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# Effect of platelet-rich autoplasma on endometrial thickness and receptor sensitivity to estrogen and progesterone

## Vliv autoplazmy obohacené o krevní destičky na tloušťku endometria a citlivost receptorů pro estrogen a progesteron

**Y. V. Zabrodina[1,2], K. Yu. Boyarsky[3,4], G. U. Akhmedyanova[1,2], Z. G. Khamidullina[1,2]**

[1] Astana Medical University, Astana, Kazakhstan
[2] Department of Obstetrics and Gynecology, No. 1 Astana medical university, Astana, Kazakhstan
[3] Department of Obstetrics and Gynecology, S. N. Davydov Pediatric Faculty SZGMU I. I. Mechnikov, Saint-Petersburg, Russia
[4] Center for Reproduction, Genesis, Saint-Petersburg, Russia

**Summary:** **Aim:** The effect of platelet-rich autoplasma on endometrial thickness and receptor sensitivity to estrogen and progesterone. **Materials and methods:** This prospective clinical study included 200 patients. The participants in the study were divided into two groups. The first control group received hormone replacement therapy (HRT). The second study group received an intrauterine infusion of platelet-rich autoplasma (PRP group). On the 19th day of the menstrual cycle, an ultrasound examination was performed to assess endometrial thickness, as well as an immunohistochemical analysis to determine receptor sensitivity to estrogen and progesterone. **Results:** In the course of the study, we found that the use of platelet-rich autoplasma increased the thickness of the endometrium by 0.85 mm; the average thickness of the endometrium in the group who received PRP therapy was 8.25 (8.25–8.61) mm; and in the group of patients who only received HRT, it was 7.40 (7.34–7.65) mm. The sensitivity of receptors to estrogen in the experimental group increased by 3.5, in the experimental group it was 75.00 (71.43–74.22), and in the control group it was 71.50 (67.05–70.85). The sensitivity of receptors to progesterone also increased by 9.0, in the experimental group it was 95.0 (91.4–93.8), and in the control group it was 86.0 (83.47–86.27). **Conclusion:** Due to the action of platelet factors, PRP therapy has a positive effect on the endometrium, increasing its thickness and improving its receptivity. Therefore, it can be concluded that this method can find great practical application to improve the outcomes of assisted reproductive technology programs.

**Key words:** platelet-rich autoplasma – infertility – thin endometrium

**Summary:** **Cíl:** Vliv autoplazmy obohacené o krevní destičky na tloušťku endometria a citlivost receptorů na estrogen a progesteron. **Materiál a metody:** Do této prospektivní studie bylo zařazeno 200 pacientek. Účastnice studie byly rozděleny do dvou skupin. První, kontrolní skupina dostávala hormonální substituční terapii (HRT – hormone replacement therapy). Druhá, studijní skupina dostávala intrauterinní infuzi autoplazmy obohacené o krevní destičky (PRP – platelet-rich autoplasma). Devatenáctý den menstruačního cyklu bylo provedeno ultrazvukové vyšetření s cílem zhodnotit tloušťku endometria a dále imunohistochemická analýza k stanovení citlivosti receptorů pro estrogen a progesteron. **Výsledky:** Během studie jsme zjistili, že po podání autoplazmy obohacené o krevní destičky se zvýšila tloušťka endometria o 0,85 mm; průměrná tloušťka endometria ve skupině na terapii PRP byla 8,25 mm (8,25–8,61 mm) a ve skupině pacientek, které dostávaly pouze HRT, byla 7,40 mm (7,34–7,65 mm). Citlivost receptorů pro estrogen se v experimentální skupině zvýšila o 3,5, přičemž v této skupině dosáhla hodnoty 75,00 (71,43–74,22) a v kontrolní skupině 71,50 (67,05–70,85). Citlivost receptorů pro progesteron se zvýšila o 9,0, hodnota v této skupině byla 95,0 (91,4–93,8) a v kontrolní skupině 86,0 (83,47–86,27). **Závěr:** Díky působení destičkových faktorů má terapie PRP pozitivní vliv na endometrium, kdy zvyšuje jeho tloušťku a zlepšuje receptivitu. Je tedy možné vyvodit závěr, že tato metoda zřejmě nalezne velké praktické uplatnění při zlepšování výsledků programů asistované reprodukce.

