

Original Article

Influence of doxycycline hyclate plus dexamethasone on clinical effectiveness, inflammatory cytokines and pregnancy outcomes in patients with chronic endometritis

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Abstract: Aim: To explore the influence of doxycycline hyclate (DOXY-h) combined with dexamethasone (DEX) on clinical effectiveness, inflammatory cytokines (ICKs) and pregnancy outcomes in patients with chronic endometritis (CE). Methods: CE patients admitted to Dongguan Hospital, Guangzhou University of Chinese Medicine between May 2024 and March 2025 were selected, with 40 cases receiving oral DOXY-h and 44 cases given oral DOXY-h plus intrauterine DEX injection being assigned to monotherapy group and combined group, respectively. The two groups were comparatively analyzed in terms of clinical effectiveness, occurrence of adverse reactions throughout treatment and pregnancy, symptom remission time, and abortion and recurrence during the one-year follow-up. Endometrial thickness (ET), flow index (FI) and resistance index (RI) were measured by color Doppler ultrasound, serum levels of interleukin (IL)-6, IL-17 and tumor necrosis factor (TNF)- α were quantified using enzyme-linked immunosorbent assay, and serum malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione (GSH) were detected with an automatic chemiluminescence immunoassay analyzer. Sexual quality of life (SQoL) evaluation was made with the Female Sexual Function Index (FSFI). Results: The combined group had significantly higher total effective rate, pregnancy rate and FSFI scores than the monotherapy group, along with a marked reduction in symptom remission time. Patients in both groups experienced no serious adverse reactions, with a similar occurrence of adverse reactions. Compared with the monotherapy group, the combined group had higher ET and FI and lower RI. In addition, the combined group showed significantly lower post-treatment levels of IL-6, IL-17, TNF- α , and MDA, as well as significantly higher levels of SOD and GSH. Conclusions: DOXY-h plus DEX is effective in treating CE, which can effectively relieve symptoms, suppress inflammation and oxidative stress, and improve the endometrial environment, thereby increasing pregnancy rates, with clinical promotion value.

Keywords: Doxycycline hyclate, dexamethasone, chronic endometritis, infertility, inflammatory response

Introduction

Chronic endometritis (CE) is a persistent inflammatory state of the endometrium characterized by endometrial edema, increased stromal cell density, plasma cell infiltration, vascularization, and contractility changes [1]. The main cause of CE is considered to be intrauterine infection of common microorganisms in the genitourinary region, such as common bacteria (*Streptococcus*, *Staphylococcus*, *Escherichia coli* and *Enterococcus faecalis*), *Mycobacterium tuberculosis*, *Mycoplasma* and *Ureaplasma* species [2]. Unlike acute endometritis, which presents with pronounced clinical manifestations, includ-

ing general fever, pelvic pain and increased vaginal discharge, CE is often asymptomatic or only minimally symptomatic and is therefore often overlooked by patients and experienced gynecologists [3]. However, delayed and ineffective treatment can lead to a range of complications such as myometritis, uterine abscess and cervical obstruction. In addition, CE is associated with infertility, recurrent abortion and recurrent implantation failure [4].

Currently, the main drugs used in clinical treatment of CE are antibiotics. Long-term oral administration of antibiotics can achieve the purpose of CE treatment, but drug resistance

