Am J Transl Res 2025;17(10):8110-8122
www.ajtr.org /ISSN:1943-8141/AJTR0167696

Original Article

Impact of platelet-rich plasma intrauterine perfusion on endometrial receptivity and pregnancy outcomes in patients with recurrent implantation failure and thin endometrium

Fangxin Peng, Min Xia, Jie Zheng, Xingxing Wang, Jie Liu, Hong Sun

Department of Reproductive Medicine, Maternal and Child Health Hospital of Hubei Province, Wuhan 430072, Hubei, China

Received July 25, 2025; Accepted September 26, 2025; Epub October 15, 2025; Published October 30, 2025

Abstract: Objectives: To evaluate the impact of autologous platelet-rich plasma (PRP) intrauterine perfusion on endometrial receptivity and pregnancy outcomes in patients with implantation failure. Methods: This retrospective cohort study included patients who visited our hospital between January 2019 and January 2024, all suffering from recurrent implantation failures and diagnosed with thin endometrium. Participants were divided into two groups: conventional-treatment (n=116) and PRP-treatment (n=104). Serum levels of estradiol 2 (E2), follicle stimulating hormone (FSH), and luteinizing hormone (LH) were measured before and 14 days after treatment. Transvaginal Doppler ultrasound assessed uterine artery, arcuate artery, and spiral artery pulsatility index (PI) and resistance index (RI) at both timepoints. Endometrial thickness was measured before and 14 days post-treatment. Pregnancy outcomes, including implantation rate, clinical pregnancy rate, ongoing pregnancy rate, and live birth rate, were recorded. Results: The PRP-treatment group showed a significant increase in endometrial thickness (P=0.037). Uterine artery PI (P=0.004) and RI (P=0.015), arcuate artery PI (P=0.037) and RI (P=0.003), and spiral artery PI (P=0.002) significantly decreased in the PRP-treatment group compared to the conventional-treatment group. Hormonal measurements indicated higher E2 (P=0.001) and lower FSH (P=0.002) and LH (P=0.002) levels post-treatment in the PRP-treatment group. Pregnancy outcomes significantly favored the PRP-treatment group, with higher implantation rates (P=0.004), clinical pregnancy rates (P=0.044), ongoing pregnancy rates (P=0.031), and live birth rates (P=0.032). Conclusion: PRP intrauterine perfusion significantly improves endometrial parameters, uterine hemodynamics, and pregnancy outcomes in patients with recurrent implantation failure and thin endometrium.

Keywords: Platelet-rich plasma, recurrent implantation failure, thin endometrium, endometrial receptivity, pregnancy outcomes, intrauterine perfusion

Introduction

Recurrent implantation failure (RIF), defined as the failure to achieve clinical pregnancy after multiple high-quality embryo transfers, alongside a thin endometrium (endometrial thickness <7 mm during the luteal phase), presents a significant challenge in assisted reproductive technology [1]. Despite optimal embryo quality and standard hormone protocols, these conditions result in persistent infertility, often due to impaired endometrial receptivity - the ability of the endometrium to support embryo attachment and development [2]. The underlying mechanisms are multifactorial, involving genetic, immune, and uterine factors [3, 4]. Current interventions, such as high-dose estrogen, vasodilators (e.g., sildenafil), and intrauterine G-CSF infusion, show inconsistent efficacy in 30-40% of cases, failing to address the underlying imbalances [5].

Furthermore, the subgroup of RIF patients with thin endometrium remains particularly challenging and has received limited attention. This condition indicates a severe disruption in endometrial receptivity, with poor response to standard treatments like high-dose estrogen or

https://doi.org/10.62347/VQDE2162

vasodilators. Research shows that this subgroup tends to not respond well to these therapies, likely due to the compounded nature of RIF and a thin endometrium [6, 7]. Evidence suggests that chronic inflammation and impaired blood vessel development may be key factors contributing to this persistent condition [8]. Recent studies propose that platelet-rich plasma (PRP) may offer significant benefits, promoting healthier blood flow and more balanced hormone levels [9]. Nonetheless, there is still a lack of detailed studies focusing specifically on the mechanisms of PRP in this patient population, highlighting the need for targeted research in this area [10].

Current treatments are not universally effective, as patients show variable responses, and the exact mechanisms remain unclear. This emphasizes the need for novel approaches to enhance uterine lining growth, particularly by improving blood flow. Adequate blood supply is crucial for endometrial growth and embryo implantation. Research suggests that better blood flow in the spiral arteries improves pregnancy outcomes [11]. For example, high pulsatility index (PI) and resistance index (RI) values on Doppler measurements indicate stiff arteries with high resistance, which can hinder the endometrium's readiness for implantation. Hormones also significantly influence endometrial receptivity by regulating molecules that prepare the endometrium for embryo attachment [12]. Estrogen and progesterone are vital for uterine lining preparation, and their levels are closely monitored during IVF cycles to optimize implantation conditions [13]. Despite this knowledge, more effective methods are needed to reliably improve endometrial health and increase pregnancy success rates.

Recent studies have shown that abnormal blood vessel formation and inflammation significantly contribute to poor endometrial receptivity [14]. PRP, derived from the patient's own blood, contains concentrated growth factors like vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), which are believed to improve endometrial function by stimulating blood vessel growth, reducing inflammation, and enhancing tissue healing [15]. PRP's bioactive molecules activate key signaling pathways, including PI3K/Akt and MAPK/ERK, which play critical roles in endometrial thickening, decidualization, and vascular growth [16]. Thus, PRP presents a promising alternative for RIF patients with thin endometrium, especially when standard treatments have failed.

Previous studies and meta-analyses have explored PRP use for RIF, but our study specifically focuses on RIF patients with thin endometrium (<7 mm). This group often responds poorly to standard therapies, representing a unique clinical challenge. Our primary objectives were to evaluate whether PRP intrauterine perfusion can effectively enhance uterine blood flow, improve hormonal balance, and increase endometrial thickness, embryo implantation, and live birth rates. Additionally, we aimed to thoroughly assess pregnancy outcomes, blood flow parameters, and hormone levels. Through this work, we hope to provide evidence supporting PRP as a beneficial treatment for this specific population, potentially improving IVF success and overcoming the limitations of current therapies.

Materials and methods

Case selection

This retrospective cohort study included 220 patients with RIF and thin endometrium, admitted to the Maternal and Child Health Hospital of Hubei Province between January 2019 and January 2024. Demographic information, implantation failure details, infertility causes, and other relevant data were collected from the hospital's case management system for each patient. All procedures adhered to the ethical guidelines set forth by the relevant institutional and national human research committees and complied with the principles of the 1964 Declaration of Helsinki and its subsequent revisions. The study was approved by the Institutional Review Board (IRB) of the Maternal and Child Health Hospital of Hubei Province. As the study involved only de-identified patient data, posing no risk to patient care, informed consent was waived by the hospital's IRB and ethics committee.

