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Antibiotics and Uterine Flushing versus Antibiotics Alone for Chronic Endometritis with Thin Endometrium in Assisted Reproductive Technology: A Single-Center Retrospective Cohort Study

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Abstract

Background: This study aimed to investigate whether uterine cavity flushing combined with antibiotic administration, improves the outcomes of assisted reproductive technology for patients with thin endometrium (<7 mm) associated with chronic endometritis.

Materials and Methods: A retrospective cohort study was conducted, including 202 patients. Subsequently, a single frozen-thawed embryo of high morphological quality (≥4AB) was transferred either in an artificial cycle or on day 7 after the luteinizing hormone (LH) peak in the natural cycle. The parameters measured included the number of CD138-positive plasma cells in the endometrial stroma, endometrial thickness on the day of embryo transfer, clinical pregnancy rate (CPR), and live birth rate (LBR).

Results: Following treatment with endometrial flushing and antibiotics (group 1), there was a significant increase in endometrial thickness compared to antibiotics alone (group 2): 9.93 ± 1.37 mm vs. 8.2 ± 0.4 mm (P<0.001). Additionally, there was a significant reduction in the number of CD138-positive plasma cells in the endometrial stroma: 0.4 ± 0.8 vs. 4.1 ± 5.2 (P<0.001). The CPR with high-quality ET was 68.6 vs. 48%, respectively (P=0.016). The take-home baby rate was 60.8 vs. 39%, respectively (P=0.002).

Conclusion: Therapy for chronic endometritis, which includes uterine flushing along with antibacterial treatment, when compared with the standard treatment method, resulted in a significant reduction in the clinical symptoms of chronic endometritis (CE) and can enhance the effectiveness of assisted reproductive technology treatments.

Keywords: Endometritis, Infertility, Live Birth, Pregnancy Rate, Treatment Outcome

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Introduction

Infertility is a significant medical and social issue. Evidence-based infertility treatment is a crucial element of sexual and reproductive healthcare (1).

Infertility carries profound social and health consequences, including social stigmatization, economic hardships, and mental health problems. As defined by the World Health Organization (WHO), infertility is a disorder of the male or female reproductive system, characterized by the absence of pregnancy after 12 months of regular unprotected sexual intercourse (1). Infertility is estimated to affect about 17.5% of the adult population, a substantial portion of the global population, with approximately 1 in 6 people experiencing infertility in their lifetime, underscoring the urgent need to improve access to affordable, high-quality infertility services for those in need (2). In the male reproductive system, infertility is most commonly caused by issues with sperm ejection, low sperm count, abnormal sperm morphology, and impaired sperm motility. In the female reproductive system, infertility can result from various abnormalities of the ovaries,

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uterus, fallopian tubes, and endocrine system. The overall prevalence of primary infertility is 9.6%, and the estimated overall prevalence of secondary infertility is 6.5% (2). In Kazakhstan, around 15-17% of married couples suffer from infertility, with female infertility comprising 50-60% of cases. There are 26,000 women diagnosed with infertility listed on the dispensary register (3).

The uterine factor plays a crucial role in the genesis of failures in *in vitro* fertilization (IVF) programs. In recent years, there has been growing interest in chronic endometritis, especially due to its suspected role in infertility, pregnancy failure, and repeated IVF failures (4-7).

Insufficient endometrial function, indicated by the presence of a thin endometrium on ultrasound examination, is one of the primary reasons for declining fertility and unsuccessful attempts at assisted reproductive technology (ART). This may result of past inflammatory diseases of the pelvic organs, postpartum endometritis, septic abortion, fibroids, or medical manipulations and operations that lead to injury of the basal layer of the endometrium (8). The chronic inflammatory process in the endometrium may hinder endometrial receptivity, thereby causing infertility (9, 10). The definition and threshold for a thin endometrium may vary among studies. However, it is commonly accepted that an endometrial thickness of less than 7 mm could be detrimental to achieving pregnancy (11). Chronic endometritis (CE) is a condition associated with a disruption in the harmonious coexistence of microorganisms and the immune system in the endometrium. Changes in the endometrial microenvironment affect its sensitivity to receptors, which can impede normal implantation (9, 12).