easily occurs in the later period of drug use, resulting in unsatisfactory efficacy [5]. Doxycycline hyclate (DOXY-h) is a water-soluble tetracycline antibiotic used for the treatment of infections caused by bacteria, rickettsia, mycoplasma and chlamydia. Recent studies have shown that doxycycline is highly effective in CE patients with recurrent implantation failure (RIF), the use of which can significantly improve the live birth rate during embryo transfer in such patients [6]. Intrauterine administration is considered an effective treatment for intrauterine disorders due to its rapid onset of action and high concentration of topical drugs. Antibiotic therapy in combination with platelet-rich plasma has been found to improve pregnancy outcomes in these patients, but platelet-rich plasma is a blood product that carries a higher risk of infection [7]. Dexamethasone (DEX) is a common glucocorticoid with good anti-inflammatory effects, as well as antiviral, anti-allergic and immunosuppressive activities. Oral antibiotics (doxycycline and metronidazole) combined with intrauterine injection (gentamicin and DEX), as a novel treatment for women with RIF and CE, has been shown to significantly improve clinical pregnancy outcomes, contributing to higher rates of implantation, clinical pregnancy and live births, compared with oral antibiotics alone [8]. Other evidence has shown that DEX combined with antibiotics can validly improve implantation and pregnancy rates, with an effect superior to oral antibiotics alone [9]. Therefore, the combined use of antibiotics and DEX for CE is feasible and warrants further investigation.

This study investigates the effects of DOXY-h plus DEX on clinical effectiveness, inflammatory cytokines (ICKs), and pregnancy outcomes in CE patients, aiming at finding an effective and safe treatment scheme for such patients.

Materials and methods

Study subjects

This study enrolled 84 CE patients who were treated at Dongguan Hospital, Guangzhou University of Chinese Medicine between May 2024 and March 2025. The monotherapy group (n=40) received DOXY-h tablets orally, while the combined group (n=44) was given DOXY-h plus intrauterine DEX injection. Ethical approval was obtained from the Dongguan Hospital,

Guangzhou University of Chinese Medicine Ethics Committee.

Eligibility criteria: diagnosis of CE by the presence of plasma cell infiltration on pathological examination, along with findings from hysteroscopy, diagnostic curettage, and clinical manifestations; normal uterine morphology and endometrium development after examination; patients with pregnancy needs; good mental state and cognitive function; age range: 20 to 35 years. Exclusion criteria: presence of related contraindications; intrauterine adhesions or uterine malformations; other gynecological diseases; women during lactation; severe damage or disorder of liver and kidney function; use of antibiotics one month prior to enrollment.

It should be noted that the post-hoc power analysis, assessed based on overall efficacy rates (67.50% for the monotherapy group and 86.36% for the combined group, $\alpha=0.05$), yielded a post-hoc power of about 61% for the existing sample size (n=40 vs. 44), which was lower than the 80% criterion. This suggests a possible risk of type II errors in this study, with some negative results possibly attributed to insufficient power of the test.

Treatment

One week before the start of treatment, all drugs related to CE treatment were discontinued. Treatment was initiated 3 to 7 days after the cessation of menstruation in all patients. Patients in the monotherapy group (n=40) received DOXY-h tablets (Jiangsu Lianhuan Pharmaceutical Co., Ltd., SFDA Approval No. H32021266, Specification: 0.1 g/tablet), 200 mg/time, once daily for 14 days. In addition to the same oral regimen, the combined group (n=44) received intrauterine injections of DEX Sodium Phosphate Injection (Guangzhou Baiyunshan Tianxin Pharmaceutical Co., Ltd., National Drug Approval Number: H44022090, 1 mL:5 mg): 5 mg of DEX Sodium Phosphate Injection was dissolved in 4 mL of 0.9% saline solution and injected transcervically and slowly into the uterine cavity with a single-use sterile hose, with the solution retained in the uterine cavity for 15 minutes per session. The injection was performed once every other day for 14 days, totaling 7 treatments. The intrauterine injection protocol was based on a previously published study [8], in which intrauterine DEX

administration has been reported to improve endometrial receptivity and pregnancy outcomes. Meanwhile, adverse reactions were closely observed and recorded during the treatment.

Outcome measures

Clinical effectiveness: A cure was defined as complete remission of clinical manifestations and signs, normal menstrual cycle and volume, and normal vaginal secretion examination and vaginal secretion culture results; significant effectiveness was defined as near-resolution of clinical symptoms, obviously reduced vaginal discharge with no peculiar smell, near-normalization of menstrual cycle, and normal endometrium and vaginal discharge culture; ineffectiveness was defined as the absence of clinical manifestations and signs, no improvement in menstrual period and menstrual flow, profuse, malodorous discharge on endometrial hysteroscopy, and positive vaginal discharge culture. Total effective rate = (clinical cure + significant effectiveness) cases/total cases × 100%.