The sample size was based on the number of eligible patients treated during the study period (January 2019 to January 2024). A post-hoc power analysis was performed using G*Power

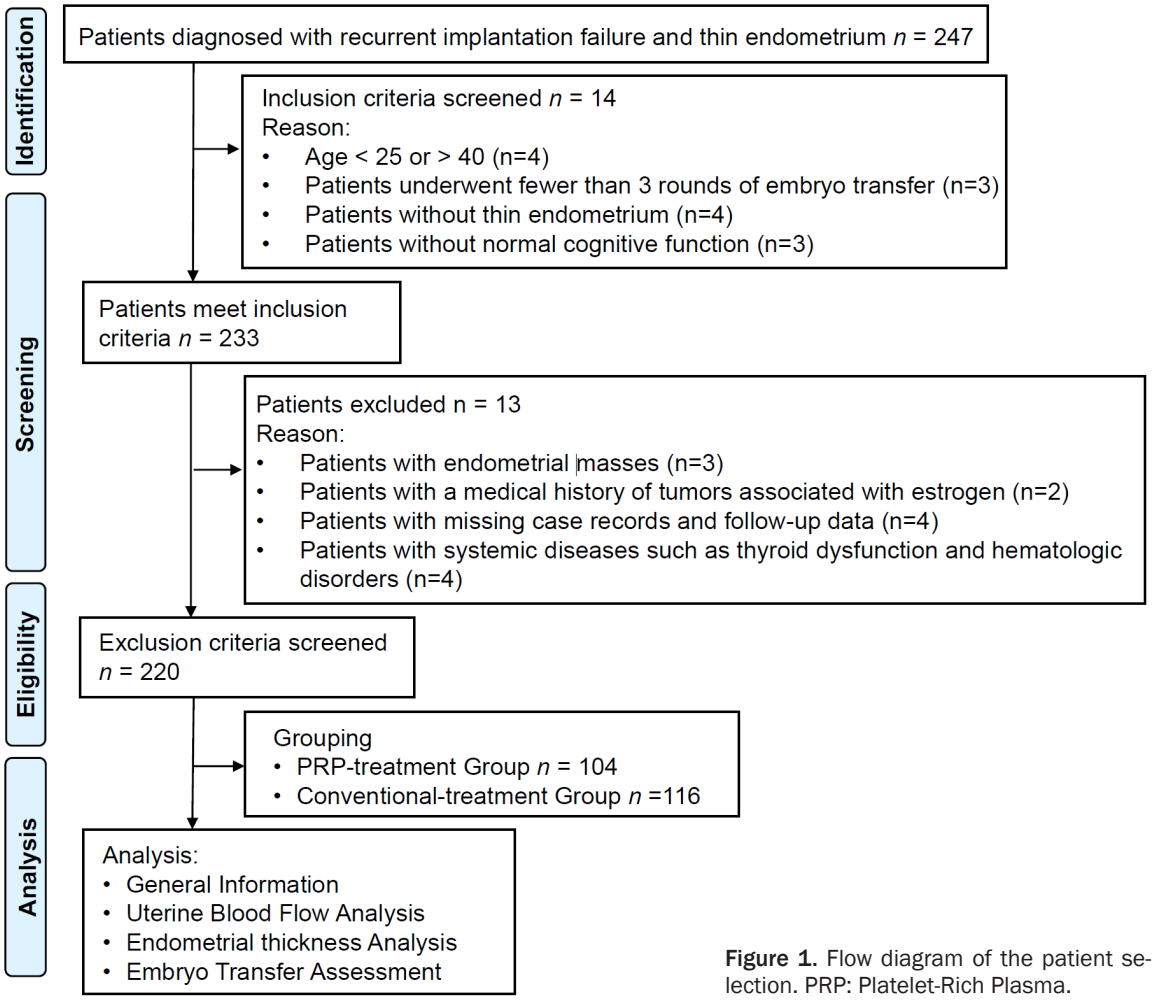

Figure 1. Flow diagram of the patient selection. PRP: Platelet-Rich Plasma.

software based on the observed live birth rates (Primary outcome: 26.7% in the conventional-treatment group vs. 40.4% in the PRP-treatment group). The analysis confirmed that the final sample size (n=220) provided over 80% power to detect this difference at a significance level of α=0.05.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients aged 25 to 40 years; (2) Patients who have undergone at least three rounds of embryo transfer, using no fewer than four viable embryos (including both fresh and frozen cycles), but have not achieved clinical pregnancy [17]; (3) Patients with thin endometrium (endometrial thickness <7 mm measured on the 7th day after the luteinizing hormone (LH) surge or human chorionic gonadotropin (hCG) administration during the mid-luteal phase) [18]; (4) Patients with normal cognitive function who are able to cooperate with various treatments and examinations.

Exclusion criteria: (1) Patients with endometrial masses; (2) Patients with a medical history of estrogen-related tumors; (3) Patients with adenomyosis; (4) Patients with bilateral hydrosalpinx; (5) Patients with missing case records or follow-up data; (6) Patients with systemic diseases such as thyroid dysfunction or hematologic disorders (**Figure 1**).

Grouping and treatment

Grouping: Patients were divided into two groups based on the treatment method: the PRP-treatment group (n=104) and the conventional-treatment group (n=116). The PRP-treatment group received intrauterine PRP infusion following conventional treatment, while the conven-

tional-treatment group received only conventional treatment.

Treatment: PRP preparation: On the third day of the menstrual cycle, 15 mL of venous blood was collected from each patient to prepare PRP. The blood was processed using a two-step centrifugation method. First, 8.5 mL of peripheral venous blood was mixed with 1.5 mL of Anticoagulant Citrate Dextrose Solution (FY41866, FEIYUBIO, China). The mixture was centrifuged at 2,500 rpm for 10 minutes at room temperature using a high-speed refrigerated centrifuge (CR22G, Hitachi, Japan). The resulting three layers included red blood cells at the bottom, plasma in the middle, and an intermediate brown layer. The plasma and brown layers were collected and subjected to a second centrifugation at 3,500 rpm for 15 minutes at 4°C to obtain the final PRP (approximately 1.5 mL). Platelet count was performed using a hematology analyzer (Sysmex XN-Series, Sysmex Corporation, Japan) to ensure a platelet concentration within the therapeutic range (1-3 million platelets/μL) [19].