**Klíčová slova:** autoplazma obohacená o krevní destičky – neplodnost – nízké endometrium

## Introduction

The state of the endometrium is important in reproductive medicine because insufficient thickness and impaired receptivity are the causes of assisted reproductive technology (ART) program failure. In support of this, there are a number of works by authors proving a positive relationship between the thickness of the endometrium and the frequency of implantation [1–7].

To date, there are many ways and methods of treatment to solve the problem of a thin endometrium. Thus, according to some authors, the thickness of the endometrium and the frequency of implantation of embryos can be improved by local damage to the endometrium [8,9]. Other authors confirm that the thickness of the endometrium increases with prolonged administration of estrogen, aspirin, and vitamin E [10,11]. However, many patients with a thin endometrium are still resistant to these treatments.

Intrauterine infusion of autologous plasma enriched with platelets (PRP – platelet-rich plasma) is one of the new and promising therapies for a thinning endometrium. PRP is obtained from fresh peripheral blood, which is centrifuged twice to increase platelet concentration by separating various blood components [12]. Platelets contain a significant number of growth factors, including an epidermal growth factor, a platelet growth factor, and a transforming growth factor, all of which stimulate cell proliferation and growth [13]. These growth factors and cytokines contained in platelets can help increase the thickness of the endometrium and improve its receptivity in patients with a thin endometrium [14,15].

To date, there are a number of papers by authors reporting the effectiveness of intrauterine administration of autoplasma enriched with platelets in the treatment of patients with a thin endometrium [16–18]. However, its effect on endometrial receptivity remains unexplored.

The aim of our study was to study the effect of platelet-rich autoplasma on endometrial thickness and receptor sensitivity to estrogen and progesterone.

## Materials and methods

This prospective clinical study was approved by the local bioethics committee. For the study, 200 patients were selected who underwent the *in vitro* fertilization (IVF) procedure from April 2022 to January 2023. The study was performed in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent was obtained from all women prior to the start of the study.

The study included women of reproductive age from 18 to 35 years who had embryo transfer canceled due to insufficient endometrial thickness (< 6 mm) in the IVF procedure, with good quality frozen embryos.

Exclusion criteria were hematological, immunological, or hormonal disorders, chromosomal and genetic abnormalities in women; congenital or acquired anomalies of the uterus; and poor quality embryos.

The study participants were divided into two groups according to a table of random numbers. The first control group (N = 100) received hormone replacement therapy (HRT group). The second group, experimental (N = 100), received an intrauterine infusion of platelet-rich autoplasma in addition to standard hormone therapy (PRP group).

On the second day of the menstrual cycle, all women had a transvaginal ultrasound examination, and standard therapy with estradiol valerate 2 mg/1 tablet was prescribed 3-times a day (the daily dosage was 6 mg). A repeated ultrasound study with an assessment of the thickness of the endometrium was performed on the 10$^{th}$ day of the menstrual cycle.

Platelet-rich autoplasma was obtained by two-stage centrifugation [12]. Preliminarily, all patients in the control group were given a complete blood count and hemostasiogram, and in the absence of deviations in the results, 15 mL of peripheral blood was placed in test tubes with an anticoagulant (dextrose citrate). Blood samples were centrifuged at 14°C for 10 min at 900 rpm. After the first stage of centrifugation, the blood is separated into three fractions: erythrocytes form a precipitate, plasma containing platelets and leukocytes is in the supernatant, and the middle fraction or an intermediate thin layer rich in leukocytes forms a leukocyte precipitate. The plasma layer and leukocyte precipitate were collected in another tube and centrifuged again at 1,500 rpm at 14°C for 15 min to precipitate platelets. The supernatant containing a small amount of platelets was removed, leaving only 0.5 mL for platelet resuspension. The resulting plasma was stored at 4°C for no more than two hours prior to intrauterine infusion.

In the experimental group, 0.5 mL of autoplasma enriched with platelets was administered via a catheter for intrauterine insemination. The daily dosage of estradiol valerate was increased to 10 mg in both groups and the procedure was continued for another 2 days.

