

“Sandwich” Technique for the Management of Chronic and Hemorrhagic Cervicitis Vs Antibiotics Alone: a Case-Control Clinical Study

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ABSTRACT

Objectives: Cervicitis is commonly caused by sexually transmitted infections. This study compares the standard antibiotic treatment with antibiotics plus cryocoagulation in cases of chronic and hemorrhagic cervicitis. Although antibiotics are typically the first line of treatment, persistent cases often require additional interventions, like cryosurgery to obtain a cure.

Material and method: Fifty women (mean age 38 years) with chronic cervicitis – based on clinical evaluations, cytology and vaginal culture – were enrolled in the present study. Twenty three participants were treated with combination therapy consisting of an initial course of antibiotics, followed by cryocoagulation and a subsequent round of antibiotics post-procedure, using a “sandwich” technique, while 27 subjects received antibiotics alone.

Results: Our study showed that the “sandwich” technique achieved a success rate of 76.2% ($p < 0.005$) after a single session for treating chronic cervicitis and hemorrhagic cervicitis (normalization in Pap smear) and 95.7% ($p < 0.05$) success rate in clinical improvement after intervention.

Conclusions: The combination of antibiotic treatment followed by cryosurgery and then another prophylactic course of antibiotics presents a promising approach for managing chronic cervicitis and recurrent cervical hemorrhage.

Keywords: chronic cervicitis, hemorrhagic cervicitis, antibiotics, cryosurgery, cryocoagulation.

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INTRODUCTION

Cervicitis is an inflammation of the cervix. It may be asymptomatic or may be linked to bleeding between menstrual cycles during intercourse, atypical vaginal discharge, pain during a pelvic exam or dyspareunia. The symptoms could continue and create a chronicity (1, 2). Sexually transmitted diseases (STDs), including *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, are frequently the cause of acute or chronic cervicitis, which is primarily an inflammation of the columnar epithelium of the uterine cervix. However, a specific infection cannot be found in a large percentage of cases, and/or cervicitis may be due to a noninfectious etiology (1, 2). In addition, several studies suggest a connection between the number of childbirths and the likelihood of developing cervicitis; women with several children appear to have a higher risk of this pathology (3, 4). Research indicates that more than 85% of females with cervical chlamydial infections exhibit no signs or symptoms of cervicitis. Therefore, annual screening for chlamydial infection is essential for sexually active females under 25 years of age (5). Additionally, the relationship between *Chlamydia*, cervicitis and abnormalities in Pap smears should not be overlooked (6). The quality of life for women with recurrent cervicitis or cervical bleeding can be greatly affected (7), thus prompt and efficient treatment is crucial (8). Untreated cervicitis can increase the risk of adverse pregnancy outcomes, including ectopic pregnancy and infertility. Antibiotics, such as doxycycline (or azithromycin), are typically the first-line treatment for cervicitis (2), while for high-risk individuals, doxycycline and ceftriaxone are preferred antibiotics (9). For doxycycline, there is no clear evidence that a woman or man received results in fertility reduction. For ceftriaxone, changes in sperm characteristics (decrease of sperm count and motility) and an increase in sperm abnormalities are some of the remedy sides effects (10, 11). On the other hand, cryosurgery has been particularly beneficial for women with chronic cervicitis and cervical hemorrhage as well as those with cervical ectopy, where a sensitive epithelium makes them more susceptible to recurrent infections, and many women experienced complete resolution of symptoms after undergoing cryosurgery

(2-4, 12). Sexual partners should be appropriately treated also. Even while antibiotics are usually the primary line of treatment, further measures are frequently needed for persistent cases to cure the patient (1, 8). Cryosurgery for example is considered a valuable remedy in cervicitis treatment, which alone does not appear to negatively impact fertility when compared to the general population (9, 13).