Treatment protocol: The treatment protocol consisted of two steps, applied to both groups. Embryos were cryopreserved using vitrification at -196°C in liquid nitrogen and thawed according to a published two-step freezing protocol with propylene glycol and sucrose, followed by a three-step thawing process [20, 21]. Patients received intramuscular injections of a long-acting gonadotropin-releasing hormone agonist (281844, Abcam, USA) at a dose of 3.75 mg every 14 days, starting from the mid-luteal phase [22]. Endometrial thickness was monitored via ultrasound every 3 days until it reached 7 mm. If the endometrial thickness did not reach 7 mm, the estradiol valerate dosage (RM-E191811, QCS, China) was increased to 8 mg per day. Once the endometrial thickness exceeded 7 mm, a daily dose of 90 mg of progesterone pessary (Cyclogest; Actavis, UK) was administered vaginally for three days to induce endometrial conversion [23, 24].

In addition to conventional-treatment, the PRP-treatment group received intrauterine PRP infusion. The day after PRP preparation, the activated PRP was administered via intrauterine infusion. Patients assumed a lithotomy position, and the cervix was exposed via endoscopic manipulation. After disinfection of the vulva and vagina, approximately 1.5 mL of prepared PRP was aspirated into a sterile syringe and connected to a fine catheter. The catheter was carefully inserted through the cervical os, and the PRP was slowly infused into the uterine cavity over 1-2 minutes. After the infusion, patients were instructed to remain in position for 30 minutes.

Blood tests

Prior to treatment and 14 days after treatment, 5 mL of fasting venous blood was collected from patients before 8 AM. The samples were centrifuged at 3,000 rpm for 5 minutes, and the supernatant was collected for enzyme-linked immunosorbent assay (ELISA) to measure estradiol (E2), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels in serum. Specific kits for E2 (ab108667, USA Abcam), FSH (ab158468, USA Abcam), and LH (ab178658, USA Abcam) were used.

Transvaginal doppler ultrasound

Prior to treatment and 14 days after treatment, patients underwent transvaginal color Doppler ultrasound exams using the Voluson S10 GE ultrasound machine (GE, USA), equipped with a 4 to 8 MHz transvaginal probe. The calculation software was used to measure the PI and RI of the uterine arteries. According to the peak systolic velocity (PSV) and end-diastolic velocity (EDV), PI and RI were calculated using the following equations: PI = (PSV - EDV)/Time-Averaged Maximum Velocity (TAMV); RI = (PSV - EDV)/PSV. The changes in uterine blood flow during the follicular phase were studied for all participants.

Outcome indicators

Primary and secondary outcomes: The primary outcome was the live birth rate. Secondary outcomes included endometrial thickness, hormone levels (E2, FSH, LH), uterine artery Doppler indices (PI, RI), implantation rate, clinical pregnancy rate, and ongoing pregnancy rate.

Endometrial thickness (Em thickness) and morphology were measured both before and 14 days after treatment. Em thickness was determined as the maximum sagittal thickness of

Table 1. Comparison of general information

Parameters	Conventional-treatment Group (n=116)	PRP-treatment Group (n=104)	t/χ^2	p
Age (years)	33.96±1.44	34.14±1.65	0.866	0.387
BMI (kg/m^2)	22.73±3.30	22.02±3.00	1.649	0.101
Duration of infertility (years)	3.71±1.66	3.57±1.82	0.593	0.554
Menstrual cycle (day)	28.99±0.43	29.01±0.29	0.525	0.600
Cause of infertility [n (%)]			2.403	0.493
Pelvic/tubal factors	61 (52.59%)	63 (60.58%)		
PCOS	17 (14.66%)	16 (15.38%)		
Endometriosis/Adenomyosis	17 (14.66%)	13 (12.50%)		
Other causes	21 (18.10%)	12 (11.54%)		
Transplantation failures	3.71±0.31	3.66±0.21	1.389	0.166
Type of infertility [n (%)]			0.170	0.680
Primary infertility	57 (49.14%)	54 (51.92%)		
Secondary infertility	59 (50.86%)	50 (48.08%)		

Note: PRP: Platelet-Rich Plasma; BMI: Body Mass Index; PCOS: Polycystic Ovary Syndrome.

the uterine cavity, with the final measurement being the average of three independent readings.

The mid-sagittal plane of the uterus was selected, ensuring the endometrium was fully included within the sampling frame. The instrument's 3D function was activated to acquire and store three-dimensional volumetric data. VOCAL (Virtual Organ Computer-Aided Analysis) software was used to calculate endometrial volume.

The embryo implantation rate was defined as the ratio of gestational sacs to the total number of transferred blastocysts, assessed at 5 weeks of gestation via ultrasound.

Clinical pregnancy was confirmed by the presence of an intrauterine gestational sac and positive fetal cardiac activity observed via ultrasound between 6 and 8 weeks of gestation [25].

The miscarriage rate was determined as the proportion of spontaneous intrauterine pregnancy losses, confirmed by ultrasound, among all clinical pregnancies [26].

The live birth rate was defined as the birth of at least one live infant.

Cumulative pregnancy rate was followed up until May 2025.

Ongoing pregnancy was defined as a viable pregnancy confirmed by ultrasound at or beyond 12 weeks of gestation.

Statistical methods

Data analysis was performed using SPSS version 29.0 (SPSS Inc., Chicago, IL, USA). For data that followed a normal distribution, continuous variables were expressed as mean ± standard deviation. For data not following a normal distribution, variables were expressed as median (interquartile range). Categorical data were presented as frequencies and percentages. Unpaired t-tests were used to compare continuous variables between groups. A *P*-value <0.05 was considered statistically significant.

Results

Comparison of general information of patients

Key parameters were compared between the groups (**Table 1**). No significant differences were found in age (P=0.387), BMI (P=0.101), duration of infertility (P=0.554), or menstrual cycle length (P=0.600). The causes of infertility, including pelvic/tubal factors, PCOS, endometriosis/adenomyosis, and other causes, also showed no significant differences (P=0.493). Additionally, there were no significant differences in the number of transplantation failures (P=0.166) or infertility type (primary vs. secondary) (P=0.680) between the groups.