The research in the relationship between CE and infertility has recently become a focus of ongoing investigation. The incidence of CE ranges widely from 2.8% to approximately 86.5%, as reported by various studies (7, 9, 12-17). This variability in incidence highlights the differing rates at which CE is diagnosed across different patient cohorts and clinical settings. CE occurs in 22% of patients in IVF programs, 14% of those with unexplained infertility, and 23.6% of women with first-trimester miscarriages (9, 18). The incidence of infertility in women diagnosed with CE is 60% (22.1% primary, 36.5% secondary), and 80% of women with CE have a history of repeated failed attempts at assisted reproductive technology (5, 19, 20). According to numerous studies, CE is the primary verified cause of pregnancy failure in 47.4-52.1% of cases (21-24).

Despite many successes and achievements, reproductive medicine overlooked the endometrial factor for a long time. Until 2010, most research focused exclusively on the quality of the embryo. Currently, numerous recent studies explore various approaches to the treatment of CE (5, 25-31). These circumstances necessitate the development and scientific substantiation of methods for treating CE. One of the innovative approaches is ultrasound low-frequency intrauterine flushing. When low-frequency ultrasound passes through a liquid, it induces several physical effects (cavitation, bubbling, thermal changes, and phonophoresis) and biological effects (bactericidal, anti-inflammatory properties, improved microcirculation, tissue regeneration, and micro-massage) in the endometrial tissue (32).

Materials and Methods

A retrospective cohort study was conducted to evaluate whether uterine cavity flushing combined with antibiotic administration enhances the effectiveness of assisted reproductive technology in patients with thin endometrium (<7 mm) associated with chronic endometritis. This study included 202 patients with thin endometrium and CE who received treatment at the PERSONA International Clinical Center for Reproductive Health from January 2020 to December 2022. We declare that our retrospective study was approved by the Ethical Committee of PERSONA International Clinical Center for Reproductive Health (KZ.PERSONA-04-09-955/18-2). All women provided informed consent for the anonymous use of their data for research purposes. Before programmed embryo transfer (ET) cycles, women were treated, based on physician preference, with antibiotic therapy in combination with uterine cavity flushing or antibiotic therapy alone. A total of 102 patients received combined treatment, and 100 were given antibiotics only (designated as group 1 and group 2, respectively) (Fig.1).

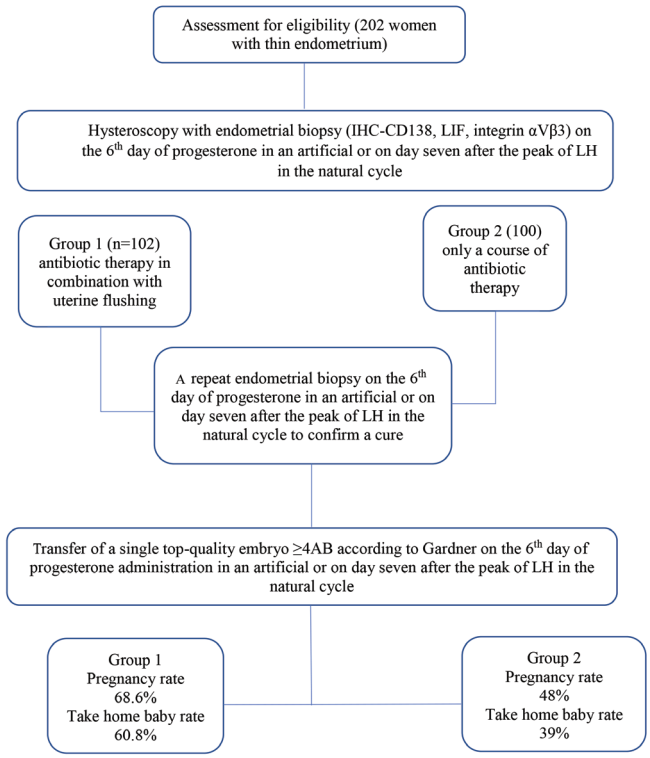


Fig.1: Flowchart of the study chronic endometritis. IHC; Immunohistochemical stain, LIF; Leukemia inhibitory factor, and LH; Lutenizing hormone.

