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Клінічні результати лікування безпліддя у пацієнток з поєднаним перебігом лейоміоми матки та хронічного ендометриту при оптимізації кріопротоколів підготовки до ембріотрансферу

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Важливою медико-соціальною проблемою сьогодення є безпліддя. Екстракорпоральне запліднення – передова методика ДРТ, що у 50% випадків допомагає успішно вилікувати безпліддя. Якісна підготовка до програм ЕКЗ і до подальшої вагітності є важливою і повинна включати в себе лікування супутньої патології, оцінку стану порожнини матки та її оптимальну підготовку з метою попередження репродуктивних невдач та ранніх акушерських втрат. Метою стало порівняти ефективність модифікованої схеми лікування хронічного ендометриту порівняно із загальноприйнятою та довести ефективність оптимізованих кріопротоколів підготовки до ембріотрансферу у пацієнток із безпліддям на тлі коморбідного перебігу лейоміоми матки та хронічного ендометриту.Проведено клінічне обстеження та порівняльний аналіз анамнестичних даних 100 жінок із безпліддям на тлі поєднаного перебігу лейоміоми матки та хронічного ендометриту. Пацієнтки були розподілені на дві групи залежно від пропонованої схеми лікування та окремо сформована група контролю. У всіх групах стимуляцію суперовуляції здійснювали за коротким протоколом із антагоністом ГнРГ. Статистичну обробку отриманих даних проводили з використанням програм «STATISTICA 7.0» та «Microsoft Excel». За статистично достовірне значення приймали $p<0,05$. Характерними особливостями пацієнток з безпліддям на тлі лейоміоми матки та хронічного ендометриту є раннє менархе, ранній початок статевого життя, більша кількість статевих партнерів, більша частка перенесених урогенітальних інфекцій, більша частота проведених внутрішньоматкових хірургічних манупіляцій. Нижча середня сумарна доза гонадотропінів, менша тривалість стимуляції та менша кількість днів введення ант-ГнРГ, притаманні групі модифікованого лікування. Вища частота настання клінічної вагітності та частота пологів реєструється у жінок другої групи, що пройшли лікування за модифікованою

схемою. Отже, проведення адекватної протизапальної та антибіотикотерапії та комплексна підготовка стану порожнини матки до ембріотрансферу є ключовими факторами успішності програм ЕКЗ.

Ключові слова: безпліддя, допоміжні репродуктивні технології, екстракорпоральне запліднення, контрольована оваріальна стимуляція, лейоміома матки, хронічний ендометрит, PRP-терапія ендометрія, ембріотрансфер, лікування.

Clinical results of infertility treatment in patients with a comorbidity of uterine leiomyoma and chronic endometritis with optimization of cryoptocols for embryo transfer preparation

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Infertility is a major medical and social issue. In vitro fertilization is an advanced ART technique that helps to successfully cure infertility. Quality preparation for an IVF protocol and the subsequent pregnancy is important and should include treatment of concomitant pathology, evaluation of the condition of the uterine cavity and its optimal preparation in order to prevent reproductive failures and early obstetric losses. This study assessed the effectiveness of optimized cryoprotocols for preparation for embryo transfer in patients with infertility and the comorbid course of uterine leiomyoma and chronic endometritis. We performed clinical examination and comparative analysis of anamnestic data of 100 women with infertility and comorbid uterine leiomyoma and chronic endometritis. The patients were divided into two groups depending on the proposed treatment scheme and the outcomes were compared to a control group. In all groups, stimulation of superovulation was carried out following a short protocol with a GnRH antagonist. We determined that patients with infertility comorbid with uterine leiomyoma and chronic endometritis, when compared to the control group patients, had a history of early menarche, early onset of sexual life, a greater number of sexual partners, a greater incidence of urogenital infections, and of performed intrauterine surgical procedures. The patients in the modified treatment group received a lower mean total dose of gonadotropins, had a shorter duration of stimulation, and fewer days of anti-GnRH administration compared to

the traditional treatment group. The patients in the modified treatment group also had a higher frequency of clinical pregnancy and delivery compared to those received conventional treatment. An appropriate anti-inflammatory and antibiotic therapy and comprehensive preparation of the uterine cavity for embryo transfer are key factors in the success of IVF protocols.