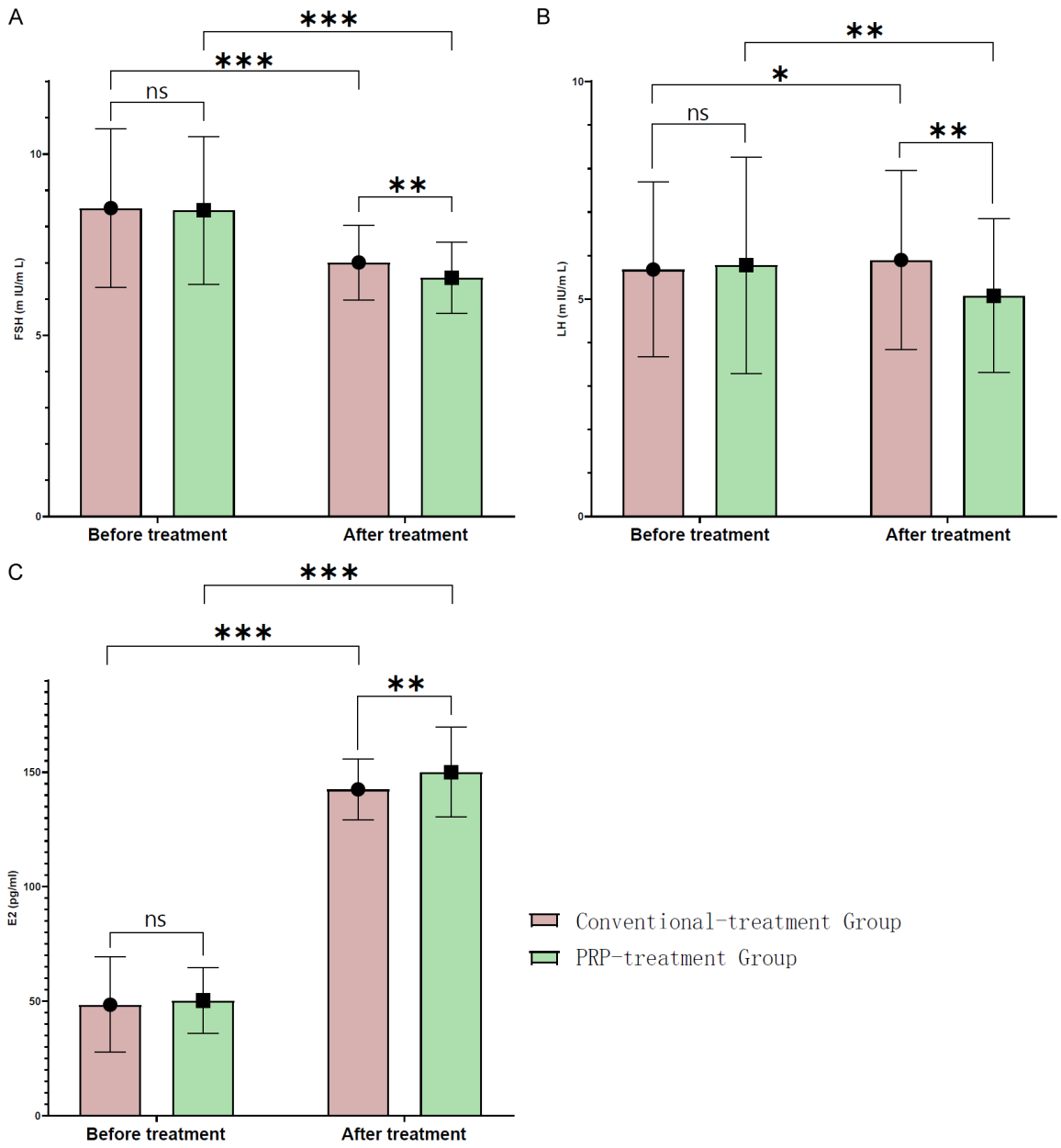

Figure 2. Comparison of hormone levels before and after treatment. A. FSH (m IU/m L); B. LH (m IU/m L); C. E2 (pg/ml). FSH: follicle stimulating hormone; LH: luteinizing hormone; E2: Estradiol 2. PRP: Platelet-Rich Plasma. ns: no significant; *: P<0.05; **: P<0.01; ***: P<0.001.

Comparison of hormone levels before and after treatment

No significant differences in FSH, LH, or E2 levels were observed between the groups at baseline (all P>0.05) (**Figure 2**). After treatment, the PRP-treatment group exhibited significantly lower FSH (P=0.002) and LH (P=0.002) levels, and significantly higher E2 (P=0.001) levels compared with the conventional-treatment group. Moreover, all three hormone levels changed significantly from baseline within each group (all P<0.05).

Comparison of uterine blood flow before and after treatment

Table 2 shows the comparison of right uterine artery indices. At baseline, no significant differences were observed in the PI or RI between the groups (both P>0.05). After treatment, both

Table 2. Comparison of right uterine arterial blood flow before and after treatment

Parameters	Conventional-treatment Group (n=116)	PRP-treatment Group (n=104)	t	p
PI				
Before treatment	2.87±0.55	2.96±0.61	1.136	0.257
After treatment	2.07±0.62*	1.84±0.52*	2.918	0.004
RI				
Before treatment	0.83±0.14	0.82±0.10	0.852	0.395
After treatment	0.72±0.11*	0.68±0.12*	2.908	0.004

Note: PRP: Platelet-Rich Plasma; PI: Pulsatility Index; RI: Resistance Index; *: P<0.05 compared to before treatment.

Table 3. Comparison of left uterine arterial blood flow before and after treatment

Parameters	Conventional-treatment Group (n=116)	PRP-treatment Group (n=104)	T	p
PI				
Before treatment	3.13±0.41	3.05±0.69	0.982	0.328
After treatment	2.15±0.66*	1.98±0.25*	2.618	0.010
RI				
Before treatment	0.90±0.07	0.89±0.06	0.245	0.807
After treatment	0.81±0.11*	0.76±0.14*	2.869	0.005

Note: PRP: Platelet-Rich Plasma; PI: Pulsatility Index; RI: Resistance Index; *: P<0.05 compared to before treatment.

Table 4. Comparison of arcuate arterial blood flow before and after treatment

Parameters	Conventional-treatment Group (n=116)	PRP-treatment Group (n=104)	t	p
PI				
Before treatment	1.89±0.65	1.87±0.61	0.291	0.772
After treatment	1.81±0.73*	1.65±0.33*	2.101	0.037
RI				
Before treatment	0.78±0.09	0.77±0.12	0.599	0.550
After treatment	0.71±0.13*	0.65±0.17*	3.047	0.003

Note: PRP: Platelet-Rich Plasma; PI: Pulsatility Index; RI: Resistance Index; *: P<0.05 compared to before treatment.

indices were significantly lower in the PRP-treatment group (PI, P=0.004; RI, P=0.004), indicating improved blood flow dynamics.

Similar patterns were observed for the left uterine artery (**Table 3**) and the mean values of both arteries (**Table 4**). At baseline, there were no significant differences in PI or RI between the groups (both P>0.05). After treatment, both PI and RI were significantly lower in the PRP-treatment group (**Table 3**: PI, P=0.010; RI, P=0.005; **Table 4**: PI, P=0.037; RI, P=0.003), suggesting enhanced arterial compliance and reduced vascular resistance.