Inclusion criteria: Women aged less than 38 years or those using donor oocytes, a history of failed IVF attempts, presence of CE confirmed by immunohistochemical staining of $CD138^{+}$ endometrial samples (showing the presence of ≥1 plasma cell per 10 high-power field), normal karyotype, negative antiphospholipid antibody

test, uterine cavity without pathology as evaluated by hysteroscopy, single ET of high quality (≥4AB) according to Gardner et al. (33), ET into the uterine cavity was performed after CE treatment, patients who planned ET within the next 6 months.

Exclusion criteria: Women over 38 years old with their own oocytes, surrogacy, severe male factor infertility, transfer of more than 1 embryo, embryo quality below 4AB according to Gardner et al. (33), abnormal karyotype, positive test for antiphospholipid antibodies, presence of uterine cavity pathology (such as endometriosis, myomas, synechiae, polyps, tumors) as confirmed by hysteroscopy, women not planning pregnancy in the next cycle after endometrial biopsy and CE treatment.

All included patients underwent diagnostic office hysteroscopy (OH) and endometrial biopsy sampling for histologic and immunohistochemical analysis for $CD138^{+}$, leukemia inhibitory factor (LIF), Integrin alpha-V/beta-3 (CD61) during the proliferative phase of the menstrual cycle on the 7th day after luteinizing hormone (LH) peak or the 6th day of progesterone administration in hormone replacement therapy cycles.

The cycle for preparation for diagnostic hysteroscopy with endometrial biopsy was initiated in the early follicular phase of the cycle on the 2nd day from the beginning of the menstrual cycle, with monitoring of estradiol and progesterone hormone levels. Hormone levels were controlled to exclude early follicular growth and ensure sufficient regression of the luteal body. Recommended hormone levels on the 2nd day of the cycle included estradiol ranging from 10 to 60 ng/L and progesterone levels ranging from 0.1 to 2.4 nmol/L. The recommended endometrial thickness on the 2nd day of the menstrual cycle was no more than 4 mm. When these conditions were met, endometrial monitoring was initiated. In the natural cycle, ovulation was monitored by ultrasound examination every 2-4 days. When the diameter of the dominant follicle reached ≥17 mm and the level of LH and estradiol, with a level not less than 200 ng/L, indicated ovulation, it was considered a confirmed fact of ovulation. In an artificial cycle, from the day of the tests or the following day, estradiol, sufficient to suppress follicular growth and support endometrial secretion, was administered (typically 2 to 8 mg per day). Ultrasound examination of the pelvic organs using transvaginal scanning, with a frequency of 4-9 MHz, was performed on a SonoScape apparatus every 2-4 days to monitor endometrial thickness and structure. The endometrial structure, echogenicity, presence or absence of inclusions, hypo/hyperechogenic areas, intrauterine synechiae, thickness, and echo-structure of the endometrium were studied by evaluating M-echo.

Hysteroscopic examination

OH was performed during the proliferative phase of the menstrual cycle on the 7th day after the peak LH+ or on the 6th day of progesterone medication in the artificial cycles. It used a 2.9-mm rigid hysteroscope with a 30° field of view (Karl Storz, Tuttlingen, Germany), and a single-flow diagnostic tube with an outer diameter of 3.2 mm. The procedure used a 300 W xenon light source, a digital camera, a 21-inch video camera, and a color screen. The uterine cavity was dilated with saline solution at a pressure of 100 mmHg. An endometrial biopsy specimen was taken using biopsy forceps (Karl Storz, Tuttlingen, Germany) from the upper uterine cavity. The entire wall of the uterine cavity and the condition of the endometrial mucosa were carefully assessed visually. Any irregularities of the endometrial surface were readily identified. All hysteroscopy procedures were performed by two authors, and images were digitally recorded.