Endometrial thickness was measured 48 h later in both groups. In the PRP group, a second dose of plasma was administered, and estrogen was continued in the control group.

Patients in both groups were connected to vaginal progesterone 200 mg 3-times a day beginning on the 12$^{th}$ day of their menstrual cycle.

The control measurement of the thickness of the endometrium was carried out on the 19$^{th}$ day of the menstrual cycle. The thickness of the endometrium was measured twice in its thickest part along the longitudinal axis of the uterus to eliminate errors, and the average value of the two measurements was considered final. On the same day, after sonography, a pipelle biopsy of the endometrium was performed; samples of the obtained material were sent to the

laboratory for immunohistochemical analysis in order to determine the sensitivity of the receptors to estradiol and progesterone.

After the biopsy, the biomaterial was fixed (10% formalin), dehydrated, and then sequentially soaked in ethanol and xylene solutions before being embedded in paraffin and formed into paraffin blocks. After that, 4-micron thick paraffin sections were cut. Hematoxylin and eosin was used to stain the sections after mounting them on a glass slide.

The expression of estrogen and progesterone receptors was measured using peroxidase and avidin-biotin techniques, where specific anti-estrogen (clone GM030) and anti-progesterone (clone XM207) antibodies were used. The amount of immunohistochemical staining and the proportion of stained cells were used to determine the score.

## Statistical analysis

Data processing was performed using the IBM SPSS Statistics 20 program for Windows. Quantitative indicators were evaluated for compliance with the normal distribution using the Kolmogorov-Smirnov criterion. Quantitative indicators having a normal distribution were described using arithmetic averages (M) and standard deviations (SD) with the boundaries of the 95% confidence interval (95% CI). In the absence of a normal distribution, quantitative data were described using the median (Me) and lower and upper quartiles (Q1–Q3). Normally distributed features were tested using the Student's parametric t-test. Non-normally distributed metric variables were analyzed using the Mann-Whitney U test. Pearson's chi-squared criterion ($\chi^2$) was used to analyze nominal variables. $P < 0.05$ was considered statistically significant.

## Results

Initially, 200 patients were included in the study: 100 in the control group, and 100 in the experimental group. However, 14 patients in the control group and four patients in the experimental group were excluded, since adequate material was not obtained for immunohistochemical analysis (Fig. 1).