The adverse reactions of the two groups during treatment, as well as clinical outcomes, were recorded. After treatment, the patients were followed up for one year to record their occurrences of adverse reactions (e.g., nausea and vomiting, abdominal pain and diarrhea, dizziness and headache) and clinical outcomes (pregnancy, abortion, and recurrence rates).

Symptom remission time was also compared between the two cohorts, including relief of lower abdominal pain, lower abdominal distension with heaviness, menostaxis, and menorrhagia.

Endometrial indexes: Color Doppler ultrasound was used to detect pre- and post-treatment endometrial thickness (ET), flow index (FI) and resistance index (RI) in the two groups.

Menstrual blood samples were collected from both groups before and after treatment to determine interleukin (IL)-6, IL-17 and tumor necrosis factor (TNF)- α levels by enzyme-linked immunosorbent assays. All test kits were provided by Shanghai Enzyme-linked Biotech, and the assays were performed according to the manufacturer's instructions.

Levels of malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione (GSH) were measured before and after treatment. The assays were based on a colorimetric method, and the absorbance was read using an automatic chemiluminescence immunoassay analyzer. The detection steps followed the corresponding kit's instructions (Shanghai Bangjing Industrial Co., Ltd., ECS031827; Shanghai Jizhi Biochemical Technology Co., Ltd., BC0170-50 tube/24 samples; Shanghai C-reagent Biotechnology Co., Ltd., CS-H96959). The intra-batch and inter-batch coefficients of variation (CV) of each index were under 5% and 10%, respectively. The reference range of serum MDA, SOD, and GSH was based on the standard curve attached to each kit instruction and the calibration value of quality controls.

Sexual quality of life (SQoL) was evaluated using the Female Sexual Function Index (FSFI) [10], which assesses six domains: desire, arousal, lubrication, orgasm, satisfaction, and pain. The scale consists of 19 items scored using a Likert scoring system. The desire dimension (items 1 and 2) has a score ranging from 1 to 5 points; for the satisfaction domain, the score range is 1 to 5 for items 15 and 16, and 0 to 5 for the remaining items. The domain scores were calculated by summing the item scores within each domain and multiplying by the respective domain factor (desire × 0.6, arousal × 0.3, lubrication × 0.3, orgasm × 0.4, satisfaction × 0.4, pain × 0.4). By adding up the scores of the six dimensions, the total FSFI score can be obtained, with the range being 2 to 36 points. A higher score suggests a better SQoL.

This study, due to the retrospective design, could not be blinded in the intervention implementation stage, but data collectors and statistical analysts were blinded to patient allocation.

Statistical methods

All statistical analyses were performed using GraphPad Prism 6. A *P*-value of <0.05 was considered statistically significant. Count data were expressed as *n* [%] and compared using Chi-square test. Quantitative data were expressed as mean ± standard deviation (SD) and analyzed using *t* test.

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Table 1. Comparison of baseline data

Groups	Monotherapy group (n=40)	Combined group (n=44)	χ^2/t	P
Age (years)	27.18±4.48	26.23±4.87	0.928	0.356
BMI (kg/m ²)	23.75±1.17	23.82±1.20	0.270	0.788
Mean course of disease (months)	11.58±5.79	10.91±5.85	0.527	0.599
Pregnancy history (n [%])	5 (12.50)	5 (11.36)	0.026	0.872
History of abortion (n [%])	14 (35.00)	19 (43.18)	0.588	0.443

Table 2. Comparison of clinical effectiveness (n [%])