Table 5 presents the comparison of bilateral uterine artery indices. At baseline, no significant differences were observed in PI or RI between the groups (both P>0.05). After treatment, the PI was significantly lower in the PRP-treatment group (P=0.002), while the RI showed a nonsignificant trend toward lower values (P=0.053).

Within each group, all indices showed significant changes from baseline to post-treatment (all P<0.05).

Comparison of endometrial thickness

Before treatment, there was no significant difference in endometrial thickness between the groups (P=0.371), indicating comparable baseline endometrial thickness (**Figure 3**). How-

Table 5. Comparison of sub-endometrial arterial blood flow before and after treatment

Parameters	Conventional-treatment Group (n=116)	PRP-treatment Group (n=104)	T	p
PI				
Before treatment	1.35±0.32	1.47±0.87	1.356	0.178
After treatment	1.05±0.22*	0.95±0.25*	3.165	0.002
RI				
Before treatment	0.71±0.18	0.67±0.20	1.768	0.078
After treatment	0.61±0.15*	0.58±0.06*	1.946	0.053

Note: PRP: Platelet-Rich Plasma; PI: Pulsatility Index; RI: Resistance Index; *: P<0.05 compared to before treatment.

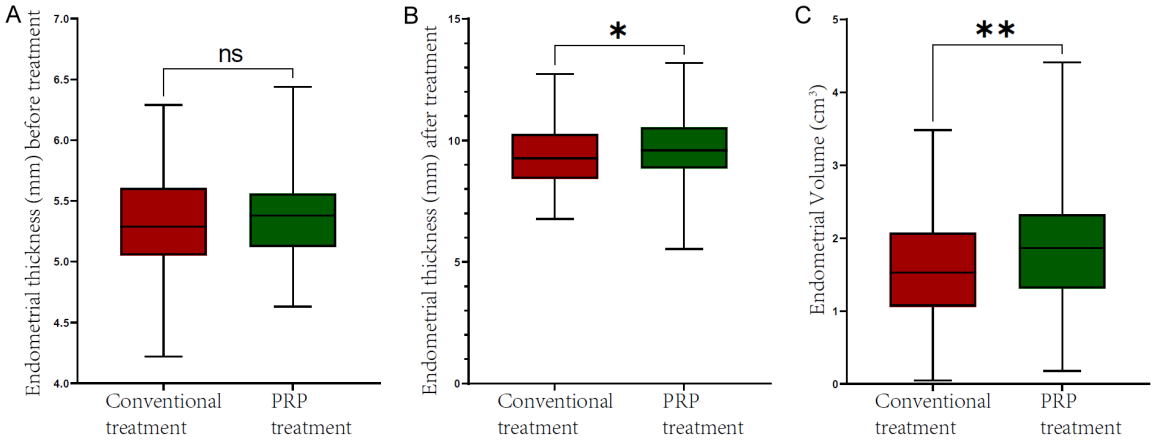

Figure 3. Comparison of endometrial thickness. A. Endometrial thickness (mm) before treatment; B. Endometrial thickness (mm) after treatment; C. Endometrial Volume (cm^3). PRP: Platelet-Rich Plasma. ns: no significant; *: P<0.05; **: P<0.01.

ever, after treatment, the PRP-treatment group showed significantly greater endometrial thickness compared to the conventional-treatment group (P=0.037), suggesting a more substantial increase in endometrial thickness in the PRP-treatment group.

Additionally, endometrial volume differed significantly between the two groups both before and after treatment. The PRP-treatment group had a significantly larger endometrial volume compared to the conventional-treatment group (P=0.003), indicating better endometrial development in the PRP-treatment group.

Comparison of embryo transfer

Regarding embryo transfer parameters, notable differences were observed between the groups (**Table 6**). The implantation rate was significantly higher in the PRP-treatment group (P=0.004), indicating better embryo attachment and development in the PRP-treatment group.

Additionally, there was a significant difference in the number of embryos transferred between the two groups (P=0.005). In the conventional-treatment group, 47 patients had one embryo transferred, and 69 had two embryos transferred. In contrast, 62 patients in the PRP-treatment group had one embryo transferred, and 42 had two embryos transferred.

Comparison of pregnancy outcomes

Several significant differences were observed in pregnancy outcomes between the two groups (**Table 7**).

No significant difference was found in biochemical pregnancy rates (P=0.232).

There was no significant difference in miscarriage rates between the groups (P=0.545). However, the PRP-treatment group demonstrated significantly higher rates of live births (P=0.032), clinical pregnancies (P=0.044), and ongoing pregnancies (P=0.031) compared to

Table 6. Comparison of embryo transfer

Parameters	Conventional-treatment Group (n=116)	PRP-treatment Group (n=104)	t/χ^2	p
Implantation rate [n (%)]	11 (9.48%)	25 (24.04%)	8.489	0.004
Number of transferred embryos [n (%)]			8.001	0.005
1	47 (40.52%)	62 (59.62%)		
2	69 (59.48%)	42 (40.38%)		

Note: PRP: Platelet-Rich Plasma.

Table 7. Comparison of pregnancy outcomes

Parameters	Conventional-treatment Group (n=116)	PRP-treatment Group (n=104)	t/χ^2	p
Biochemical Pregnancy [n (%)]	8 (6.90%)	12 (11.54%)	1.430	0.232
Miscarriage [n (%)]	19 (16.38%)	14 (13.46%)	0.366	0.545
Live birth [n (%)]	31 (26.72%)	42 (40.38%)	4.615	0.032
Ongoing Pregnancy [n (%)]	50 (43.10%)	59 (56.73%)	4.074	0.044
Clinical pregnancy [n (%)]	33 (28.45%)	44 (42.31%)	4.630	0.031

Note: PRP: Platelet-Rich Plasma.

the conventional-treatment group. Additionally, the proportion of patients with ongoing pregnancies was higher in the PRP-treatment group (P=0.044), further supporting improved reproductive success in this group.

No adverse reactions, such as intrauterine infection, significant vaginal bleeding, or severe abdominal pain, were reported in the PRP-treatment group following intrauterine infusion.

Discussion

This study addressed two significant challenges in assisted reproductive technology: RIF and thin endometrium. We investigated whether autologous PRP intrauterine perfusion could offer a new therapeutic approach. Unlike traditional treatments like hormone replacement or vasodilators, PRP regulates the endometrial environment in several ways, potentially restoring impaired receptivity and improving pregnancy outcomes. This novel approach, based on tissue repair and regeneration, offers a new strategy for patients unresponsive to standard treatments, aiming to overcome the RIF treatment bottleneck and provide more options for clinical decision-making.

