

**Застосування кріоконсервованих препаратів
фетоплацентарного комплексу як методу лікування
безпліддя, спричиненого хронічним ендометритом:
клінічний випадок**

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**The Use of Cryopreserved Medications from
the Feto-Placental Complex as a Method for Treating
Infertility Caused by Chronic Endometritis: a Case Report**

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The utilization of umbilical cord blood and placenta exhibits a favorable influence on the management of chronic endometritis. Significant endometrial injuries can lead to adverse outcomes including amenorrhea, infertility, and miscarriage. Chronic endometritis (CE) presents as a condition characterized by prolonged, mild inflammation within the endometrial tissue, marked by plasma cell infiltration into the stromal area. Recent investigations indicate that 45% of infertile patients, particularly those grappling with recurrent implantation failure, are afflicted by chronic endometritis. Presently, standard treatment protocols primarily involve oral antibiotics, contingent upon culture and gram stain results derived from endometrial aspiration or biopsy. Nevertheless, there is a lack of universally defined antibiotic regimens tailored specifically for chronic endometritis.

Therapy with cryopreserved stem cells from the feto-placental complex is a part of Clinical Trials "Investigation of the possibility and effectiveness of the use of cryopreserved cord blood stem cells and placenta preparations for the correction of reproductive function disorders of psychosomatic origin in women and men" №0119U100443. Method of immunohistochemistry (IHC) for CD138 in the biopsy of the endometrium was used for proving diagnosis of chronic endometritis. A 36 year-old woman presented to our IVF department, complaining of the absence of pregnancy for a period of 3 years. She had a history of endometriosis, chronic endometritis, one spontaneous abortion at 3-4 weeks of development and one laparoscopy and hysteroscopy (fallopian tubes were passable). The patient also has left adrenal adenoma, left breast fibroadenoma and pituitary microadenoma, for which she was treated with 0.5 mg of cabergoline. The overall physical and systemic assessments were normal. A transvaginal ultrasound examination revealed a uterus measuring 54 × 38 × 44 mm, with a subserosal focal area of decreased echogenicity measuring 6 × 4 mm on the posterior wall of the uterus. The endometrial thickness was 8.8 mm on the 20th day of the menstrual cycle. The right ovary measured 26 × 14 mm, with antral follicles of 6 mm (No. 1) and 3 mm (No. 4). The left ovary measured 34 × 23 mm, with antral follicles of 5 mm (No. 2), suggestive of age-appropriate antral follicle count and raising suspicion for adenomyosis. A pipelle biopsy with immunohistochemical examination confirmed the presence of CD138 plasma cells in the endometrial stroma. The husband had a child from a previous marriage and underwent treatment with an andrologist for oligoasthenoteratozoospermia. Considering the patient's medical history, it was decided to initiate therapy using cryopreserved placental and cord blood medications, followed by the application of assisted reproductive technologies.

The treatment regimen included subcutaneous administration of cord blood concentrate, intramuscular injection of cord blood suspension, and thrice administration of placental homogenate over one calendar month. In the first menstrual cycle following treatment, the patient achieved natural conception and delivered a girl after 9 months, whose stem cells were also cryopreserved.

Chronic endometritis commonly manifests as either asymptomatic or presenting with irregular symptoms, such as abnormal uterine bleeding, chronic pelvic pain, dyspareunia, or vaginal discharge, persisting chronically and displaying a protracted course of progression. This pathophysiological state ultimately undermines the reproductive capacity of afflicted individuals. Consequently, chronic endometritis is frequently overlooked, even within the domain of reproductive medicine, owing to its nuanced clinical presentation and insidious nature. As a result of this diverse clinical symptoms, the lack of common diagnostic criteria and treatment strategy further study is needed on the use of cryopreserved stem cells for the treatment of the infertility caused by chronic endometritis.

**Терапевтичний ефект пуповинної крові та плаценти
при лікуванні хронічного ендометриу у пацієнток
із повторними невдачами імплантації**

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**Therapeutic Effect of Umbilical Cord Blood and Placenta
in the Treatment of Chronic Endometritis in Patients with
Repeated Implantation Failures**

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The use of the umbilical cord blood and placenta has a positive effect on the treatment process of chronic endometritis in women with repeated implantation failures (RIF). Healthy endometrium is one of the main factors in pregnancy. Serious injuries to the endometrium in women can cause amenorrhea, infertility, miscarriage. Chronic endometritis (CE) is a disorder of prolonged, continuous, mild endometrial inflammation, which is characterized by plasma cell infiltration into the endometrial stromal area. Recently, 15–25% of infertile patients had chronic endometritis, especially those with recurrent implantation failure. Standard treatment of chronic endometritis revolves primarily around oral antibiotics, depending on the culture and gram stain findings of the endometrial aspiration/biopsy. There is no defined antibiotic regimen for chronic endometritis.

In the period from October 2022 to November 2023, 58 infertile RIF patients with diagnosis "chronic endometritis", proved by immunohistochemistry (IHC) method for CD138, underwent the CE treatment in the Centre of Human Reproduction (Clinic of Professor Feskov). The study is a part of Clinical Trials "Investigation of the possibility and effectiveness of the use of cryopreserved cord blood stem cells and placenta preparations for the correction of reproductive function disorders of psychosomatic origin in women and men" №0119U100443. Patients groups were as follows: standard CE treatment (32 women, Group 1); standard CE treatment with additional intramuscular administration of preparations of placenta and umbilical cord blood (26 patients, Group 2). The age of RIF patients was 32-38 years old. All the women had not less than 2 unsuccessful IVF attempts in the past. Diagnosis "chronic endometritis" was confirmed by IHC for CD138. Use of antibiotics and immunomodulators was considered as a standard CE treatment.

Results of CE treatments in Groups 1 and 2 were compared. Chi-squared test was used for data analysis. $P < 0.05$ was considered statistically significant. Main results and the role of chance: the course of CE treatment was about 1 month for the patients of both groups. Intramuscular injections of cord blood suspension and homogenized placenta were used as a part of treatment of chronic endometritis for Group 2 patients. The control immunohistochemistry for CD138 was done at the end of the treatment in both groups. The control IHC was done for 24 women from Group 2, as the natural pregnancy has been achieved in two patients from Group 2 before the control was done. The strong positive effect of intramuscular administration of placenta and umbilical cord blood preparations on chronic endometritis treatment was demonstrated. After CE treatment, CD138 was found negative in 6 patients in Group 1 and in 10 patients in Group 2 (18.8% vs. 41.7%; $df = 1$, $\chi^2 = 4.609$, χ^2 critical = 3.841, $P < 0.05$). Patients with negative CD138 control are prepared for the next IVF attempt.

The study demonstrates the efficacy of incorporating intramuscular administration of cord blood suspension and placenta preparations alongside the standard treatment for chronic endometritis. Patients, who received this additional treatment, exhibited a notably higher rate of negative CD138 control post-treatment. Statistical analysis using the Chi-squared test highlights the significance of the observed differences between treatment groups, with Group 2 showing a statistically significant increase in the proportion of patients with negative CD138 control compared to Group 1. These findings suggest a strong positive effect of the adjunctive treatment on chronic endometritis, particularly among women with recurrent implantation failures, offering promising prospects for improving reproductive outcomes. Moving forward, larger-scale clinical trials and long-term follow-up studies are warranted to further explore the efficacy of umbilical cord blood and placenta preparations in CE treatment and to integrate these findings into clinical practice for optimizing reproductive health and fertility outcomes.