Groups	Monotherapy group (n=40)	Combined group (n=44)	χ^2	P
Cure	17 (42.50)	23 (52.27)		
Significant effectiveness	10 (25.00)	15 (34.09)		
Ineffectiveness	13 (32.50)	6 (13.64)		
Total effective rate	27 (67.50)	38 (86.36)	4.260	0.039

Table 3. Comparison of adverse reactions (n [%])

Groups	Monotherapy group (n=40)	Combined group (n=44)	χ^2	P
Nausea and vomiting	2 (5.00)	2 (4.55)		
Abdominal pain and diarrhea	0 (0.00)	1 (2.27)		
Dizziness and headache	1 (2.50)	2 (4.55)		
Overall occurrence	3 (7.50)	5 (11.36)	0.363	0.547

Comparison of symptom remission time

Symptom remission time was significantly shorter in the combined group than in the monotherapy group for all symptoms assessed (abdominal pain, abdominal distension with heaviness, menostaxis, and menorrhagia) ($P<0.05$; **Table 4**).

Comparison of pregnancy, abortion, and recurrence rates within one year

During the one-year follow-up, the rates of pregnancy, miscarriage, and recurrence were 42.50%, 12.50%, and 10.00% in the monotherapy group, and 65.91%, 6.82%, and 11.36% in the combined group, respectively. The inter-group comparison revealed an obviously higher pregnancy rate in the combined group versus the monotherapy group ($P<0.05$; **Table 5**), while no marked difference was identified between groups in abortion rate and recurrence rate ($P>0.05$).

Results

Comparison of baseline data

No significant differences were observed between the two groups in terms of age, body mass index (BMI), mean course of disease, pregnancy history, or abortion history ($P>0.05$; **Table 1**).

Comparison of therapeutic effects

The total effective rate was significantly lower in the monotherapy group than in the combined group (67.50% vs. 86.36%; $P<0.05$) (**Table 2**).

Incidence of adverse reactions

No serious adverse reactions were observed in either group during treatment. Any mild adverse reactions that occurred resolved spontaneously after medication discontinuation. The overall incidence of adverse reactions was 7.50% in the monotherapy group and 11.36% in the combined group, with no statistical significance ($P>0.05$; **Table 3**).

Comparison of evaluation results of SQoL

Patient SQoL was evaluated using the FSFI. As shown in **Table 6**, no significant difference was found in the total FSFI score between groups prior to treatment ($P>0.05$). The post-treatment total FSFI score increased markedly in both groups, with a significantly higher score in the combined group ($P<0.05$).

Comparison of endometrial conditions

The pre-treatment ET, FI, and RI were not statistically different between the monotherapy and combined groups ($P>0.05$). After treatment, both groups showed significant elevations in ET

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Table 4. Comparison of symptom remission time

Symptom remission time (d)	Monotherapy group (n=40)	Combined group (n=44)	t	P
Lower abdominal pain	12.10±3.42	10.14±2.80	2.884	0.005
Lower abdominal distension with heaviness	13.28±3.26	9.98±2.50	5.233	<0.001
Menostaxis	12.55±4.13	10.55±3.47	2.410	0.018
Menorrhagia	12.18±3.26	10.64±2.72	2.358	0.021

Table 5. Comparison of pregnancy rate, abortion rate and recurrence rate within one year (n [%])

Groups	Monotherapy group (n=40)	Combined group (n=44)	χ^2	P
Pregnancy rate	18 (42.50)	29 (65.91)	4.635	0.031
Abortion rate	5 (12.50)	3 (6.82)	0.785	0.376
Recurrent rate	4 (10.00)	5 (11.36)	0.041	0.840

Table 6. Comparison of total FSFI score

Groups	Monotherapy group (n=40)	Combined group (n=44)	t	P
Before treatment	19.32±3.77	19.07±2.57	0.358	0.721
After treatment	24.43±3.04	27.55±3.72	4.184	<0.001
t	6.673	12.441		
P	<0.001	<0.001		

Note: FSFI, Female Sexual Function Index.

and FI and a significant reduction in RI ($P<0.05$). Moreover, these changes were significantly more pronounced in the combined group than in the monotherapy group ($P<0.05$; **Figure 1**).