Keywords: Infertility, assisted reproductive technologies, in vitro fertilization, controlled ovarian stimulation, uterine leiomyoma, chronic endometritis, PRP therapy of the endometrium, embryo transfer.

Introduction

Today, infertility has emerged as a significant medical and societal concern. According to the WHO, about 17.6 million people in the world experience infertility at least once in their life [1]. In recent years, combined infertility causes have become more common rather than purely male or female disorders resulting in reduced fertility. At the same time, idiopathic (unexplained) infertility is also being diagnosed more frequently. The advancements in reproductive medicine have ushered an era of assisted reproductive technologies, aimed at solving the problems of infertile couples. For instance, in vitro fertilization is an advanced ART technique that, according to the data worldwide [2], helps to successfully cure infertility in approximately 50% of the cases.

However, a correct and early diagnosis of infertile couples is not the only necessary factor which can improve the results of assisted reproduction. An important role in this process is played by the uterine cavity assessment and proper preparation for pregnancy. Implementing well-fitted and compound preparation plans prior to IVF programs helps to prevent potential reproductive failures (including repeated implantation failures, known as RIF) and early obstetric losses (recurrent pregnancy loss (RPL), and spontaneous abortion).

In recent years, researches have been focusing on a well-known gynaecological pathology, chronic endometritis, which is recognized one of the leading causes of RIF and RPL, as well as the cause of unexplained infertility [3,4]. In these cases, its prevalence can reach over 30% [5], and therefore this pathology should not be ignored while choosing a management plan for infertile women, especially those with unsuccessful IVF in the anamnesis. In rare cases, uterine cavity inflammation is recognised as the only cause of reproductive failure. However, in most cases, this pathology is characterized by a comorbid course with other structural, hormonal or immunological disorders that affect fertility.

About 10-15% of infertile women, according to the study by Bosteels et al. [6], have structural abnormalities of the uterine cavity as well as certain hormonal or infection pathologies, such as endometrial polyps, uterine fibroids, intrauterine adhesions or complete/partial septum, and chronic endometritis. Worldwide, between 48.5 and 72.4 million couples of reproductive age suffer from infertility related to the uterine factors. In addition to infertility, such patients also complain of chronic pelvic pain, dyspareunia, and metrorrhagia [7]. Uterine leiomyoma, endometriosis, and chronic endometritis are the most common causes of uterine cavity disorders.

Uterine leiomyoma is the most common benign tumour of the genitals, and can produce an extremely adverse effect on the female reproductive tract. Fibroids can cause deformation of the uterine cavity, preventing implantation of the embryo. The effect of myoma on pregnancy outcomes is mainly related to its location. Intramural and subserous myomas generally do negatively affect the pregnancy; however, submucosal fibroids are associated with reduced implantation and pregnancy rates in patients undergoing IVF treatment. The mechanisms preventing implantation include increased contractions of the myometrium, abnormal vascularization, and cytokine profile disorders. Accordingly, such patients have a lower rate of implantation and live births [8]. The likelihood of developing uterine fibroids increases 3.7 times after three episodes of pelvic inflammatory disease,

3.2 times after chlamydial infection and 5.3 times following the use of intrauterine devices (IUDs) [9]. Some studies also report a pathogenetic relationship between the myoma and previous uterine infections and chronic inflammation [10,11].

Chronic endometritis is a resistant endometrial inflammation that is usually asymptomatic or has intermittent symptoms such as abnormal uterine bleeding, chronic pelvic pain, dyspareunia, or vaginal discharge over a long period of time with a tendency to persist and slowly progress, eventually reducing the reproductive potential [12]. Accumulated evidence regarding the adverse effects of chronic endometritis on ART treatment suggests that it impairs the implantation by affecting endometrial decidualization and leads to poor pregnancy outcomes in women with repeated implantation failures in IVF cycles prior to embryo transfer [13].