The average age of patients in the first group was 32.0 years, and in the

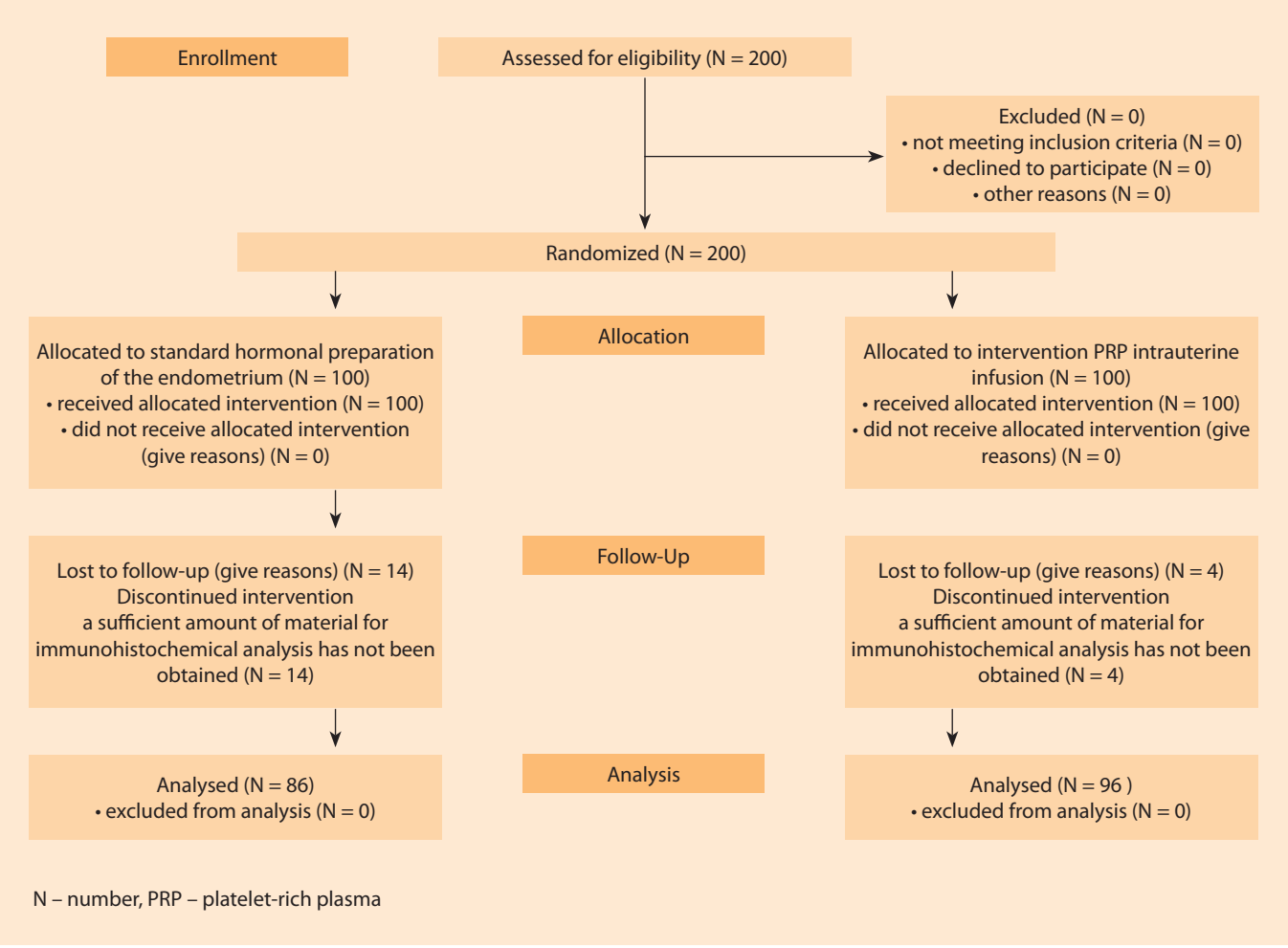


**Fig. 1. Flow chart of the study.**
Obr. 1. Vývojový diagram studie.

**Tab. 1. Demographic characteristic of patients in two groups.**
Tab. 1. Demografické charakteristiky pacientů ve dvou skupinách.

| Variables | Control group (N = 86) | Intra uterine PRP infusion group (N = 96) | P value |
|---|---|---|---|
| mean age (years) | 32.0 (30.49–31.86) | 33.0 (31.56–32.70) | 0.068 |
| BMI (kg/m²) | 25.12 (24.51–25.74) | 24.12 (23.60–24.76) | 0.191 |
| infertility duration (years) | 3.89 (3.43–4.33) | 4.23 (3.79–4.67) | 0.179 |
| **Infertility kinds** | | | 0.540 |
| primary infertility | 46.5% (40) | 46.9% (45) | |
| secondary infertility | 53.5% (46) | 53.1% (51) | |
| **Etiology of infertility** | | | 0.001 |
| endocrine factor | 20.9% (18) | 19.8% (19) | |
| male factor | 15.1% (13) | 16.7% (16) | |
| tubal-peritoneal factor | 20.9% (18) | 5.2% (5) | |
| endometriosis | 16.3% (14) | 24.0% (23) | |
| polycystic ovary syndrome | 11.6% (10) | 2.1% (2) | |
| idiopathic | 4.7% (4) | 4.2% (4) | |
| combined | 10.5% (9) | 28.1% (27) | |

Qualitative indicators are given as percentage, quantitative data are described using the median (Me) and the lower and upper quartiles (Q1–Q3).
N – number, PRP – platelet-rich plasma

second it was 33.0 years. There was no statistically significant difference in age (P = 0.068), duration of infertility (P = 0.191), and body mass index (P = 0.179) in both groups. Demographic characteristics of patients are presented below in the table (Tab. 1).

