

**ANNOTATION**  
**of the dissertation work Zabrodina Yuliya on the topic: "Clinical efficacy of using platelet-enriched autoplasm in patients with thin endometrium in assisted reproductive technology programs" submitted for the degree of Doctor of Philosophy (PhD) in the specialty 8D10102 – "Medicine."**

**Relevance**

Infertility is a global health and social problem affecting about 200 million people. According to WHO, the rate of infertile marriage in the world is about 17.5%, that is, every sixth person in the world suffers from infertility. In Kazakhstan, this indicator varies in the range of 12-15,5%, which poses a great threat to the demographic situation in the country. The incidence of clinical pregnancy in the world after in vitro fertilization (IVF) programs is 25,5-34,1%, so much attention is paid to the implementation and continuous improvement of ART programs. Despite more than 40 years of experience in improving technologies, over 60% of IVF cycles end without. And in this structure, the failure of endometrial susceptibility accounts for two-thirds of all causes of implantation failures. The incidence of thin endometrium among infertile patients in assisted reproductive technology programs varies from 2,4% to 8,5%.

To date, there are many methods of treating endometrial pathology, but some patients with "refractory" thin endometrium are not sensitive to any of them. Accordingly, the search for alternative therapy for endometrial pathology continues. A new approach in the treatment of the "thin" endometrium is the use of platelet-rich plasma (PRP). Platelet-rich plasma is an autologous biotherapeutic peripheral blood preparation that has a regenerative effect on damaged tissues due to the increased content of growth factors, anti-inflammatory cytokines, and antimicrobial substances contained in platelets and released during their activation.

For more than a decade, PRP has been used for various diseases in ophthalmology, orthopedics and surgery, but the question of its use in reproductology remains open to this day. There is scientific evidence of a positive effect of autoplasm on endometrial growth, but whether this method of therapy has a positive effect on the outcome of pregnancy remains controversial to date.

**Purpose of the Study:** To improve the outcomes of assisted reproductive technologies in infertile patients by developing an algorithm for using platelet-rich autoplasm as part of a comprehensive treatment of women with thin endometrium.

**Research objectives:**

- 1) To determine the clinical and anamnestic features of patients with infertility caused by the "thin" endometrium;
- 2) To evaluate the effectiveness of platelet-rich plasma as part of complex treatment in women with thin endometrium in terms of its thickness and receptivity;
- 3) Compare the frequency of pregnancy in the study groups and track the long-term result-the outcome of pregnancy.
- 4) Identify possible side effects and complications of PRP-therapy;

5) To develop and implement an algorithm for the use of platelet-rich autoplasm in the complex treatment of women with thin endometrium.

**Object and subject of the Study:**

A randomized controlled trial was conducted. Randomization was performed using the random number method.

For the study, 200 patients with thin endometrium were selected who underwent the procedure of in vitro fertilization in the medical center "Center for Perinatal Prevention" in the period from September 2021 to September 2023. Before the start of the study, all women received written informed consent to participate.

**Research methods**

- 1) Clinical (collection of clinical and anamnestic data)
- 2) Intervention ((intrauterine infusions of platelet-rich autoplasm))
- 3) Instrumental (ultrasound of the pelvic organs, pipel-biopsy of the endometrium)
- 4) Laboratory (determination of the level of b-hCG in the blood, immunohistochemical examination for the sensitivity of estrogen and progesterone receptors)
- 5) Statistical (statistical processing of received data)

**Scientific novelty:**

- 1) For the first time in Kazakhstan, a targeted and in-depth study of the effectiveness of PRP therapy in women with pathology of the thin endometrium in terms of its thickness and receptivity was conducted.
- 2) New data have been obtained that demonstrate the undoubted effectiveness of PRP therapy in improving the outcomes of assisted reproductive technology programs.
- 3) For the first time, an algorithm for the use of platelet-rich autoplasm in the complex treatment of women with thin endometrium in assisted reproductive technology programs was developed and implemented.

**Practical significance:**

The proposed complex of therapeutic measures using hormone replacement therapy in combination with platelet-rich plasma for small endometrial pathology will increase the effectiveness of assisted reproductive technology programs and improve reproductive outcomes in women with a history of infertility.

An algorithm for using platelet-rich autoplasm as part of the complex treatment of women with thin endometrium in assisted reproductive technology programs to help practitioners was developed and implemented.

**Key Points for Defense:**

1. The formation of a "thin" endometrium is associated with a high frequency of interventions, accompanied by curettage of the walls of the uterine cavity.
2. The effectiveness of the proposed treatment regimen is proven by improving the anatomical and functional state of the endometrium, which is manifested in an increase in the thickness and receptivity of the endometrium.
3. The use of platelet-rich autoplasm significantly increases the chances of delivery and reduces the number of miscarriages.

4. The thickness of the endometrium on the day of embryo transfer affects the likelihood of pregnancy. The thickness threshold value for patients with a "thin" endometrium, equal to 8,10 mm, at which the probability of pregnancy in ART programs is higher.

5. PRP therapy has a minimal number of side effects, so it can be offered as an effective and safe method of treating women with a "thin" endometrium in assisted reproductive technology programs.