There is no a single accepted procedure for treating chronic endometritis in IVF protocols. Antibacterial therapy remains the first line treatment; additionally, there are publications that suggest the effectiveness of PRP and antioxidant therapy, the use of progestogens and filgrastim in the complex treatment of chronic endometritis.

A meta-analysis by Jingjing Liu showed that women with treated chronic endometritis using antibacterial therapy had significantly improved clinical pregnancy and live birth rates compared to the patients with persistent untreated CE [14]. This is why in IVF programs evaluating the uterine cavity and the state of the endometrium are critically important for further successful implantation of the embryo, and preparing the uterus for pregnancy is no less important than the stimulation of superovulation.

The comorbidity of uterine leiomyoma and chronic endometritis is not an uncommon occurrence which is being increasingly diagnosed in infertile women or can cause miscarriages and implantation failure. Reproductive doctors need to take into account the risk factors of chronic inflammation of the uterine cavity, and screen for markers of chronic endometritis prior to the embryo transfer and carry out appropriate treatment of associated gynaecological pathology. Therefore, optimization of controlled ovarian stimulation protocols and cryocycles of embryo transfer in infertile patients with the comorbidity of uterine leiomyoma and chronic endometritis is a pressing need in order to prevent reproductive failures and early obstetric losses.

Materials and Methods

We carried out a clinical examination and comparative analysis of anamnestic data of the 100 infertile women with uterine leiomyoma and chronic endometritis. The patients were divided into two clinical groups depending on the proposed treatment scheme.

The first clinical group included 42 infertile patients (32.31%) with uterine leiomyoma and chronic endometritis, who received the conventional therapy of chronic endometritis after undergoing ovarian stimulation followed by delayed embryo transfer in cryocycle protocols after 3-4 months in the natural cycle with progesterone support of the luteal phase. Hormone replacement therapy protocols were not used for the patients included in the study due to the presence of hormone-dependent uterine tumours, namely uterine leiomyomas.

The second clinical group included 58 women (44.62%) with infertility against the background of leiomyoma and chronic endometritis. After the ovarian stimulation protocol, the patients underwent antibiotic therapy in combination with intrauterine administration of filgrastim on days 5, 6, and 7 of the menstrual cycle and endometrial PRP therapy procedures on days 10-12 of the cycle as the compound treatment of chronic endometritis.

Additionally, the IVF protocol included the following: prior to the COS and after the oocyte retrieval up to the day of the embryo transfer in the cryocycle, the patients received supporting therapy which included a vitamin complex with inositol FT500Plus (1 sachet once per day) and alpha-lipoic acid supplement Pelvidol (a prophylactic dose of 1 tablet once daily for 3-4 months) and a course of probiotics to restore microbiome of the uterine cavity. The patients underwent delayed cryotransfer after the modified therapy of chronic endometritis. In some patients, cryoprotocols were carried out exclusively in natural cycle with progesterone support in the luteal phase.

The control group consisted of 30 women (23.07%) with diagnosed infertility caused by male pathology. In this group, embryo transfer protocols were carried out either in cryocycle using hormone replacement therapy or in natural cycle.

Controlled ovarian stimulation of superovulation was performed according to a short protocol with a GnRH antagonist in all three groups. Stimulation with recombinant FSH «Puregon» lasted for 9-11 days, starting on day 2-3 of the menstrual cycle and with further monitoring of the stimulated cycle on days 6, 8, and10 of stimulation. When the follicles reached the required average size of 14 mm, preferably on day 5-7 of stimulation, the antagonist «Orgalutran» in a dose of 0.5 mg was additionally administered for 4 to 6 days (until the end of stimulation) to prevent premature luteinisation. The duration of stimulation was determined by the extent of follicular growth. In the cases where three or more follicles were over 18 mm in size, a trigger for the final maturation of oocytes «Ovitrel» was prescribed in a dose of 6.500 IU. Thirty-six hours after administering the ovulation trigger, oocyte retrieval was performed in the operating room under general anaesthesia. Aspiration of oocytes was carried out using a Cook Puncture Needle (size 17G) and transvaginal ultrasound control.