Our results demonstrated that following PRP treatment, patients experienced increased endometrial thickness and volume, along with reductions in the RI and PI of uterine, arcuate, and spiral arteries. These changes likely contributed to higher embryo implantation rates [27]. Unlike previous therapies with single mechanisms, PRP provided dual benefits: promoting endometrial growth and improving uterine blood flow [28, 29]. Optimizing blood flow parameters, particularly lowering spiral artery RI, is crucial for enhancing microcirculation in the endometrial basal layer, which is essential for embryo implantation [30, 31]. A low-resistance blood flow ensures better nutrient and oxygen delivery, and may also enhance the local biochemical environment during the “implantation window” by modulating local cytokines and immune balance [32]. These findings align with previous studies emphasizing the importance of optimal endometrial conditions for successful embryo implantation [33]. Additionally, patients receiving PRP treatment required fewer embryos to achieve similar or better pregnancy outcomes, suggesting either improved embryo quality or enhanced endometrial conditions, leading to more efficient embryo utilization.

Notably, patients in the PRP group showed improved hormone levels, including significantly higher E2 and FSH and LH levels. These hormonal changes were directly associated with endometrial thickening and may indicate PRP’s positive influence on the hypothalamic-pitu-

itary-ovarian axis or local ovarian function [34, 35]. The combined improvements in hormones, blood flow, and tissue structure provided a robust physiological foundation for PRP's role in enhancing endometrial receptivity [36]. These results support previous studies showing that PRP increases integrin αvβ3, a key molecule for endometrial receptivity, further validating the molecular mechanisms underlying PRP's beneficial effects [37].

The observed lack of significant difference in miscarriage rates between groups warrants further investigation. The most plausible explanation is that PRP primarily improves endometrial receptivity and early implantation but may not significantly affect factors leading to later miscarriages, such as embryonic aneuploidy, which is a major cause of pregnancy loss, particularly in patients with a history of RIF [27, 38]. Comparing our findings with those of other studies, the positive impact of enhancing endometrial conditions on pregnancy outcomes appears consistent [39]. The PRP-treatment group demonstrated significant advantages in key pregnancy outcomes: higher implantation rates, clinical pregnancy rates, ongoing pregnancy rates, and live birth rates. The improvement in live birth rates holds the most critical clinical value, marking the achievement of the ultimate treatment goal. This outcome surpassed the efficacy of previously reported interventions, such as intrauterine G-CSF perfusion or high-dose estrogen therapy, especially in patients with previously refractory thin endometrium [40]. This success was closely linked to the multi-faceted enhancement of receptivity. Increased implantation rates reflected improved embryo-endometrium interaction, while higher ongoing pregnancy and live birth rates strongly suggested that PRP not only promoted initial embryo adhesion and invasion but also sustained pregnancy stability by enhancing decidualization of endometrial stromal cells, optimizing early placental development, and regulating maternal-fetal immune tolerance, including promoting regulatory T-cell function [41, 42].

This study further supports earlier hypotheses regarding PRP's multiple mechanisms of action. Its effectiveness stems not only from the direct stimulation by growth factors but also from a three-pronged approach: activating endogenous stem cells to promote tissue regeneration; modulating immune cell types, such as promoting M2 polarization of macrophages to reduce local inflammation; and synergistically increasing angiogenic factors like VEGF and PDGF to encourage new blood vessel formation via key signaling pathways [43, 44]. This multi-target, networked approach gives PRP unique advantages in treating complex conditions like RIF and thin endometrium, overcoming the limitations of traditional single-pathway treatments.

In our study, PRP was prepared and administered on the third day of the menstrual cycle, corresponding to the early follicular phase. This timing was selected based on preliminary evidence suggesting that the early follicular phase is critical for endometrial preparation and hormonal regulation [45]. During this time, the endometrium is relatively quiescent, which may optimize the regenerative effects of PRP. However, the optimal timing for PRP administration remains debated. Some suggest administering PRP during the luteal phase, when progesterone levels are high, to enhance endometrial maturation and embryo implantation [46]. Administering PRP at this time could potentially boost endometrial receptivity by combining the benefits of progesterone with PRP's growth factors. Future studies should compare the efficacy of PRP when administered at different phases of the menstrual cycle. This will help identify the best timing for treatment to improve pregnancy outcomes. Personalizing PRP treatment based on each patient's hormone profile and endometrial characteristics could further improve success rates, leading to more targeted and effective treatments.

In our study, we also evaluated the safety of PRP perfusion. Patients who received PRP infusion exhibited no adverse reactions, such as intrauterine infection, significant vaginal bleeding, or severe abdominal pain. These findings are consistent with previous reports indicating that PRP therapy is associated with minimal side effects. For instance, Peng et al. [47] reported no significant increase in complications, such as intrauterine infections or severe abdominal pain, after PRP treatment. Similarly, Enatsu et al. [48] found no serious adverse effects from PRP use, which supports our find-

ings. Together, these results suggest that PRP perfusion is a safe procedure with minimal risk. Its favorable safety profile makes PRP a promising adjunctive treatment for improving endometrial receptivity and pregnancy outcomes. The absence of significant adverse reactions further supports PRP as a viable option for patients with RIF and thin endometrium.

This study has several limitations. It was conducted at a single medical center and is retrospective in nature, which may limit the generalizability of the findings. We did not investigate the molecular mechanisms underlying PRP's effects. Additionally, the follow-up period was short, preventing us from assessing the long-term impacts on reproductive health. Differences in how patients responded to treatment may also have influenced the effectiveness. Future studies should aim to conduct larger, multi-center, randomized controlled trials. They should explore PRP's efficacy in specific subgroups, such as patients with very thin uterine linings or those who have undergone uterine adhesiolysis. Including molecular-level studies could help clarify how PRP works. Long-term follow-up studies should also be implemented to monitor the safety of the treatment and the health of offspring born as a result. Such an approach would provide a clearer understanding of the long-term benefits and risks of PRP.

In conclusion, our findings suggest that autologous PRP intrauterine perfusion may offer a promising treatment for patients with RIF and thin endometrium. PRP administration was associated with increased endometrial thickness, improved uterine blood flow, and more balanced hormone levels, leading to improved pregnancy outcomes in our study group. The treatment targeted multiple biological processes, including tissue repair, immune regulation, and blood vessel formation. This multi-target approach offered advantages beyond conventional therapies. Larger multi-center trials are needed to confirm these results and further evaluate the long-term safety and effectiveness of PRP. PRP represents a potentially valuable option for supporting reproductive health in challenging cases.

Disclosure of conflict of interest

None.

