36].

Most recently, Aghajanzadeh et al. analyzed 30 women between the ages of 18 and 40 years with a history of recurrent implantation failure [37]. Endometrial preparation with estradiol 6mg/day was started on day 2 or 3 of the menstrual cycle, and the endometrial lining was evaluated on day 9 or 10 of the cycle [37]. Women with endometrial thickness $\leq$ 7mm were given intrauterine autologous PRP infusion the same day, and embryo transfer was performed 48–72 h later [37]. There was a 6.7% increase in the implantation rate; however, this was not statistically significant [37]. There also was no statistically significant difference in the clinical pregnancy rate, chemical pregnancy rate, or ongoing pregnancy rate between the control and the PRP group [37]. The small sample size as well as the inclusion of women with thrombotic defects into the study may have impacted the results.

Most recently, Zargar et al. performed a prospective randomized study including 80 women with RIF [38]. The inclusion criteria included at least two prior IVF failures and age < 41 years. Women in the PRP group (n=40) received 1.5 ml of intrauterine PRP 48 h before ET. For those with endometrial thickness < 7 mm, another PRP injection was performed 48 h after the first injection, followed 48 h later by the ET. The clinical and live birth rates were higher in the PRP group, though not statistically so (12.5 and 12.5% compared to 5 and 2.5%) [38]. The authors concluded that the use of PRP in women with RIF does not significantly improve the outcome. However, 80 women underwent a mixture of fresh and frozen cycles (25% in the PRP arm underwent a fresh ET compared to 10% in the control group), making the results and interpretation of the study suspicious. Ideally the investigators should have used all fresh or all FET cycles rather than a mixture of both [38].

Conclusions

Autologous PRP is a novel alternative approach to treatment and management of certain 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 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 sizes. There are currently few ongoing RCTs worldwide evaluating the role of PRP in poor ovarian reserve, recurrent implantation failure, and thin endometrium in ART. It remains to be seen whether PRP is of any value in menopausal women, but the early results are discouraging. In addition, a standardized PRP preparation protocol is crucial to reproduce consistent and accurate results in all future studies. Until definitive large RCTs are available, PRP use should be considered experimental.

Data availability Not applicable

Code availability Not applicable

Declarations

Competing interests The authors declare no competing interests.

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