Fertilization of oocytes and cultivation of embryos to the blastocyst stage were carried out in the embryological laboratory with subsequent vitrification on the day 5-6 of fertilization. Assessment of oocyte quality and maturity was performed prior to intracytoplasmic sperm injection (ICSI) procedure after denudation graded by meiotic status. Metaphase II (MII) oocytes were defined as mature and 2PN oocytes were deemed as normally fertilised. Fertilization results were evaluated 16-19 hours after the ICSI procedure, while the division and release of blastocysts were evaluated on the 3rd and 5th-6th days respectively. Embryos at the blastocyst stage were evaluated using qualitative indicators according to the Gardner system.

Following the treatment of chronic endometritis according to either the conventional or modified therapy, the patients underwent delayed cryotransfer of 1 or 2 embryos into the uterine cavity with a Cook Catheter under the transabdominal ultrasound control. After embryo transfer, the patients received progesterone therapy for 15 days.

Statistical processing of the data was carried out using the STATISTICA 7.0 and Microsoft Excel software packages. Descriptive statistical analysis was performed taking into account the number of study groups, compliance with the normal distribution, as well as equality of variances. $p<0.05$ was considered statistically significant.

Results

The analysis of clinical and anamnestic data of the patients suffering from infertility with comorbid uterine leiomyoma and chronic endometritis has identified a number of characteristics that affected outcomes of infertility treatment in IVF protocols.

The average age of the women included in the study ranged from 25 to 40 years. There were no significant age differences between the patients of the first and second clinical groups compared to the control group.

Compared to the control group, the patients with uterine leiomyoma and chronic endometritis in both clonical groups had an earlier menarche and an earlier onset of sexual life (Table 1).

The majority of patients in the first and second clinical groups had 3 to 5 sexual partners, while in the control group, the majority had up to 2 sexual partners (Table 2).

Table 1

Age of menarche and onset of sexual life in women involved in study (Mean±SD)

	Group one (n=42), standard therapy	Group two (n=58), modified therapy	Control group (n=30), male factor infertility
Menarche, age	12.02 ± 1.35*	12.18 ± 1.58*	13.42 ±1.12
Sexual life onset, age	15.45 ± 1.32*	15.55 ± 1.35*	18.20 ± 1.75

*- statistically significant results, $p<0.05$

Analysis of the incidence of gynaecological disorders (Fig. 1) in patients with infertility comorbid with uterine leiomyoma and chronic endometritis, who received both standard and modified treatments, showed a significantly higher percentage of urogenital infections in both clinical group compared to the control group.

The frequency of intrauterine surgical interventions and procedures, including hysteroscopy, surgical abortions, and caesarean sections, was 28% higher in the first clinical group and 30% higher in the second clinical group compared to the control group (Fig. 2).

Taking into account the clinical and anamnestic information discussed above, the patients were prescribed different treatment protocols for chronic endometritis, either a standard scheme or modified treatment, in order to evaluate the effectiveness of the modified treatment and its impact on IVF outcomes.

Analysis of the controlled ovarian stimulation (COS) protocols in infertile patients with uterine

Table 2

Number of sexual partners in patients with infertility comorbid with uterine leiomyoma and chronic endometritis, n (%)

	Group one (n=42), standard therapy	Group two (n=58), modified therapy	Control group (n=30), male factor infertility
Up to 2	12 (28.57 %)*	18 (31.03 %)*	22 (73.33 %)
3 to 5	20 (47.62 %)*	25 (43.10 %)*	5 (16.67 %)
6 and more	10 (23.82 %)	15 (25.86 %)	3 (10.00 %)