Address correspondence to: Min Xia, Department of Reproductive Medicine, Maternal and Child Health Hospital of Hubei Province, No. 745 Wuluo Road, Hongshan District, Wuhan 430072, Hubei, China. E-mail: drxmin1980@163.com

References

[1] Pirtea P, Cedars MI, Devine K, Ata B, Franasiak J, Racowsky C, Toner J, Scott RT, de Ziegler D and Barnhart KT. Recurrent implantation failure: reality or a statistical mirage?: consensus statement from the july 1, 2022 lugano workshop on recurrent implantation failure. Fertil Steril 2023; 120: 45-59.

[2] Dahiphale SM, Dewani D, Dahiphale JM, Agrawal M, Dave A, Pajai S and Jyotsna G. A comprehensive review of the endometrial receptivity array in embryo transfer: advancements, applications, and clinical outcomes. Cureus 2024; 16: e67866.

[3] Pantos K, Grigoriadis S, Maziotis E, Pistola K, Xystra P, Pantou A, Kokkali G, Pappas A, Lambropoulou M, Sfakianoudis K and Simopoulou M. The role of interleukins in recurrent implantation failure: a comprehensive review of the literature. Int J Mol Sci 2022; 23: 2198.

[4] Ata B, Kalafat E and Somigliana E. A new definition of recurrent implantation failure on the basis of anticipated blastocyst aneuploidy rates across female age. Fertil Steril 2021; 116: 1320-1327.

[5] Ma J, Gao W and Li D. Recurrent implantation failure: a comprehensive summary from etiology to treatment. Front Endocrinol (Lausanne) 2022; 13: 1061766.

[6] Kasius A, Smit JG, Torrance HL, Eijkemans MJ, Mol BW, Opmeer BC and Broekmans FJ. Endometrial thickness and pregnancy rates after IVF: a systematic review and meta-analysis. Hum Reprod Update 2014; 20: 530-541.

[7] Gleicher N, Kim A, Michaeli T, Lee HJ, Shohat-Tal A, Lazzaroni E and Barad DH. A pilot cohort study of granulocyte colony-stimulating factor in the treatment of unresponsive thin endometrium resistant to standard therapies. Hum Reprod 2013; 28: 172-177.

[8] Kurmanova G, Ashirbekov Y, Kurmanova A, Mamedaliyeva N, Moshkalova G, Anartayeva G, Salimbayeva D and Tulesheva A. Altered expression of C4BPA and CXCL1 genes in the endometrium of patients with recurrent implantation failure after in vitro fertilization and thin endometrium. Diagnostics (Basel) 2024; 14: 1967.

[9] Lin Y, Qi J and Sun Y. Platelet-rich plasma as a potential new strategy in the endometrium treatment in assisted reproductive techno-

logy. Front Endocrinol (Lausanne) 2021; 12: 707584.
[10] Li M, Kang Y, Wang Q and Yan L. Efficacy of autologous intrauterine infusion of platelet-rich plasma in patients with unexplained repeated implantation failures in embryo transfer: a systematic review and meta-analysis. J Clin Med 2022; 11: 6753.
[11] Schiffer V, Evers L, de Haas S, Ghossein-Doha C, Al-Nasiry S and Spaanderman M. Spiral artery blood flow during pregnancy: a systematic review and meta-analysis. BMC Pregnancy Childbirth 2020; 20: 680.
[12] Luddi A, Pavone V, Semplici B, Governini L, Criscuoli M, Paccagnini E, Gentile M, Morgante G, Leo V, Belmonte G, Zarovni N and Piomboni P. Organoids of human endometrium: a powerful in vitro model for the endometrium-embryo cross-talk at the implantation site. Cells 2020; 9: 1121.
[13] Muneeba S Jr, Acharya N and Mohammad S. The role of dydrogesterone in the management of luteal phase defect: a comprehensive review. Cureus 2023; 15: e48194.
[14] Dudley AC and Griffioen AW. Pathological angiogenesis: mechanisms and therapeutic strategies. Angiogenesis 2023; 26: 313-347.
[15] Xu P, Wu Y, Zhou L, Yang Z, Zhang X, Hu X, Yang J, Wang M, Wang B, Luo G, He W and Cheng B. Platelet-rich plasma accelerates skin wound healing by promoting re-epithelialization. Burns Trauma 2020; 8: tkaa028.
[16] Artimovič P, Badovská Z, Toporcerová S, Špaková I, Smolko L, Sabolová G, Kriváková E and Rabajdová M. Oxidative Stress and the Nrf2/PPARγ axis in the endometrium: insights into female fertility. Cells 2024; 13: 1081.
[17] Yuan B, Luo S, Mao J, Luo B and Wang J. Effects of intrauterine infusion of platelet-rich plasma on hormone levels and endometrial receptivity in patients with repeated embryo implantation failure. Am J Transl Res 2022; 14: 5651-5659.
[18] Wang Y, Tang Z and Teng X. New advances in the treatment of thin endometrium. Front Endocrinol (Lausanne) 2024; 15: 1269382.
[19] Dhurat R and Sukesh M. Principles and methods of preparation of platelet-rich plasma: a review and author's perspective. J Cutan Aesthet Surg 2014; 7: 189-197.
[20] Testart J, Lassalle B, Belaisch-Allart J, Hazout A, Forman R, Rainhorn JD and Frydman R. High pregnancy rate after early human embryo freezing. Fertil Steril 1986; 46: 268-272.
[21] Lassalle B, Testart J and Renard JP. Human embryo features that influence the success of cryopreservation with the use of 1,2 propanediol. Fertil Steril 1985; 44: 645-651.
[22] Liao X, Li Z, Dong X and Zhang H. Comparison between oral and vaginal estrogen usage in inadequate endometrial patients for frozen-thawed blastocysts transfer. Int J Clin Exp Pathol 2014; 7: 6992-6997.
[23] Ghobara T, Gelbaya TA and Ayeleke RO. Cycle regimens for frozen-thawed embryo transfer. Cochrane Database Syst Rev 2017; 7: CD003414.
[24] Groenewoud ER, Cantineau AE, Kollen BJ, Macklon NS and Cohlen BJ. What is the optimal means of preparing the endometrium in frozen-thawed embryo transfer cycles? A systematic review and meta-analysis. Hum Reprod Update 2017; 23: 255-261.
[25] Liu K, Cheng H, Guo Y, Liu Y, Li L and Zhang X. Autologous platelet-rich plasma intrauterine perfusion to improve pregnancy outcomes after implantation failure: a systematic review and meta-analysis. J Obstet Gynaecol Res 2022; 48: 3137-3151.
[26] Hajipour H, Nejabati HR, Latifi Z, Hamdi K, Bahrami-Asl Z, Fattahi A and Nouri M. Lymphocytes immunotherapy for preserving pregnancy: mechanisms and challenges. Am J Reprod Immunol 2018; 80: e12853.
[27] Russell SJ, Kwok YSS, Nguyen TTN and Librach C. Autologous platelet-rich plasma improves the endometrial thickness and live birth rate in patients with recurrent implantation failure and thin endometrium. J Assist Reprod Genet 2022; 39: 1305-1312.
[28] Kusumi M, Ihana T, Kurosawa T, Ohashi Y and Tsutsumi O. Intrauterine administration of platelet-rich plasma improves embryo implantation by increasing the endometrial thickness in women with repeated implantation failure: a single-arm self-controlled trial. Reprod Med Biol 2020; 19: 350-356.
[29] Chen X, Chen M, Liu M, Qi L, Liu Z, Chen C, Liang B, Yang X, Zhang T, Li Y and Lian R. Intrauterine infusion of autologous platelet-rich plasma modulates endometrial immune status and improves pregnancy outcomes in patients with persistent chronic endometritis. Front Immunol 2025; 16: 1528522.
[30] Omran E, El-Sharkawy M, El-Mazny A, Hammam M, Ramadan W, Latif D, Samir D and Sobh S. Effect of clomiphene citrate on uterine hemodynamics in women with unexplained infertility. Int J Womens Health 2018; 10: 147-152.
[31] Liao J, Yang S, Chen K, Chen H, Jiang F, Zhang W and Wu X. A predictive model for first-trimester pregnancy inception after IVF-ET based on multimodal ultrasound evaluation of endometrial receptivity. BMC Med Imaging 2022; 22: 158.