Histologic examination of endometrial specimens

Endometrial samples were fixed in neutral buffered 10% formalin and were further processed with alcohol and xylene solutions. They were then embedded in paraffin for histologic analysis. Thin sections of no more than 5 μm were made on a microtome and stained with eosin and hematoxylin to prepare histologic slides. A single consultant histopathologist examined all endometrial biopsy specimens. Criteria for histologic diagnosis of CE included the following features: superficial stromal edema, increased stromal density, pleomorphic stromal inflammatory infiltrate with a predominance of lymphocytes and plasma cells, blood supply and microcirculation disorders, and atrophic changes in the studied endometrial samples.

Immunohistochemical study

Endometrial tissue for immunohistochemical study was collected on either the 6th day after progesterone administration in artificial cycles or on the 7th day of the menstrual cycle after LH+ peak. The state of endometrial receptivity during the "window of implantation" was examined. The immunohistochemical study was performed using mono and polyclonal antibodies (Ventana Medical Systems, Inc. USA) based on the peroxidase method on paraffin sections that were 3 μm thick, following the standard protocol. Reaction manifestations were evaluated using the Ultraview universal dab detection kit + System visualization system (Ventana Medical Systems, Inc. USA). For the examination of $CD138^{+}$ expression, paraffin sections were stained using rabbit monoclonal antibodies (USA) and for the assessment of LIF levels, polyclonal antibodies (UK) were used. If the desired receptor was present in the endometrial cells, antibodies bound to it, and fluorescence could be observed when viewing the glass under a special microscope, indicating a positive test result. $CD138^{+}$ expression (monoclonal rabbit antibody, USA) was evaluated in 10 fields of view at 400× magnification by counting immunopositive cells. CE was diagnosed if there were more than 1 CD138-positive plasma cell per 10 HPF in a section. The expression of the LIF signaling molecule (polyclonal, UK) was determined according to the standard protocol on the membranes of cells of the surface epithelium of endometrial glands by counting the number of stained cells in 10 fields of view at a magnification of 400. Integrin αVβ3 expression was determined

using mouse monoclonal antibodies to integrin αVβ3 (ab7166, UK) as described by Creus et al. (34), using a semi-quantitative counting scale (1-4).

Treatment of chronic endometritis

The treatment of CE was conducted in two stages. The first stage aimed at eradicating the pathogenic agent. It included a course of fluoroquinolones (Zentiva, Czech Republic) for 10 ± 4.5 days at a dose of 800 mg per day, along with ultrasound flushing of the uterine cavity with chlorhexidine for 5 days. The ultrasound flushing of the uterine cavity was performed using the Fotek AK 101 apparatus, flushing the uterine cavity for 5 minutes (characteristics of uterine flushing apparatus are reported in Supplemental file, See Supplementary Online Information at www.ijfs.ir). Low-frequency ultrasound flushing of the uterine cavity was carried out in the first phase of the cycle, starting from the 5th day of the menstrual cycle. This involved multiple sessions lasting 5 minutes, with an exposure power of 25 kHz and a flow rate of the drug at 100-150 ml/minutes. Chlorhexidine was the used medium. Treatment was designed for 2 cycles. If there were positive signs of CE depending on immunohistochemistry, the treatment was continued for 2 cycles, and patients received one additional cycle if needed. After the treatment, all patients underwent a repeat endometrial biopsy on the 6th day after progesterone administration in an artificial cycle or on the 7th day after the LH peak in the natural cycle to confirm possible recovery, defined as the presence of ≥1 residual plasma cell.

Repeat endometrial biopsy and immunohistochemical study

All patients who underwent post-treatment had a repeat endometrial biopsy during the secretory phase of the menstrual cycle on the 7th day after LH peak or the 6th day of progesterone administration, using a Pipelle de Cornier biopsy catheter. We contacted the women by telephone and inquired about the outcomes of their results after ET.