*- statistically significant results, p<0.05

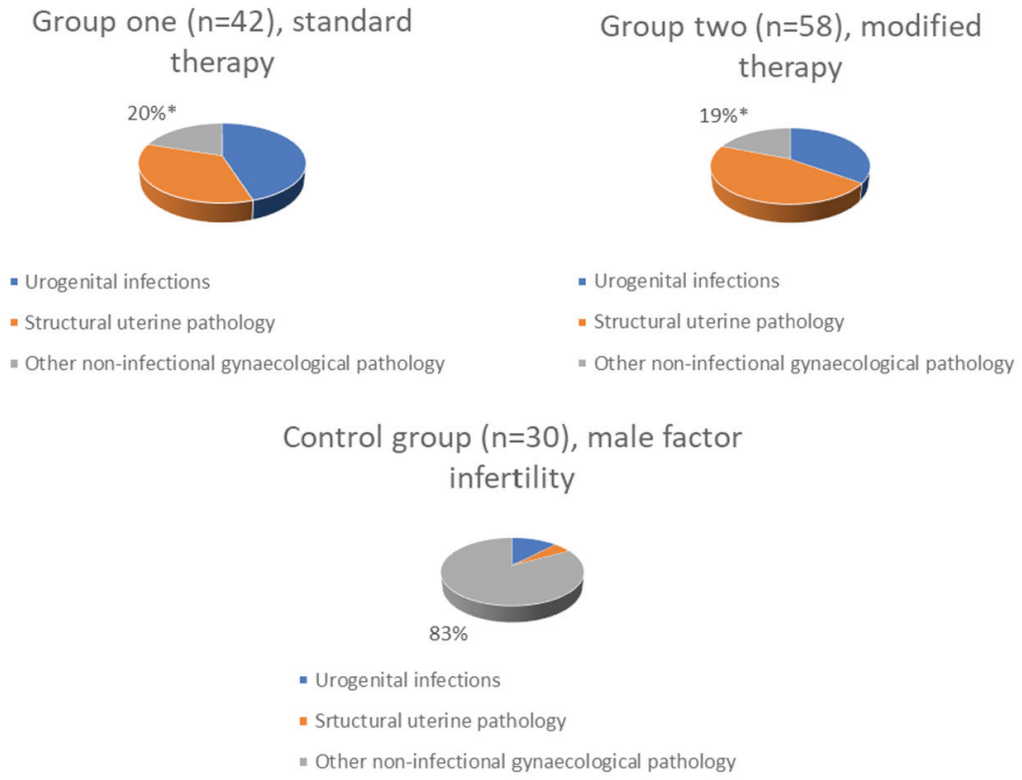

Figure 1. Frequency of gynaecological disorders in patients with infertility comorbid with uterine leiomyoma and chronic endometritis, (%)

* - statistically significant results, p<0.05.