There was also no statistically significant difference in the type of infertility (P = 0.540). In the group of patients receiving hormone replacement therapy, primary infertility occurred in 40 (46.5%) patients, and in the second PRP group in 45 (46.9%) patients (P > 0.05). Secondary infertility in the first group was observed in 46 (53.5%) patients, and in the second group in 51 (53.1%) patients. However, there was a difference in the factor of infertility (P = 0.001). In the first group, endocrine (20.9%) and tubal-peritoneal (20.9%) factors are predominant; in the second group, combined factors (28.1%) and infertility caused by endometriosis (24.0%) prevail (Fig. 2, 3).

In the course of the study, we found that the use of platelet-rich autoplasma increased the thickness of the endometrium by 0.85 mm; the average thickness of the endometrium in the group who received PRP therapy was 8.25 (8.25–8.61) mm; and in the group of patients who received only hormone replacement therapy it was 7.40 (7.34–7.65) mm. The sensitivity of receptors to estrogen in the experimental group increased by 3.5, in the experimental group it was 75.00 (71.43–74.22), and in the control group it was 71.50 (67.05–70.85). The sensitivity of receptors to progesterone also increased by 9.0; in the experimental group it was 95.0 (91.4–93.8); and in the control group it was 86.0 (83.47–86.27). For the analyzed trait, the significance level was P < 0.05. Confidence interval for the difference was 95% (Tab. 2).

## Discussion

One of the most crucial elements for a successful embryo implantation is an endometrium that is sufficiently thick. As a result, endometrial preparation is considered to be a crucial stage in programs using assisted reproductive technologies. However, there are a number of patients who have a thin endometrium. Modern methods of treating a thin endometrium are limited, and no treatment is the standard of medical care. One of the new ways to correct the thickness of the endometrium is the use of autoplasma [17]. Chang and colleagues published the first study on the application of autologous platelet-rich plasma to increase endometrial thickness in 2015 [18].

In light of this, a 2017 pilot study revealed 10 patients who had a history of cancelled embryo transfers because of a thin (7 mm) endometrium [19]. The authors assessed how PRP affected the thickness of the endometrium. After the first injection of activated autoplasma, the endometrium's thickness rose for 48 hours until reaching a thickness of more than 7 mm following additional PRP injections.

Molina A. and Sanchez J. studied the effect of intrauterine infusion of autoplasma enriched with platelets in patients with a history of a refractory thin endometrium; a total of 19 women took part in the study [20]. In all cases, endometrial thickness exceeded 9 mm with a double injection of plasma.

The results of the work of Brazilian researchers have shown that PRP can affect the sensitivity of uterine mucosal receptors, increasing the chances of clinical pregnancy in patients with a thin endometrium [21].

Since then, a number of studies have demonstrated that it is effective in the treatment of patients with a thin endometrium and repeated implantation failure [22–25].

One of the latest studies on the use of PRP therapy in patients with a thin endometrium was a study published in August 2022 by Hassan S. Abduljabbar et al. In total, the study included 70 patients undergoing IVF between September 2020 and May 2021 in Jeddah, Saudi Arabia. All participants were divided into two groups (intervention and control) by simple randomization, with 35 in each group. In the intervention group, 0.5 mL of PRP was injected into the uterine cavity using an intrauterine insemination catheter on the day of egg collection. Before embryo transfer, the average endometrial thickness reached 8.6 ± 0.9 mm in the intervention group and 7.4 ± 0.6 in the control group ($P < 0.001$). The authors concluded that the use of PRP therapy in IVF/intracytoplasmic sperm injection (ICSI) procedures increases the thickness of the endometrium [26].