Characteristics of the assisted reproductive technology program

Ovarian stimulation was performed using a long protocol of gonadotropin-releasing hormone (GnRH) agonist, a short protocol of GnRH agonist, or a GnRH antagonist protocol. The initial FSH dose was determined according to the patient's age and ovarian reserve, predicted by the anti-Mullerian hormone level and basal follicle count. For the final maturation of oocytes, human chorionic gonadotropin (hCG) in 10,000 IU (Chorapur 5,000 IU, Ferring Pharmaceuticals, Germany) was administered when the leading follicle reached a diameter greater than 18-21 mm, as measured by transvaginal ultrasonography. Ovum retrieval took place 36 hours after the hCG injection. The choice of protocols was based on the physician's preference. A single frozen-thawed embryo of high morphological quality, as per Gardner criteria (≥4AB), was transferred on day 6 of progesterone administration (vaginal micronized progesterone, 200 mg) in an artificial cycle or on day 7 after the LH peak in the natural cycle after the treatment. The luteal phase was supported with vaginal progesterone.

Statistical analysis

The data obtained in the study were subjected to statistical analysis using variation statistics with the free version of the JamoviTM program and "Microsoft Excel" (2016). The quantitative indicators were summarized using the arithmetic mean and standard deviation (mean ± SD). The data were presented as mean ± SD. Independent t test used to determine the significance of the difference between the means. Qualitative variables were described using absolute (n) and relative (%) values. Chi-square test was used to compare the clinical pregnancy rate (CPR) and the live birth rate (LBR). The critical level of significance (p) was set at 0.05 for testing statistical hypotheses.

Results

A total of 202 women with CE and thin endometrium were included in the study. Demographic and clinical characteristics were compared between the groups (Table 1). The mean age in the main group was 37.1 ± 5.48 years, and in group 2, it was 37.6 ± 5.35 years. The duration of infertility ranged from 1 to 20 years: in the main group, the mean duration was 6.11 ± 3.87 years, and in the control group, it was 6.83 ± 4.4 years. The number of miscarriages, abortions, and repeated implantation failures did not differ significantly between the two groups. When analyzing the structure of infertility, the frequency of primary infertility in the main group was 45%, while in the control group, it was 47.1%, and secondary infertility occurred with approximately equal frequency in both groups (Table 1).

Table 1: Clinical characteristics of women with chronic endometritis and thin endometrium

Categories	Group 1	Group 2	P value
Age (Y)	37.16 ± 5.48	37.63 ± 5.35	0.697
Infertility duration (Y)	6.11 ± 3.87	6.83 ± 4.4	0.224
AMH (ng/mL)	2.038 ± 1.87	1.88 ± 2.01	0.164
BMI (kg/m^2)	23.47 ± 3.93	23.57 ± 3.69	0.452
Primary infertility	45	47.1	0.769
Secondary infertility	55	52.5	0.770
Previous IVF attempts	3.8 ± 0.835	3.6 ± 0.744	0.352
Miscarriage	15.6	14	0.738
Abortion	12.7	15	0.645
Ectopic pregnancy	17.6	22	0.440

Continuous data are presented as mean ± standard deviation (SD), and categorical data are presented as number (%). Independent t test was used. The limit of significance is a P≤0.05. AMH; Anti-mullerian hormone, BMI; Body mass index, and IVF; *In vitro* fertilization.

After treatment of chronic endometritis, the results of ultrasound examination of endometrial thickness during the " window of implantation," on the 6th day of proges-

terone preparations in HRT cycles or on the 7th day after ovulation, showed a significant increase (Table 2).

Table 2: Comparison of CD138-positive cells, leukemia inhibitory factor (LIF), integrin αVβ3 expression and endometrial thickness before and after treatment in two groups

Categories	Group 1	Group 2	P value
$CD138^+$ before treatment	13.1 ± 9.5	13.4 ± 7.2	0.788
$CD138^+$ after treatment	0.4 ± 0.8	4.1 ± 5.2	<0.001
Endometrial thickness before treatment	6.5 ± 0.611	6.5 ± 0.626	0.848
Endometrial thickness after treatment	9.93 ± 1.37	8.2 ± 0.4	<0.001
LIF before treatment	3.59 ± 1.53	3.33 ± 1.78	0.371
LIF after treatment	8.05 ± 1.172	5.76 ± 1.83	<0.001
Integrin αVβ3 before treatment	1.17 ± 0.55	0.96 ± 0.79	0.720
Integrin αVβ3 after treatment	3.63 ± 0.52	2.4 ± 0.91	<0.001

Data are expressed as means ± SD unless stated otherwise. Independent t test was used. The limit of significance is a P≤0.05.