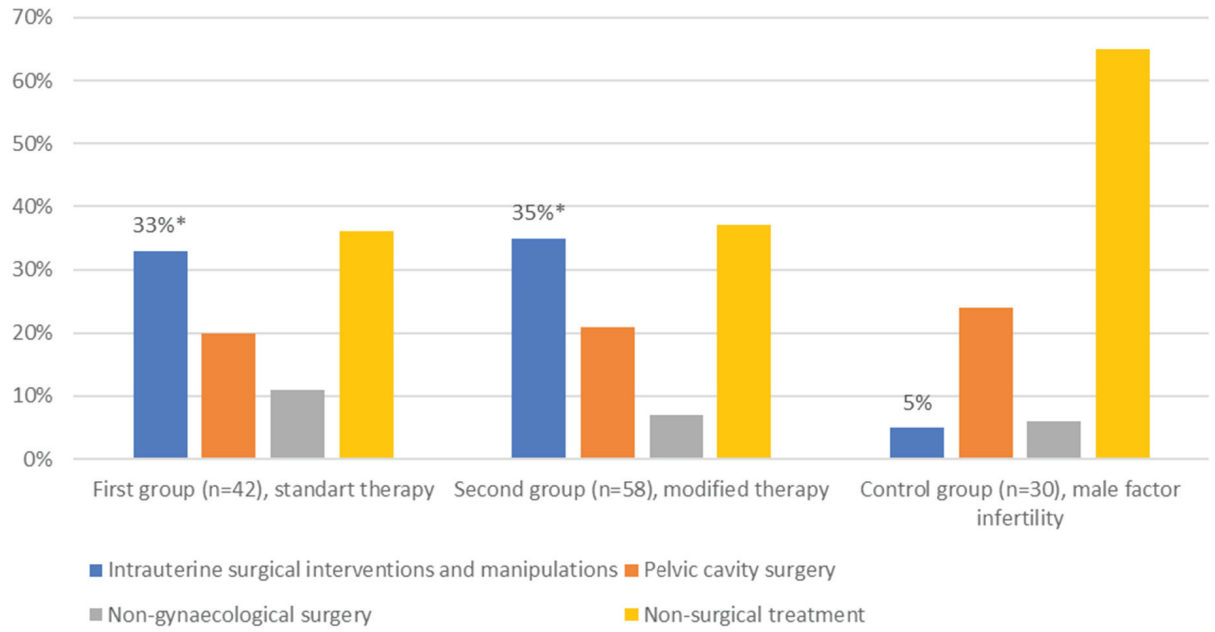

Figure 2. Types of uterine interventions and treatments in the anamnesis of patients with infertility comorbid uterine leiomyoma and chronic endometritis, (%)

* - statistically significant results, p<0.05

leiomyoma and chronic endometritis showed that the initial dose of recombinant FSH, the duration of stimulation and duration of ant-GnRH Orgalutran administration were significantly higher (p<0.05) in the group with the standard therapy of chronic endometritis compared with the same values in both the modified therapy group and control group (Table 3).

The analysis of clinical data showed that endometrium thickness was lower at the modified treatment group (10.20 ± 1.92 mm), compared to the standard therapy group (11.78 ± 1.73 mm). A comparison of the embryological protocol outcomes showed significant difference (p<0.05) between the number of retrieved oocytes, including mature ones (MII), the number of normally fertilized oocytes (2PN) and blastocyst outcomes in both clinical groups compared to the control group. We observed better quantitative and qualitative outcomes in the modified treatment group (Table 4).

The efficiency of IVF, including of the cryoprotocols to prepare for embryo transfer, was evaluated using a number of indicators (Table 5). Pregnancy rates (including clinical pregnancy rate and full term birth rate) in the mod-

Table 3

Controlled ovarian stimulation protocol results in patients with infertility against the background of uterine leiomyoma and chronic endometritis due to different treatment schemes

	Group one (n=42), standard therapy	Group two (n=58), modified therapy	Control group (n=30), male factor infertility
Initial dose of recombinant FSH, IU	225.02 ± 15.51*	210.32 ± 25.01	204.23 ± 11.56
Duration of stimulation, days	11.3 ± 1.43*	10.5 ± 1.21	10.2 ± 1.32
Average total dose of gonadotropins per stimulation cycle, IU	2362.71 ± 325.71	2271.46 ± 420.13	2150.37± 462.34
Duration of anti-GnRG Orgalutran administration, days	5.29 ± 0.59*	4.82 ± 0.78	4.56 ± 0.89

* - statistically significant results, p<0.05

Table 4

Results of COS protocol in patients with infertility comorbid with uterine leiomyoma and chronic endometritis receiving different treatment protocols, Mean ±SD

	Group one (n=42), standard therapy	Group two (n=58), modified therapy	Control group (n=30), male factor infertility
Endometrial thickness on the trigger day, mm	11.78 ± 1.73*	10.20 ± 1.92	9.61 ± 1.23
Follicles, N sized ≥18 mm	12.15 ± 1.22*	13.55 ± 0.93*	15.75 ± 1.56
Retrieved oocytes, N	10.62 ± 2.45*	11.25 ± 2.91	12.05 ± 2.10
MII oocytes, N	9.11 ± 1.05*	9.90 ± 1.23*	10.95 ± 1.62
2PN fertilized oocytes, N	7.51 ± 0.96*	8.50 ± 1.01*	9.67 ± 2.13
Blastocysts, N	3.32 ± 1.02*	4.25 ± 0.63	4.05 ± 1.93

* - statistically significant results, p<0.05

Table 5

Pregnancy outcomes in patients with infertility comorbid with uterine leiomyoma and chronic endometritis and receiving different treatment schemes, n (%)