Comparison of inflammatory cytokine levels

Before treatment, the levels of IL-6, IL-17 and TNF- α were comparable between groups ($P>0.05$). After treatment, IL-6, IL-17, and TNF- α levels were significantly decreased in both groups, with lower levels observed in the combined group compared with the monotherapy group ($P<0.05$; **Figure 2**).

Comparison of oxidative stress-associated indices

No significant differences were observed between the two groups in baseline levels of MDA, SOD, and GSH (all $P>0.05$). After treatment, both cohorts showed a significant decrease in MDA and significant increases in SOD and GSH, with the combined group having lower MDA and higher SOD and GSH levels ($P<0.05$, **Table 7**).

Discussion

Chronic endometritis remains a clinical challenge today. CE may be associated with abnormal uterine bleeding, intrauterine pathological features such as polyps or fibroids, and various reproductive disorders including infertility, RIF, and recurrent miscarriage [11]. The clinical symptoms of endometritis are often mild and easily overlooked. Endometritis is a complex disease. First of all, there is no universally accepted diagnostic approach or criteria for CE [12]. Second, the treatment of endometritis is predominantly empirical, with

unsatisfactory treatment outcomes and the development of drug resistance [13]. Finally, non-invasive methods for evaluating treatment response are lacking.

Intrauterine infection is a major cause of CE, so antibiotics are commonly used to treat CE [14]. However, long-term antibiotic use can enhance the drug resistance of pathogenic bacteria, which can compromise the efficacy of commonly used antibiotics and make it difficult to completely resolve endometrial inflammation with antibiotics alone [15]. Therefore, antibiotics are usually used in combination with other drugs to achieve better therapeutic effects. Intrauterine drug administration is a common approach in obstetrics and gynecology that allows for more direct, rapid, and localized drug delivery, while reducing systemic adverse reactions. DEX is a common glucocorticoid that is extensively applied in many infection-related diseases because of its antibacterial and anti-inflammatory actions. In animal experiments, intrauterine DEX injections into buffalo with endometritis significantly improved pregnancy rates [16].

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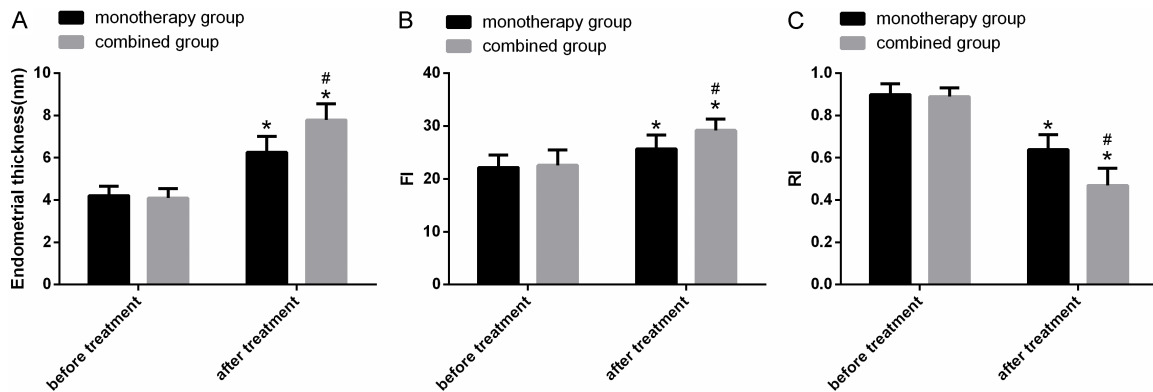


Figure 1. ET, FI and RI detected by color Doppler ultrasound in two groups. A. Pre- and post-treatment ET. B. Pre- and post-treatment FI. C. Pre- and post-treatment RI. Notes: * $P < 0.05$ vs. baseline (before treatment) in the same group; # $P < 0.05$ vs. the monotherapy group at the same time point; ET, Endometrial thickness; FI, flow index; RI, resistance index.