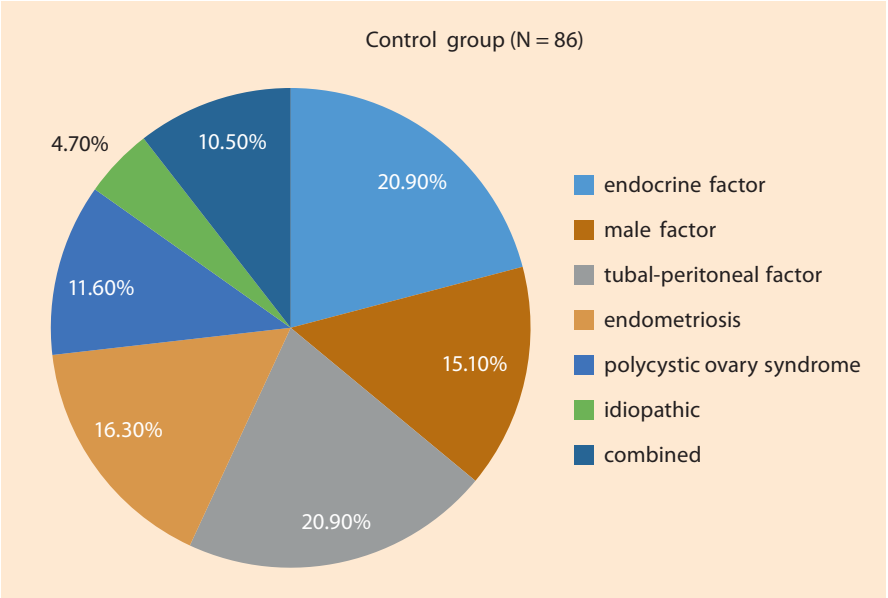


**Fig. 2. Distribution by infertility factor in the control group.**
Obr. 2. Distribuce podle faktoru neplodnosti v kontrolní skupině.

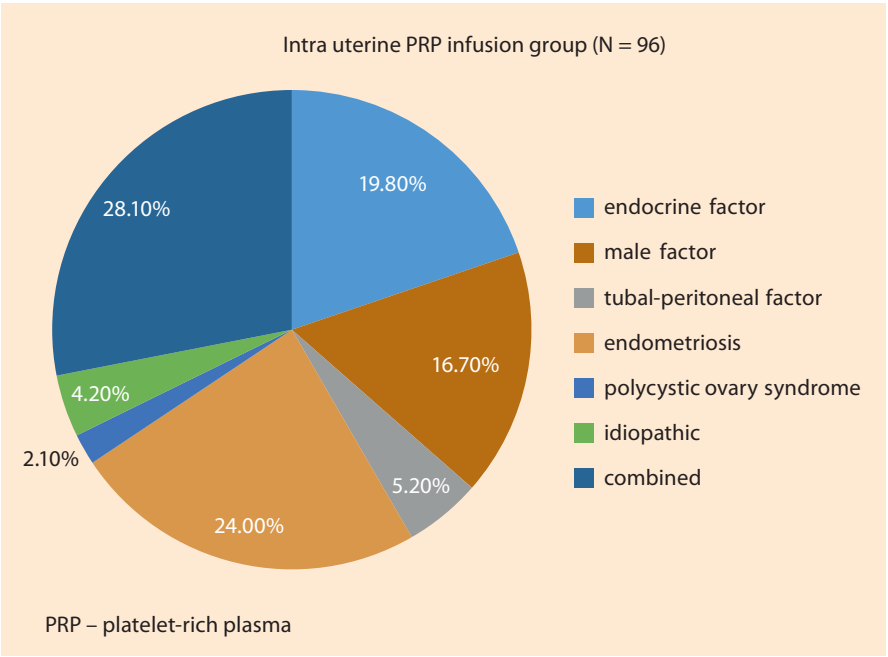


**Fig. 3. Distribution by infertility factor in the intra uterine PRP infusion group.**
Obr. 3. Distribuce podle faktoru neplodnosti ve skupině s intrauterinní infuzí PRP.

**Tab. 2. Results of the study: endometrial thickness, receptor sensitivity to progesterone and estradiol.**
Tab. 2. Výsledky studie: tloušťka endometria, citlivost receptorů na progesteron a estradiol.

| Variables | Control group (N = 86) | Intra uterine PRP infusion group (N = 96) | P value |
|---|---|---|---|
| Endometrial thickness (mm) | 7.40 (7.34–7.65) | 8.25 (8.25–8.61) | < 0.001 |
| Receptor sensitivity to estrogen (%) | 71.50 (67.05–70.85) | 75.00 (71.43–74.22) | 0.006 |
| Receptor sensitivity to progesterone (%) | 86.00 (83.47–86.27) | 95.00 (91.33–93.65) | < 0.001 |

N – number, PRP – platelet-rich plasma

In our study, 182 patients were analyzed in whom embryo transfer was canceled in the previous IVF cycle because adequate endometrial thickness was not achieved. The control group received hormone replacement therapy, and the experimental group received intrauterine infusion of platelet-rich autoplasma in addition to standard hormone therapy. The groups were comparable in age, type of infertility, anthropometric data, and duration of infertility.