	Group one (n=42), standard therapy		Group two (n=58), modified therapy		Control group (n=30), male factor infertility	
Pregnancy outcomes	18	42.86 %	29	50.00 %	16	53.33 %
Biochemical pregnancy	3	7.14 %	2	3.45 %	2	6.67 %
Ectopic pregnancy	1	4.26 %	0	0 %	0	0 %
Clinical pregnancy	14	33.33 %	27	46.55 %	14	46.67 %
Spontaneous abortion	3	7.14 %	3	5.17 %	2	6.67 %
Preterm birth	2	4.76 %	2	3.45 %	1	3.33 %
Full term birth	9	21.43 %	20	34.48 %	11	36.67 %

* - statistically significant results, p<0.05

ified treatment group were significantly higher compared to the standard treatment group. In the modified treatment group, clinical pregnancy rate was 13.22% higher (p<0.05) and frequency of full term birth was 13.05% higher (p<0.05) compared to the traditional treatment group. The rate of spontaneous abortions was lower in the second clinical group compared to the first clinical group.

These results suggest that proposed optimized treatment of comorbid uterine leiomyoma and chronic endometritis has a potential to improve the effectiveness of infertility therapy.

Discussion

We studied the effectiveness of a modified treatment scheme for chronic endometritis in infertile patients with uterine leiomyoma, and the impact of this treatment on clinical outcomes of IVF protocols. The analysis of clinical and anamnestic characteristics of these patients shows that surgical interventions and urogenital infections are important risk factors for the development of chronic endometritis. What is more, Cicinelli et al. showed that CE is a common disease in women with repeated implantation failure, and appropriate antibiotic therapy has significantly increased the rate of successful pregnancy in women without signs of CE compared to women who had this pathology [3]. Since chronic endometritis leads to repeated implantation failures, the screening for immunohistochemical marker CD138 is recommended for such patients. A study by Lie Li et al. showed that in patients with chronic endometritis and implantation failure, antibiotic therapy and PRP therapy of endometrium can improve the success of reproductive outcomes after IVF programs [15]. Oral antibiotics are a conventional treatment for CE. However, many patients do not respond well to widely used antibiotics such as doxycycline, ciprofloxacin, and metronidazole [16], prompting the search for new and alternative treatment methods. Vitagliano et al. report that patients with chronic endometritis treated with antibiotic therapy had better pregnancy and implantation rates [17]. In our study, the same trend was found in the mod-

ified treatment group, where the incidence of clinical pregnancy and term delivery was higher, and the number of spontaneous abortions was lower compared to the group of patients which received traditional therapy. Recent studies have shown that endometrial PRP therapy can be used as an effective treatment for CE [18]. In a case report by Li F et al., 5 infertile women with CE achieved histological endometrial recovery and 100% positive serum β-hCG using intrauterine infusion of 0.5-0.8 mL of PRP every 2 days for 3 cycles [19]. Autologous intrauterine PRP therapy in patients with chronic endometritis can improve the response to treatment and increase the success rate [18], the findings which are corroborated by the results of our study. We assessed the response to ovarian stimulation using a number of indicators, such as the number of follicles and retrieved oocytes. Higher such rates were recorded in the group receiving modified treatment, as the patients received antibiotic therapy in combination with intrauterine procedures: intrauterine filgrastim infusion and PRP-therapy of the endometrium. Hosseini et al. described the effect of PRP on the development of primordial and antral follicles in vitro [20]. This folliculogenesis stimulator also produces a number of growth factors that stimulate growth and regeneration. So, the use of this therapy is a justified component in the complex treatment of chronic endometritis of infertile women.

Taken together, an appropriate anti-inflammatory and antibiotic therapy, as well as comprehensive preparation of the uterine cavity for embryo transfer, which includes diagnostic and, if necessary, surgical hysteroscopy, endometrial PRP therapy, and endometrial thickness monitoring, are key factors in the success of in vitro fertilization protocols. The clinical outcomes demonstrated in this study include the frequency of clinical pregnancy and frequency of childbirth in women with infertility comorbid with uterine leiomyoma and chronic endometritis who were treated according to the modified protocol.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Bioethics Committee of Ternopil National Medical University, protocol No 68 of 12 April 2022.

Informed Consent Statement: Written informed consent has been obtained from the patients to publish this paper.

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