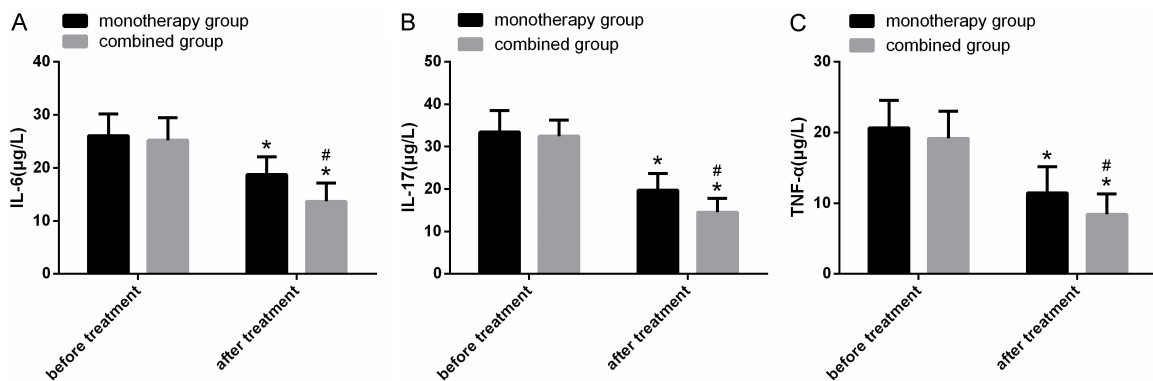


Figure 2. Enzyme-linked immunosorbent assay of menstrual blood IL-6, IL-17 and TNF- α levels in patients. A. Pre- and post-treatment IL-6. B. Pre- and post-treatment IL-17. C. Pre- and post-treatment TNF- α . Notes: * $P < 0.05$ vs. pre-treatment in the same group; # $P < 0.05$ vs. the monotherapy group at the same time point; IL, interleukin; TNF, tumor necrosis factor.

Table 7. Oxidative stress comparison

Groups	Monotherapy group (n=40)	Combined group (n=44)	t	P
MDA (nmol/mL)				
Pre-treatment	35.38±5.34	34.98±6.14	0.317	0.752
Post-treatment	19.62±4.19	15.39±3.54	5.012	<0.001
SOD (U/L)				
Pre-treatment	14.22±3.72	13.32±2.91	1.241	0.218
Post-treatment	24.20±6.24	28.14±6.59	2.807	0.006
GSH (μg/mL)				
Pre-treatment	179.65±12.33	182.36±12.79	0.987	0.327
Post-treatment	256.88±24.49	314.84±28.99	9.847	<0.001

Note: MDA, malondialdehyde; SOD, superoxide dismutase; GSH, glutathione.

Intrauterine administration of DEX and antibiotics has also been shown to improve pregnancy outcomes in CE patients [9]. Based on these

data, we believe that intrauterine injection of DEX in addition to conventional antibiotic therapy may have a better therapeutic effect. As expected, the combined group showed notably higher total effective rate, pregnancy rate and total FSFI scores than the monotherapy group, with no serious adverse reactions that can be resolved spontaneously. These findings indicate that the combination of DOXY-h and DEX is an effective and safe treatment for CE, significantly improving pregnancy rates and patients' quality of life. We also found that DOXY-h + DEX significantly shortened the remission time of symptoms, includ-

ing lower abdominal pain, lower abdominal distension with heaviness, menostaxis, and menorrhagia.