The expression level of $CD138^+$ cells before treatment was not statistically different between the groups (13.1 ± 9.5 and 13.4 ± 7.2, respectively, P=0.788). The $CD138^+$ negative result after treatment was significantly higher in group 1 than in group 2 (Table 2). In the standard therapy group with antibiotics, the indices of inflammatory markers decreased by threefold; nevertheless, these indices had negative effects on implantation and pregnancy outcomes. The data from the immunohistochemical study of the expression of signaling molecules before and after treatment showed a direct relationship between inflammatory endometrial disorders and dysfunction of the receptor apparatus. This study proved a significant decrease in implantation factors-LIF and cell adhesion molecule-αVβ3 integrin in women with chronic endometritis. In patients in the complex treatment group with ultrasound flushing of the uterine cavity after treatment, the expression level of LIF increased significantly compared with the control group. The expression rates of αVβ3 integrin before treatment did not differ between the study groups. Expression rates in the main group after treatment were maximal compared with the control group.

The obtained results of the immunohistochemical study of implantation factors, after complex treatment with ultrasound flushing of the uterine cavity, prove the restoration of the expression of implantation signaling molecules in patients with CE and failed ART programs. In women with infertility and chronic endometritis, the basis of endometrial receptivity impairment is inflammation, which is expressed as the formation of foci of fibrosis, an increased marker of the immune inflammatory response, and decreased expression of signaling cells during the presumed "window of implantation" In the context of assisted reproductive technology programs, the endometrial receptor status is extremely important. The state of the endometrial receptivity contributes to the choice of stimulation regimen and may also indicate a lack of hormone receptivity, affecting the outcome of treatment.

Treatment efficacy was evaluated after the transfer of a single thawed embryo of high morphologic quality according to Gardner ≥4AB, by the frequency of clinical pregnancy and their outcomes. The rate of clinical pregnancy per transfer was significantly higher in group 1 compared to group 2 (68.6 vs. 48%, P=0.016.) Correspondingly, the LBR was significantly higher in the main group (60.8 vs. 39%, P=0.002, Fig.2).

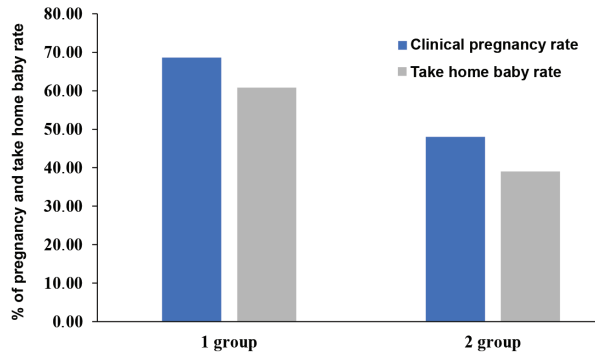


Fig.2: The clinical pregnancy and "take-home baby rate" achieved in the first *in vitro* fertilization (IVF) cycle within 6 months after treatment in women previously diagnosed with chronic endometritis. Chi-square test was used. The limit of significance is a P≤0.05.

During the study, there were no adverse reactions to treatment with ultrasound cavity flushing and no complications associated with hysteroscopy, including significant bleeding, infection, or fluid absorption.As a result of the study, it was proved that complex treatment of CE using ultrasound flushing of the uterine cavity is more than 50% effective compared to standard therapy. In addition to a decrease in $CD138^+$, there was an improvement in the endometrial blood supply and implantation markers (LIF, cell adhesion molecule - integrin), indicating the restoration of endometrial receptivity, thus improving the implantation potential and increasing the chances of pregnancy and bearing a pregnancy.

Discussion

In this study, we demonstrated, for the first time, that combined treatment involving uterine flushing and antibiotic administration, as described, improved CE as confirmed by repeated biopsy. This treatment resulted in a reduced number of CD138-positive plasma cells and subsequently led to increased endometrial thickness and improved pregnancy rates following frozen-thawed embryo transfer. The combination of antibiotic administration and low-frequency ultrasound generated with the FOTEK uterine flushing device may contribute to the successful prevention and treatment of inflammatory diseases of female genital organs of various etiologies and localizations.