#### **Approval of the Dissertation:**

The main provisions of the work were presented at the international scientific and practical conference of young scientists and students dedicated to the 30th anniversary of independence of the Republic of Kazakhstan of NJSC "Astana Medical University" 2021, the 64th International scientific and practical conference of students and young scientists "Medical Science, education, practice: problems and solutions" of NJSC "Medical University". University of Astana 2022, conferences with international participation "Multidisciplinary approach in providing obstetric and gynecological care" Astana 2022, international scientific and practical conference of students and young scientists "Science and youth: discoveries and prospects" NJSC "Medical University of Astana" 2023, conferences with international participation "Multidisciplinary approach in providing obstetric and gynecological care" Astana providing obstetric and gynecological care "Astana 2023, IV International Scientific and practical Conference" Multidisciplinary approach in providing obstetric and gynecological care" Astana 2024, XLVI International Scientific and Practical Conference "Eurasia Science" Moscow 2022.

The results of the study are presented in 12 scientific publications, including 6 theses, 6 scientific articles. Among them, 1 work in the publication of the rating agency Scopus, 1 publication in the publication Web of science, 3 articles in journals recommended by the Committee for Control in the Field of Education and Science of the Republic of Kazakhstan and 1 article in a peer-reviewed foreign journal.

2 certificates protected by copyright of the Republic of Kazakhstan were obtained on the topic of the dissertation.

The results of the work were implemented in the departments of assisted reproductive technologies of "ECO CPP" LLP in Astana, "Astana Ecolife" LLP, "Ecomed Plus" LLP, "Health and Science Center M1" LLP, "Stork Home" LLP.

Approbation of the doctoral thesis was held at the extended meeting of the Department of Obstetrics and Gynecology No. 1 (Protocol No. 19 of 05.07.2024).

#### **Conclusions**

1. The formation of a "thin" endometrium is associated with a high frequency of interventions in the uterine cavity. The most frequent surgical interventions in the studied groups of patients were uterine curettage, which accounted for a quarter of all invasive manipulations (25% and 28%). In 17-18% of cases, hysteroscopies were performed, including excision of defects in the uterine cavity and cervical canal walls. In the structure of gynecological pathology, the leading position was occupied by chronic endometritis, which occurred in 20% and 14% of cases.

2. At the time of inclusion in the study, the endometrial thickness in the middle luteal phase was less than 7 mm and had no statistically significant differences ( $p=0.694$ ), averaging 5,71 mm in the control group and 5,78 mm in the intervention group. After our treatment, a more pronounced increase in endometrial thickness was observed in the intervention group ( $p<0,001$ ). The endometrial thickness in the control group reached 7,50 (7,14; 7,60), and in the intervention group 8,70 (8,42; 8,79) mm, the increase was  $1,65 \pm 0,70$  mm and  $2,83 \pm 0,71$  mm, respectively. Statistical analysis of endometrial receptivity indicators in both groups showed a significant increase in all indicators after PRP therapy ( $p=0,001$ ).

3. The use of platelet-rich autoplasm significantly increases the chances of pregnancy. So, in the first group of 86 performed transfers, biochemical pregnancy occurred in 31 patients, which was 36.05%. In the second group, a positive result of beta-hCG was recorded in 50 patients, which corresponds to 52,08%. The incidence of clinical pregnancy in the first group was 31,40%, in the second 46,88%. The incidence of biochemical pregnancy was higher by 16,03% and clinical pregnancy by 15,48% in the group receiving PRP infusions in addition to hormone replacement therapy. This difference was statistically significant for both indicators ( $p=0,037$  and  $p=0,035$ ).

4. Analysis of the outcomes of assisted reproductive technology programs showed that the birth rate in the group after PRP therapy was 17,8% higher, this difference is statistically significant ( $p=0,032$ ). Miscarriages were 12,6% more common in the first group, where only hormone replacement therapy was used as therapy ( $p=0,042$ ). The percentage of ectopic pregnancies was also higher in the first group, but this indicator was not statistically significant ( $p=0,155$ ). Thus, the risk of miscarriage in the control group of patients was 3,74 times higher (95% CI for OR = 0,64-21,98) compared to the intervention group.

5. Of the 100 patients who underwent PRP therapy, 32% reported unpleasant sensations at the time of plasma injection into the uterine cavity, 11% had minor pulling pains in the lower abdomen within 1 day after the procedure, and 57% did not notice any unpleasant reactions. Also, there were no possible infectious and other complications after manipulations.

#### **Practical recommendations**

1. In patients with thin endometrium, routine pipel-biopsy is not recommended, since there is a direct correlation between endometrial thickness and receptor expression, and therefore receptivity can be inferred based on endometrial thickness.

2. As a threshold level, the thickness of the endometrium value of 8,10 mm was determined, which increases the probability of pregnancy and live birth, and can be used as a target value for endometrial thickness, at which embryo transfer is recommended.

3. For the preparation of platelet-rich autoplasm, it is recommended to use the method of double centrifugation: the 1st stage - 10 minutes at a speed of 900 revolutions per minute, the 2nd stage-15 minutes with a crust of 1500 revolutions per minute.

4. Patients with a thin endometrium are recommended to receive intrauterine PRP

therapy on 8, 10 days of the menstrual cycle and 48 hours before embryo transfer.

5. PRP therapy has a minimal number of side effects, so it can be offered as an effective and safe method of treating women with a "thin" endometrium in assisted reproductive technology programs.

6. The use of autologous platelet-rich plasma (PRP) is not accompanied by allergic reactions, infectious consequences or other negative effects, which makes it a safe natural source of mitogens and growth factors with an intense proliferative capacity.

**Volume and Structure of the Dissertation:**

The dissertation is presented on 141 pages of typewritten text. The dissertation consists of an introduction, a literature review, a chapter materials and methods of research, results, conclusions, a list of sources used, practical recommendations, and an appendix. The work is illustrated with 30 tables and 38 figures. The bibliographic index includes 192 literary sources.