[32] Mary B, Asokan N, Jerabkova-Roda K, Larnicol A, Busnelli I, Stemmelen T, Pichot A, Molitor A, Carapito R, Lefebvre O, Goetz JG and Hyenne V. Blood flow diverts extracellular vesicles from endothelial degradative compartments to promote angiogenesis. EMBO Rep 2023; 24: e57042.
[33] Awonuga AO, Camp OG, Abu-Soud HM, Rappolee DA, Puscheck EE and Diamond MP. Determinants of embryo implantation: roles of the endometrium and embryo in implantation success. Reprod Sci 2023; 30: 2339-2348.
[34] Kim H, Shin JE, Koo HS, Kwon H, Choi DH and Kim JH. Effect of autologous platelet-rich plasma treatment on refractory thin endometrium during the frozen embryo transfer cycle: a pilot study. Front Endocrinol (Lausanne) 2019; 10: 61.
[35] Zamaniyan M, Peyvandi S, Heidaryan Gorji H, Moradi S, Jamal J, Yahya Poor Aghmashhadi F and Hossein Mohammadi M. Effect of platelet-rich plasma on pregnancy outcomes in infertile women with recurrent implantation failure: a randomized controlled trial. Gynecol Endocrinol 2021; 37: 141-145.
[36] Chang Y, Peng J, Zhu Y, Sun P, Mai H, Guo Q, Guo J, Liang X and Chen P. How platelet-rich plasma (PRP) intra-uterine injection improve endometrial receptivity of intrauterine adhesions in women: a time-series-based self-controlled study. J Reprod Immunol 2023; 156: 103796.
[37] Mouanness M, Ali-Bynom S, Jackman J, Seckin S and Merhi Z. Use of intra-uterine injection of platelet-rich plasma (PRP) for endometrial receptivity and thickness: a literature review of the mechanisms of action. Reprod Sci 2021; 28: 1659-1670.
[38] Ban Y, Yang X, Xing Y, Que W, Yu Z, Gui W, Chen Y and Liu X. Intrauterine infusion of leukocyte-poor platelet-rich plasma is an effective therapeutic protocol for patients with recurrent implantation failure: a retrospective cohort study. J Clin Med 2023; 12: 2823.
[39] Yan H, Li X, Dai Y, Shi J, Wu Y, Gu Z, Zhang C, Li Q, Zhang B, Lv S and Leng J. Bladder endometriosis: symptoms and pregnancy outcomes. J Minim Invasive Gynecol 2025; 32: 22-30, e21.
[40] Jiang YL, Lin YY, Chen CX, Li YX, Xie HY and Zheng BH. Current research of assisted reproductive technology for women with early endometrial cancer and atypical endometrial hyperplasia after conservative treatment. Front Endocrinol (Lausanne) 2024; 15: 1377396.
[41] Zhang W, Tang R, Xiao X, Liu J, Li M and Wang X. A comparative study on the efficacy of subendometrial versus intrauterine platelet-rich plasma injections for treating intrauterine adhesions: a retrospective cohort study. J Minim Invasive Gynecol 2025; 32: 378-385, e371.
[42] Mercan R, Guzel Y, Usta İ and Alper E. Embryo versus endometrial receptivity: untangling a complex debate. Front Endocrinol (Lausanne) 2025; 16: 1537847.
[43] Masoomikarimi M and Salehi M. Modulation of the immune system promotes tissue regeneration. Mol Biotechnol 2022; 64: 599-610.
[44] Miceli V, Zito G, Bulati M, Gallo A, Busà R, Iannolo G and Conaldi PG. Different priming strategies improve distinct therapeutic capabilities of mesenchymal stromal/stem cells: Potential implications for their clinical use. World J Stem Cells 2023; 15: 400-420.
[45] Sfakianoudis K, Simopoulou M, Grigoriadis S, Pantou A, Tsioulou P, Maziotis E, Rapani A, Giannelou P, Nitsos N, Kokkali G, Koutsilieris M and Pantos K. Reactivating ovarian function through autologous platelet-rich plasma intraovarian infusion: pilot data on premature ovarian insufficiency, perimenopausal, menopausal, and poor responder women. J Clin Med 2020; 9: 1809.
[46] Kalakota NR, George LC, Morelli SS, Douglas NC and Babwah AV. Towards an improved understanding of the effects of elevated progesterone levels on human endometrial receptivity and oocyte/embryo quality during assisted reproductive technologies. Cells 2022; 11: 1405.
[47] Peng J, Li M, Zeng H, Zeng Z, Huang J and Liang X. Intrauterine infusion of platelet-rich plasma is a treatment method for patients with intrauterine adhesions after hysteroscopy. Int J Gynaecol Obstet 2020; 151: 362-365.
[48] Enatsu Y, Enatsu N, Kishi K, Otsuki J, Iwasaki T, Okamoto E, Kokeguchi S and Shiotani M. Clinical outcome of intrauterine infusion of platelet-rich plasma in patients with recurrent implantation failure. Reprod Med Biol 2022; 21: e12417.