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The Role of Platelets Rich Plasma (PRP) in Recurrent Implantation Failure (RIF)

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Abstract

Infertility therapy has been advocated using a variety of ways. The implantation of many embryos is still a problem, despite the presence of a variety of assisted reproductive technologies (ART). C-reactive protein, growth factor, prostaglandin and other binding molecules are released by the endometrium when it's receptive to fertilisation. It is critical for embryo implantation if the endometrium be in the proper condition. Repeated implantation failure (RIF) is defined by the European Society of Human Reproduction and Embryology as the absence of a gestational sac in the 5-week old ultrasonography after three different embryo transfers. Autologous blood samples are used to obtain platelet-rich plasma (PRP), which has a concentration of 4–5 times that of circulating blood. ART research aimed at increasing the success rate and reducing the cost of treatment may be beneficial. The purpose of this research was to determine if intrauterine perfusion of autologous platelet-rich plasma (PRP) improves pregnancy rates in patients with RIF. Methods: Study participants were divided into two groups: Group A (PRP group), which comprised 37 women who underwent intrauterine infusion of PRP 48 hours prior to embryo transfer (ET), and Group B (Control group), which included 37 women who did not receive PRP. This study found no significant differences in demographic data or time spent unsuccessfully trying to conceive between the two groups. In terms of AMH levels, the two groups did not vary significantly. When comparing the PRP group to the control group, the AFC was considerably greater in the PRP group. The PRP group had a statistically greater endometrial thickness than the control group after treatment. In comparison to the control group, the PRP group had statistically substantially more recovered oocytes. In comparison to the control group, the PRP group had considerably more MII oocytes. Between the two groups, the number of embryos transplanted was statistically indistinguishable. There was a statistically significant difference in the number of blastocysts formed by PRP compared to the control group. The PRP group had an 81.1 percent rate of normal fertilisation compared to the control group, which was statistically significant (45.9 percent). Compared to the control group, the PRP group had a clinical pregnancy rate of 48.6 percent, which was statistically significant (18.9 percent). No statistically significant difference was seen when it came to spontaneous miscarriage rates between the PRP and control groups. To summarise, PRP infusion seems to be a safe and successful treatment for enhancing endometrial receptivity, implantation, and pregnancy, all without causing harm to the patient. Furthermore, PRP is inexpensive and made from your own blood, so there's no need to worry about immune responses or infection transmission.

Key words: Platelets Rich Plasma, PRP, Recurrent Implantation Failure, RIF.

1. Introduction

Recurrent Implantation Failure (RIF) has a significant impact on the chances of successfully conceiving a child via IVF. The disease's pathophysiology is unknown, and there is no agreement among doctors or academics on its diagnostic criteria or therapy. Nonetheless [1].

Multiple embryos fail to implant despite advances in the area of assisted reproductive technologies. The responsiveness of the endometrium is a major factor in the failure of IVF [2].

In order for the mother and foetus to work together effectively throughout pregnancy, an embryo of high quality must be implanted. Endometrial damage, modifications in stimulation procedures, intrauterine granulocyte colony-stimulating factor before embryo transfer, blastocyst aided hatching transfer, and pre-implantation genetic diagnostics for aneuploidy have all been employed as therapeutic treatments in the management of RIF [3].

Endometrium changes dramatically after implantation in the human body. Researchers believe that endometrial tissue has receptors for growth factors and other substances that aid in the development of the endometrium and the developing embryo [4].

It is a platelet-rich plasma with a normal plasma fibrinogen level that is known as platelet rich plasma (PRP). With its ability to restore injured tissues, PRP has been intensively studied in the area of regeneration during the last three decades [5].

For orthopaedic, dermatological, ophthalmological, and neurological, vascular, and connective tissue damage repair PRP has been shown to be a successful and safe therapy [6].

In women with a thin endometrium, PRP might be utilised as a novel therapy to increase the thickness of the endometrium. Because it is made from the patient's own blood, PRP is thought to be completely safe for usage [7].

Women who have recurrent implantation failure (RIF) may benefit from the unique and likely beneficial therapy of local injection of PRP [8].

However, there is still a need for additional investigation in this area.

The purpose of this research was to determine if intrauterine perfusion of autologous platelet-rich plasma (PRP) improves pregnancy rates in patients with RIF.