The PRP preparation procedure has not yet been standardized. Consequently, the ideal platelet concentration has not been determined. We used the double centrifugation method in order for the platelet count to exceed 1,000,000/mL to achieve a therapeutic effect. Plasma was injected twice on the 10$^{th}$ and 12$^{th}$ day of the menstrual cycle at 0.5 mL administered using a catheter for intrauterine insemination.

In 2021, a study was published in the Human Reproduction Update journal where various models were created to replicate the *in vitro* implantation process. According to these models, the uterus is more receptive to blastocyst implantation during the mid-secretory phase, specifically on days 7–10 [27]. Another study, published in June 2022, indicates that the implantation window for transferring blastocysts occurs between the third and seventh days of progesterone administration [28]. The results of endometrial biopsies conducted after varying periods of progesterone administration revealed that the endometrium of patients reaches a state of receptivity over a wide range of time intervals, from 2.5 to 8 days of progesterone administration. In most clinics, blastocyst transfer occurs after 5 days of progesterone intake. An assessment of endometrial receptivity during this period using endometrial receptivity analysis (ERA) identified a displacement of the implantation window in 34.2% of the examined patients. Within this group, 25.0% had a pre-receptive endometrium [29]. Approximately a quarter of women experience delayed development of the endometrium during the luteal phase [30]. Consequently, we decided to perform an endometrial biopsy to assess its receptivity on the 19$^{th}$ day of the menstrual cycle, taking into account that our study included women with endometrial pathology.

In our study, we observed an increase in the thickness of the endometrium and an improvement in its susceptibility to estrogen and progesterone after intrauterine infusions of autoplasma enriched with platelets in these patients. In the course of the study, we found that the use of platelet-rich autoplasma increased the thickness of the endometrium by 0.85 mm; the average thickness of the endometrium in the group who received PRP therapy was 8.25 (8.25–8.61) mm; and in the group of patients who received only hormone replacement therapy, it was 7.40 (7.34–7.65) mm. The sensitivity of receptors to estrogen in the experimental group increased by 3.5, in the experimental group it was 75.00 (71.43–74.22), and in the control group it was 71.50 (67.05–70.85). The sensitivity of receptors to progesterone also increased by 9.0; in the experimental group it was 95.0 (91.4–93.8); and in the control group it was 86.0 (83.47–86.27). In this cycle, we did not transfer embryos to patients, since the endometrial pipelle biopsy may affect the outcome of assisted reproductive technology programs.

Our data support previously published reports of the effectiveness of PRP in increasing endometrial thickness and improving endometrial receptivity. Thus, in the future, PRP therapy may become a good alternative for the treatment of patients with a thin endometrium and the cancellation of embryo transfer cycles. Platelet-rich autoplasma is easy to prepare, it is economical, minimally invasive and carries a minimal risk of infection transmission, since its own blood is used for its preparation.

## Study limitations

Eighteen participants were omitted from the study because sufficient material could not be obtained for an immunohistochemistry investigation.

## Conclusion

Thus, we deduced that PRP therapy has a positive effect on the endometrium by increasing its thickness and increasing its receptivity as a result of platelet factors. PRP is a safe technique since it is developed from autologous blood samples, which minimizes the danger of spreading infectious diseases and immunological reactions. In our study, the experimental group of patients who got PRP had a much thicker endometrium and had more sensitive receptors. As a result, we can draw the conclusion that this method has a wide range of real-world applications for enhancing auxiliary reproductive technologies.

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## ORCID authors

Y. V. Zabrodina 0000-0001-8972-0300
K. Yu. Boyarsky 0000-0002-2000-1567
G. U. Akhmedyanova 0000-0002-5410-7781
Z. G. Khamidullina 0000-0002-0902-5269

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*Yuliya V. Zabrodina, MD*
*Astana Medical University*
*Beibitshilik St 49/A*
*010000 Astana*
*Kazakhstan*
*zabrodinayuliya@mail.ru*

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