One common cause of reproductive failure after ART programs is the endometrial factor (9, 10). Patients with a thin endometrium pose a significant challenge for re-

productive specialists. A thin endometrium is typically defined as less than 7 mm on ultrasound and often results in canceled embryo transfers (11, 35, 36). The causes of a thin endometrium can include previous trauma to the endometrium from procedures like curettage, cesarean section, or chronic endometritis. After excluding other uterine pathologies, treating a thin endometrium remains a significant challenge and is often empirical. CE is known to have adverse effects on fertility and IVF outcomes. Frequent changes in antibiotics do not necessarily yield the desired results in improving infertility due to CE. Previous studies have demonstrated that CE patients treated with antibiotics often require multiple courses before complete recovery. For example, Cicinelli et al. (5) reported that, despite antibiotic treatment, CE persisted in 25% of patients after three serial courses. Vitagliano et al. (23) conducted a systematic review and meta-analysis, concluding that patients with cured CE had significantly higher ongoing pregnancy rates/LBR (OPR/LBR), CPR, and implantation rates (IR) compared to patients with persistent CE. However, the IVF outcome was comparable between women with cured CE and those without CE. On the other hand, Johnston-MacAnanny et al. (37) found that the CE group had better pregnancy rates after antibiotic therapy, but still had lower pregnancy rates compared to the non-CE group.

A particular strength of our study was investigating a combined therapy approach (antibiotics with uterine flushing), which may offer a novel method to improve endometrial receptivity and potentially enhance ART success rates. Additionally, it contributes to the existing literature by generating data on the comparative effectiveness of antibiotics alone versus combined therapy, thereby filling a gap in understanding optimal treatment strategies for patients with CE and thin endometrium in assisted reproduction.

However, there were several limitations in our study. Firstly, its small cohort from a single center restricts the generalizability of findings. The retrospective study design introduces the possibility that differences in patient populations could contribute to some observed variance, despite the cohort being selected based on the receipt of endometrial biopsies rather than prospective clinical diagnoses, representing a constraint in our study.

Acknowledging that the main effect of endometrial flushing with the Fotek device a mechanical stimulation of the endometrium, promoting local blood circulation and potentially enhancing endometrial receptivity, the lack of comparative devices for assessing the mechanical effects of flushing further underscore the uniqueness and potential limitations of our study. While our research offers valuable insights into the impact of the Fotek device, the absence of comparative data restricts broader conclusions regarding its mechanical effects compared to other devices.

The use of uterine flushing in obstetric and gynecological practice deserves special attention as a simple, potentially efficient, and cost-effective method with reduced complications and relapses. Reproductive specialists are increasingly interested in uterine flushing as a potential treatment for CE. It is considered a straightforward approach that may shorten treatment duration, reduce complications, and minimize relapses.

Prospective controlled clinical trials are needed to evaluate the impact of uterine flushing, possibly in combination with antibiotics, on IVF outcomes and the improvement of LBR in patients with CE-associated thin endometrium.

Conclusion

Our study demonstrates that the therapy for CE, as described, which includes uterine flushing in combination with antibacterial therapy, significantly reduces the clinical symptoms of CE and can enhance the effectiveness of ART programs. The treated group showed a substantial increase in endometrial thickness, improvement in histological findings, restoration of endometrial cytoarchitecture, reduction in CD138-positive plasma cells, and synchronized gland maturation. This combined treatment holds promise for improving implantation potential and increasing the likelihood of successful pregnancy and childbirth.

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Authors' Contributions

V.L.; Was responsible for designing the experiment, Evaluating the results, and Writing the manuscript. Y.A., R.V.; Participated in patient follow-up, Performing hysteroscopy, Contributed to the manuscript, and Writing the manuscript. A.R.; Participated in data analysis and Manuscript writing. A.A.; Participated in the histologic evaluation of the samples and Writing of the manuscript. Sh.K.; Participated in patient follow-up and Evaluation of the results. A.S.; Contributed to result evaluation and Manuscript writing. All authors read and approved the final manuscript.

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