2. Patients and Methods

Study design

A prospective randomized, controlled clinical study

Study location and duration

It is a multi-centric study that was conducted for 1 year between January, 2021 and December, 2021.

Study participants

Sample Size Calculation:

The required sample size was calculated using the IBMª SPSSª SamplePowerª version 3.0.1 (IBMª Corp., Armonk, NY, USA). Based on intensive literature review, the incidence of positive pregnancy test in the study conducted by Rageh et al. (2020) was 43% in the PRP group and 15% patients in the control group. Total number of 74 patients (37 in each group) was calculated to detect an expected difference of 1% difference in the overall incidence of bleeding. At 95% level of significance and power of 80%.

Method of randomization

Cases were randomly be divided into two equal groups using computer generated random tables according to the surgical technique used.

Study groups

This study included 74 infertile women with history of RIF who were classified into two groups:

- **Group A (PRP group):** included 37 females who received intrauterine infusion of PRP 48 hours before embryo transfer (ET).
- **Group B (Control group):** included 37 females who didn't receive PRP.

Inclusion criteria

- Infertile women with a history of recurrent implantation failure who had failed to achieve a clinical pregnancy with at least four good quality embryos transfers
- 18<Age<40
- 19<BMI<29
- Non endocrine, hematologic and autoimmune disorders
- Non chromosomal and genetic abnormalities
- Non uterine anomalies, surgical history, endometriosis, adenomyosis, hydro salpinx, uterine fibroids, Polycystic ovary syndrome.

Exclusion Criteria:

- Cervicitis or any recent fever condition
- Use of corticosteroids (in up to 3 weeks before the procedure) or non-steroid anti-inflammatories (in up to 2 weeks before procedure)
- Anemia, thrombocytopenia, platelet dysfunction syndrome, hypofibrinogenemia
- Septicemia, active infections with Pseudomonas, Klebsiella or Enterococcus
- History of cancer
- Patient's tendency for withdrawal

Detailed methodology

Patient evaluation

History taking

Every patient was subjected to careful history taking with stress on:

Personal history

- Age
- Special habits particularly smoking
- Occupation
- Address
- Telephone number
- Previous marriage or children

Clinical history

For female partners: Obstetric and Gynecological history:

- Menstrual history.
- History of infertility, whether primary or secondary.
- History of investigations, operations, interventions or trials of assisted reproduction.
- For male partners
- History of infertility, whether primary or secondary.
- History of investigations, urological or andrological operations, interventions or trials of assisted reproduction.

Physical examination

General examination was done for: -

- BMI calculation: - The formula for BMI is weight in kilograms divided by height in meters squared. (Weight (kg) / [height (m)]2
- **Signs of PCO:**
  - ✓ excessive hair growth (hirsutism) – usually on the face, chest, back or buttocks.
  - ✓ weight gain.
  - ✓ thinning hair and hair loss from the head.
  - ✓ oily skin or acne.
- Signs of hypo or hyperthyroidism.

Abdominal and pelvic examination

Baseline trans-vaginal (2D) ultrasound

- Was done on day 2 of pre stimulation cycle
- Using GE Voluson P6 ultrasound machine (GE Medical Systems, USA) with 7.5 MHz transvaginal probe.
- **Was done to:-**
  - ✓ Evaluate ovarian morphology as antral follicular count (AFC) follicles measuring 2-10 mm in mean diameter of both ovaries were counted. Also, ovarian volume was calculated according to the formula for an ellipsoid (0.526 x length x height x width).
  - ✓ Exclude uterine anomalies (septate uterus, subseptate uterus, bicornuate uterus) and uterine polyp.
  - ✓ Exclude tubal pathologies like hydrosalpinx (which if found tubal disconnection should be done before ICSI procedure)

Baseline laboratory investigations

- Complete blood count (CBC).
- Virology tests (hepatitis B&C, HIV)
- Basal hormonal profile:
  - ✓ Follicle stimulating hormone (FSH).
  - ✓ Luteinizing hormone (LH).
  - ✓ Estradiol (E2).
  - ✓ Thyroid stimulating hormone (TSH).
- Serum AMH measurement: 5ml of venous blood was collected from the patient on day 2-3 of stimulation cycle, centrifuged at 1500 rpm, for 10 min , the supernatant serum aspirated by pippete and analyzed

by using the Elecsys ® AMH assay (Roche , La Roche Ltd , Germany) on a cobas e 601 analyzer at one central measuring site (clinical pathology department, Al Azhar university hospitals).