The endometrium is the site of embryo implantation and the placenta attachment where nutrients for later fetal growth come from. Successful connection between the embryo and the endometrium is essential for implantation and the maintenance of pregnancy. Endometrial inflammatory mediators, including leukocytes, immunoglobulins, and cytokines, play an essential role in regulating the immune response and trophoblast growth during implantation, while CE can impair endometrial receptivity and create a hostile microenvironment that interferes with normal implantation [17]. CE is associated with an increased pro-inflammatory immune response, which are often related to adverse pregnancy outcomes [18]. IL-6, IL-17, and TNF- α are common pro-inflammatory cytokines, and their levels usually rise with the severity of inflammation. Previous studies have reported significantly elevated levels of pro-inflammatory cytokines such as IL-6, IL-1 β and TNF- α in the menstrual blood of CE patients [19]. The results of this study showed that compared with the monotherapy group, IL-6, IL-17 and TNF- α in the combined group were more significantly reduced after treatment, ET and FI were higher, and RI was lower. This suggests that DOXY-h plus DEX effectively alleviates endometrial inflammation, thereby increasing ET and potentially improving pregnancy outcomes. On the other hand, oxidative stress is essentially a loss of balance between reactive oxygen species (ROS) production and intrinsic antioxidant mechanisms, which is closely linked to female reproductive health and fertility, and has been implicated in CE onset and progression [20, 21]. MDA is an oxidative stress marker, while SOD and GSH are antioxidants. An excessive MDA increase plus SOD and GSH exhaustions can aggravate oxidative stress imbalances and further promote endometritis progression [22]. In our study, post-treatment MDA levels in the combined group decreased significantly from baseline and were markedly lower than those in the monotherapy group, while SOD and GSH presented a rising trend and were significantly higher versus DOXY-h monotherapy. These results suggest that DOXY-h plus DEX is effective in inhibiting endometrial oxidative stress.

The inhibitory effect of DEX on oxidative stress may be related to its regulation of the mitogen-activated protein kinase (MAPK) axis, a pathway showing a strong association with ROS-induced oxidative damage [23, 24]. Additionally, the anti-inflammatory mechanism of DEX may be related to its inhibition of inflammatory signaling pathways like nuclear factor (NF)- κ B, as well as their downstream pro-inflammatory effectors. Specifically, by suppressing the phosphorylation of the mitogen-activated protein kinase (MAPK) axis, including c-Jun N-terminal kinase (JNK), extracellular signal-regulated protein kinase (ERK), and p38 MAPK, DEX up-regulates NF- κ B inhibitor α (I κ B- α) expression to block the nuclear translocation of NF- κ B, thereby down-regulating cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) [24, 25].

Several limitations of this study should be noted. First, the small sample size included and the lack of blinding and randomization may introduce retrospective bias. Future prospective, multi-center, large-scale studies should incorporate statistical adjustments, such as Bonferroni correction, to control for type I errors from multiple comparisons, thereby enhancing the robustness and reliability of the findings. Second, the short follow-up time makes it impossible to track the outcomes of long-term pregnancy and live birth, and we did not evaluate the impact on drug resistance and uterine microbiota. Future studies with a 3-5-year follow-up are needed to prospectively assess the influence of these two treatment schemes on drug resistance and the uterine microbiota. Third, this study lacked basic research. Further experiments on endometrial histopathology or cellular pathways are warranted to provide in vivo molecular evidence for DEX's regulation of the NF- κ B/MAPK axis and to conduct basic translational experiments to elucidate its anti-inflammatory and antioxidant mechanisms. Finally, this study only analyzed patients with chronic endometritis. Subsequently, subgroup analyses should be conducted for patients with infertility and recurrent implantation failure, and additional information such as the type of infertility, the number of previous embryo transfers, and the history of miscarriage should be included. This will help to further clarify the optimal indications for the combined regimen and provide specific clinical guidance for infer-

tile patients and those with recurrent implantation failure.

Conclusively, DOXY-h plus DEX is effective and safe in the treatment of CE, which can promote symptom relief, improve the endometrial environment, inhibit inflammation and oxidative stress, and enhance pregnancy success and SQoL, having high clinical value for promotion and application.

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Disclosure of conflict of interest

None.

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