Intervention

Protocol of controlled ovarian hyperstimulation (COH)

- FSH and HMG administration was started daily injection (150–225 IU/day) for patients with normal AMH (1.3–2.6 ng/ml) and more (mean =300 IU/day) for patients with extreme low AMH values (0.8 ng/ml) or less.
- The FSH and HMG dose were adjusted according to usual parameters of follicle growth determined by serum estradiol concentrations and ultrasound monitoring.
- A potent, third-generation GnRH antagonist, injected subcutaneously once daily starting on day 6 of Stimulation.
- An intramuscular injection of 10000 IU of human chorionic gonadotrophin was performed after obtaining follicles 18 to 20mm.

Folliculometry follow up

- All patients underwent for serial ultrasound examinations using GE Voluson P6 ultrasound machine (GE Medical Systems, USA) with 7.5 MHz transvaginal probe on day 6 to assess follicular growth and repeated every other day till the leading follicle reached 16 mm then was performed daily till the largest follicle reached 18 mm.
- When at least two follicles had reached 18 mm in diameter, final oocyte maturation was induced by intramuscular injection of 10,000 IU HCG (Choriomon ® active ingredient per vial contains Chorionic Gonadotropin 5000 I.U, IBSA, Switzerland).
- Then the patients were reported to the assisted reproduction unit, 34-36 hours after HCG administration for oocyte retrieval.

PRP preparation and injection

Preparation

Injection

- One milliliter PRP was injected into the patients' uterine cavity using an embryo transfer catheter 48 hours before embryo transfer.
- In order to eliminate the effects of catheter insertion, the same catheter was applied to the patients in the control group 48 hours before the embryo transfer without any injections.

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 26 (IBM, Inc. Chicago, USA). Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non-parametric data and mean, standard deviation for parametric data after testing normality using Kolmogorov-Smirnov test.

3. Results

As shown in table (1), the mean age of the females in PRP group was 29.05 ± 3.46 years and the mean age in the control group was 28.49 ± 3.39 years, with no statistically significant difference between the two groups.

The mean BMI of the females in PRP group was 25.67 ± 2.04 kg/m^2 and the mean BMI in the control group was 26.21 ± 2.03 kg/m^2, with no statistically significant difference between the two groups.

There was no statistically significant difference in the residence between the two groups.

As shown in table (2), the mean duration of infertility in PRP group was 3.38 ± 1.11 years and the mean duration of infertility in the control group was 3.41 ± 1.07 years, with no statistically significant difference between the two groups.

In the PRP, the causes of infertility included anovulation/PCO in 6 cases (16.2%), tubal factors in 11 cases (29.7%), male factors in 7 cases (18.9%) and mixed causes 13 cases (35.1%) while in the control group the causes of infertility included anovulation/PCO in 5 cases (13.5%), tubal factors in 12 cases (32.4%), male factors in 8 cases (21.6%) and mixed causes 12 cases (32.4%). There was no statistically significant difference in the causes of infertility in the two study groups.

Table (1) Sociodemographic data of the cases within the study groups.

Variables	PRP group (N=37)	Control group (N=37)	Test of significance
Age (years)	29.05 ± 3.46	2^.49 ± 3.39	t= 1.116 P = 2.908
BMI (kg/m^2)	25.67 ± 2.04	26.21 ± 2.03	t= 1.621 P = 0.110
Residence			
Urban	**18 (48.6%)**	**23 (62.2%)**	χ2= 1.367
Rural	**19 (51.4%)**	**14 (37.8%)**	P= 0.342

Quantitative data expressed as (mean ± SD) **t= independent samples t-test**

Qualitative data are expressed as number (percentage within group) **χ2: chi square test**

Table (2) Duration and causes of infertility in the cases within the study groups.

Variables	PRP group (N=37)	Control group (N=37)	Test of significance
Duration of infertility (Years)			
Mean ± SD	3.38 ± 1.11	3.41 ± 1.07	t= - 0.107
Range	2-5	2-5	P = 0.915
Causes of infertility			
Anovulation/PCO	**6 (16.2%)**	**5 (13.5%)**	χ2= 0.241
Tubal factors	**11 (29.7%)**	**12 (32.4%)**	P= 0.971
Male factor	**7 (18.9%)**	**8 (21.6%)**	
Mixed causes	**13 (35.1%)**	**12 (32.4%)**	

Quantitative data expressed as (mean ± SD) and range **t= independent samples t-test**
Qualitative data are expressed as number (percentage within group) **χ2: chi square test**

Table (3) Endometrial thickness before and after treatment in the cases within the study groups.

Variables	PRP group (N=37)	Control group (N=37)	Test of significance
Endometrial thickness before treatment (mm)			
Mean ± SD	4.20 ± 0.70	4.34 ± 0.65	t = -0.873
Range	3.2 – 5.6	3.3 – 5.6	P = 0.386
Endometrial thickness after treatment (mm)			
Mean ± SD	10.05 ± 1.57	7.44 ± 0.82	t = 8.973
Range	6.7 – 13.2	5.8 – 9.2	P < 0.001*
Percent of change (%)	146.34 (48.89-234.29)	69.38 (26.42-133.33)	z = -5.438 P < 0.001*
P1	< 0.001*	< 0.001*	

Quantitative data expressed as (mean ± SD) and range or median (Range).
t= Independent samples t-test
***: Statistically significant (p<0.05)**
P1: Comparison of before treatment and after treatment in each group

Table (4): Number of retrieved oocytes and M II oocytes in the cases within the study groups

Variables	PRP group (N=37)	Control group (N=37)	Test of significance
Retrieved oocytes			
Median	8	3	z = -11.528
Range	5-10	2-4	P < 0.001*
M II oocytes			
Median	6	2	z = -10.644
Range	3-9	1-3	P < 0.001*

Quantitative data expressed as median and range **z= Mann Whitney U-test**
***: Statistically significant (p<0.05)**

As shown in table (3), the mean endometrial thickness before treatment in the PRP group was 4.20 ± 0.70 mm (Range 6.7-13.2) and the mean endometrial thickness in the control group was 4.34 ± 0.65 mm (Range 5.8 -9.2), with no statistically significant difference between the two groups (p=0.386).

The mean endometrial thickness after treatment in the PRP group was 10.05 ± 1.57 mm (Range 6.7-13.2) and the mean endometrial thickness in the control group was 7.44 ± 0.82 mm (Range 5.8 -9.2), the mean endometrial thickness was statistically significantly higher in the PRP group as compared with the control group.

In both groups, there was a statistically significant increase in the endometrial thickness after treatment as compared with the before treatment value. However, the percent of endometrial thickness increase was statistically significantly higher in the PRP group as compared to the control group (p< 0.001).

As shown in table (4), The median number of retrieved oocytes in the PRP group was 8 (Range 5-10) and the median number of retrieved oocytes in the control group was 3 (Range 2-4), the number of retrieved oocytes was statistically significantly higher in the PRP group as compared with the control group.

The median number of MII oocytes in the PRP group was 6 (Range 3-9) and the median number of MII oocytes in the control group was 2 (Range 1-3), the number of MII oocytes was statistically significantly higher in the PRP group as compared with the control group.

Table (5) Number of embryo transferred and Blastocyst formation in the cases within the study groups

Variables	PRP group (N=37)	Control group (N=37)	Test of significance
Number of embryo transferred			
Median	2	1	z = -1.648
Range	1-2	1-3	P = 0.249
Blastocyst formation			
Median	3	0	z = -4.002
Range	0-8	0-2	P < 0.001*

Quantitative data expressed as median and range
z= Mann Whitney U-test
***: Statistically significant (p<0.05)**

Table (6) Pregnancy outcomes of the cases within the study groups.

Variables	PRP group (N=37)	Control group (N=37)	Test of significance
Normal fertilization			
No	**7 (18.9%)**	**20 (54.1%)**	$\chi 2$= 9.855
Yes	**30 (81.1%)**	**17 (45.9%)**	P= 0.002*
Clinical pregnancy			
No	**19 (51.4%)**	**30 (81.1%)**	$\chi 2$= 7.309
Yes	**18 (48.6%)**	**7 (18.9%)**	P= 0.007*
Spontaneous miscarriage			
Total number of positive clinical pregnancy	**(n=18)**	**(n=7)**	
No	**14 (77.8%)**	**5 (71.4%)**	FET= 1.452
Yes	**4 (22.2%)**	**2 (28.6%)**	P= 0.268

Qualitative data are expressed as number (percentage within group) **$\chi 2$: chi square test**
FET: Fischer's exact test ***: Statistically significant (p<0.05)**

As shown in table (5), the median number of embryo transferred in the PRP group was 2 (Range 1-2) and the median number of embryo transferred in the control group was 1 (Range 1-3), with no statistically significant difference between the two groups.

The median number of blastocyst formation in the PRP group was 3 (Range 0-8) and the median number of blastocyst formation in the control group was 0 (Range 0-2), the number of blastocyst formation was statistically significantly higher in the PRP group as compared with the control group.

As shown in table (6), the incidence of normal fertilization in the PRP group was 81.1% that was statistically significantly higher as compared to the control group (45.9%).

The incidence of clinical pregnancy in the PRP group was 48.6% that was statistically significantly higher as compared to the control group (18.9%).

The incidence of Spontaneous miscarriage in the PRP group was 22.2% and 28.6% in the control group with no statistically significant difference between the two groups.

3. Discussion

Age, infertility length and the number of unsuccessful IVF cycles were not associated with pregnancy outcomes in the present study's other clinical variables. Because of this, there are no predictive variables for PRP therapy success. However, it is possible that this conclusion is due to a limited number of instances, and a bigger research is needed to corroborate this finding.

No statistically significant difference existed between the two groups in terms of the underlying reason for infertility in the present investigation. 35.1 percent of mixed causes of infertility occurred in the PRP group and 32.4 percent of mixed causes in the control group during the research.

Mixed infertility was responsible for the largest number of infertility cases (42.8 percent and 47.9 percent, respectively, for the PRP and control groups), according to Nazari et al (2020). [9].

Male variables accounted for 71% of infertility in the PRP group and 56% in the control group, respectively, according to a research by Rageh et al. (2020). [10].

This research found no statistically significant difference between the PRP and control groups in terms of the median number of embryos transferred (Range 1-2) or the median number of embryos transferred (Range 1-3) in terms of the median number of embryos transferred (Range 1-3).

Nazari et al. (2020) found that in the PRP group, 1.9 0.8 embryos were transferred and in the control group, 1.7–0.6 embryos, with no statistically significant difference [9].

This is to remove the benefit of having a greater number of embryos transplanted, which might lead to bias in the findings.

Mean endometrial thickness following PRP therapy was statistically greater than that of the control group in the present research.

To back up their findings, Abaid et al. (2019) discovered a significant difference between the PRP and control groups when it comes to endometrial thickness on the day of IUI.

This is in line with the findings of Chang et al., who examined the effect of autologous PRP in patients undergoing frozen embryo transfer cycles who had thin endometrium. Following PRP treatment, all patients' ET increased 48 to 72 hours later and increased to more than 7 millimetres on the day of progesterone delivery [11].

Autologous PRP may also be used to improve ET in women with refractory endometrium, according to Garcia-Velasco, et al [12]. PRP was shown to be helpful in individuals with a thin endometrium during a pilot study including patients who had previously had cycles terminated owing to inadequate endometrial development (7 mm) [13].

For many years, the endometrial function and endometrial receptivity have been considered as key limiting factors in the development of pregnancies. Since practically all areas of IVF have been improved: ovulation stimulation, embryo culture and transfer - pregnancy rates have not been sufficient [14].

Pregnancy outcomes may improve as a consequence of increased endometrial thickness as a result of PRP injection, according to these findings and those of the present research.

The thickness of the endometrium is critical to implantation and pregnancy. Embryo transfer is typically skipped by women who have an endometrium that is persistently thin. Endometrial preparation has been the subject of several studies, but no one procedure has emerged as the gold standard. Recent studies on intrauterine G-CSF injection have shown conflicting findings. G-CSF has been shown to promote endometrial development and pregnancy, according to certain studies. As G-CSF promotes the differentiation and proliferation of neutrophilic granulocytes, it may increase endometrial development and hence enhance pregnancy outcomes. Endometrial development and receptivity may be improved with local infusion of PRP containing various growth factors and cytokines. PRP is easier to get and less expensive than G-CSF since it is derived from a patient's own blood [15, 16].

Kim et al., on the other hand, found that the EMT increased on average by just 0.6 millimetres. This discrepancy, however, was not significant statistically. A significant increase in EMTs had no effect on pregnancy outcomes. Two of the six clinical pregnancies had an increase in EMT, whereas four had a reduction [17].

Autologous PRP intrauterine treatment, according to the authors, enhanced the endometrial receptivity of patients with refractory endometrium in ways that could not be examined by EMT.

A meta-analysis of studies looking at the predictive value of euploid embryo transfer (ET) as a predictor of pregnancy outcomes found no evidence that ET had any effect [18, 19].

Compared to the control group, which had a MII oocyte median of 2, the PRP group had statistically substantially more MII oocytes than the control group, with a median number of MII oocytes ranging from 3 to 9.

This was in accordance with Mehrafza et al. (2019), who found that the number of M II oocytes in a cohort of 64 females who had had more than two unsuccessful embryo transfer cycles had been treated with PRP was 10.756.48. When compared to a group given granulocyte colony-stimulating factor (GCSF), this figure was statistically considerably greater [20]

In the present research, the PRP group had an 81.1 percent rate of proper fertilisation, which was statistically greater than the control group (45.9 percent).

This was a more frequent occurrence than the rate of fertilisation reported by [20]. (58.3 percent)

Compared to the control group, the PRP group had a clinical pregnancy rate of 48.6%, which was statistically significant (18.9 percent).

According to Abaid et al. (2019), the PRP group had a pregnancy rate of 8/23 (34.8 percent), which was considerably greater than the control group's rate of 3/20 (15 percent) [21].

There were considerably more chemical pregnancies in the intervention group than in the control group (53.06 percent vs 27.08 percent, p value= 0.009), according to Nazari et al. (2020). PRP group had a clinical pregnancy rate of 44.89 percent compared to 16.66 percent in the control group, which was statistically significant [9].

According to Rageh et al. (2020), the study group had 32 pregnancies (43%), whereas the control group had only 11 pregnancies (15%), with 75 people in each group. When it comes to pregnancy, the study and control groups vary significantly (p-value 0.001), according to this study [10].

Injecting PRP resulted in a chemical pregnancy rate of 43.3 percent and a clinical pregnancy rate of 40.3, according to Mehrafza and colleagues (2019). [20].

Patients with refractory thin endometrium were enrolled in a trial by Kim and his colleagues to see whether intrauterine injection of PRP would enhance pregnancy outcomes. A total of 20 women were recruited, and among those with poor prognoses, a clinical pregnancy rate of 30% and a live birth rate of 20% were attained [17]

Eftekhar et al. found that the PRP group had considerably greater implantation and per-cycle clinical pregnancy rates [22]

The findings of Nazari et al. show that PRP intrauterine infusion has a positive effect on pregnancy implantation. Only one miscarriage and one molar pregnancy occurred among the 18 RIF patients who had PRP treatment [23].

The rate of spontaneous miscarriage in the PRP group was 22.2 percent, whereas the rate in the control group was 28.6 percent. There was no statistically significant difference between the two groups. This was in

agreement with the findings of Obidniak et al. [24] who found no difference in the pregnancy loss rate between the PRP group and the control group.

Jackman and colleagues (2020) reported that 80 percent of PRP recipients had a continuing clinical pregnancy and 20 percent experienced an early spontaneous miscarriage or a chemical pregnancy. In this investigation, however, the risk of spontaneous miscarriage in the PRP was greater than that reported by the authors [25].

The study's primary strengths include: 1) The study and control groups were statistically equivalent, hence there was little chance of bias. This research will not include individuals who have haematological or immunological problems, hormonal problems; chromosomal and genetic abnormalities; or uterine abnormalities of any kind, regardless of whether they were acquired or congenital. A single infertility specialist gynaecologist conducted all of the Blastocyst transfers, all of which were done under ultrasound monitoring.

The study's biggest weakness was the minimal number of participants in each group.

4. Conclusion

Endometrial receptivity, implantation, and pregnancy are all improved by PRP infusion, which is a painless treatment for a variety of medical issues. Furthermore, PRP is inexpensive and made from your own blood, so there's no need to worry about immune responses or infection transmission.

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