Given that little is known about combined remedy protocols in the cervicitis treatment, the aim of this clinical study is to compare standard antibiotic treatment with combination cryosurgery (cryocoagulation) in cases of persistent cervicitis and recurrent cervix hemorrhage. We hypothesize that a combination therapy comprising an initial course of antibiotics, followed by cryosurgery, and a subsequent round of antibiotics post-procedure – using a “sandwich” technique – could yield promising results. □

MATERIALS AND METHOD

This study was conducted in two hospitals in Greece, including the private hospital «Rea Maternity Hospital» in Athens and the University Hospital of Alexandroupolis, from January 2020 to November 2024. All participants were diagnosed with chronic cervicitis based on clinical evaluation (Figures 1-2), cytology PAP smear and vaginal culture. A total of 50 women aged 24 to 48 years, with a mean age of 36, were included

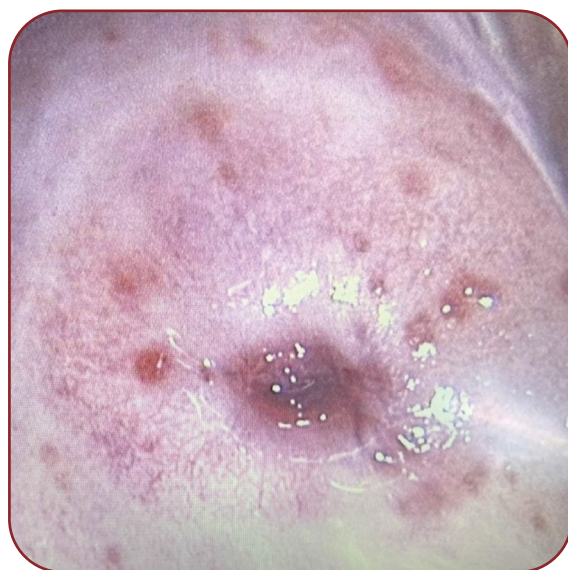


FIGURE 1. Chronic cervicitis

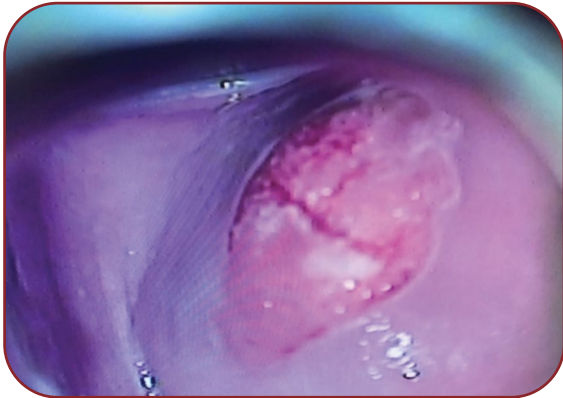


FIGURE 2. Chronic hemorrhagic cervicitis

in the study. All patients were informed and consented to participate in this study. Patients were divided into two groups, with the first one (case group) comprising 23 subjects and the second one (control group), 27 patients.

In the case group, infections were identified as follows: three patients (14.2%) had *Chlamydia*, two subjects (9.5%) had *Streptococcus*, one patient (4.7%) had *Escherichia coli*, while data for the remaining patients were unknown. Similarly, in the control group, four patients (14.8%) had *Chlamydia*, two subjects (7.4%) had *Streptococcus*, two patients (7.4%) had *Escherichia coli*, and data for the remaining ones were unknown. Given that doxycycline effectively targets most pathogens responsible for cervicitis, empiric antibiotherapy with this antibiotic was selected. Thus, in the case group, each woman initially received antibiotic treatment for cervicitis and recurrent hemorrhage: doxycycline of 100 mg x 2 for 10 days after a diagnostic work-up. However, as symptoms persisted, cryosurgery was performed about 15-20 days later. Cryosurgery was performed with a cryoprobe applied for 3-4 minutes on the cervix with a special device at the temperature of -30 to -40 degrees Celsius (Figures 3-4), two times, after a five-minute pause: double cryo. The procedure cooled the ectocervix and the endocervix in cases that it was necessary and destroyed by freezing the cells in the pathological and hemorrhagic area. This technique eliminates the pathological tissue and allows good healing of the cervix with new cells. The cryosurgery was followed 15 days by a second course of antibiotics: doxycycline of 100 mg x 2 for 10 days to increase the efficiency of the treatment.



FIGURE 3. Cryosurgery device



FIGURE 4. Cryosurgery procedure

In the control group, four patients (14.8%) had *Chlamydia*, two subjects (7.4%) had *Streptococcus*, two patients (7.4%) had *Escherichia coli* and data for the remaining ones were unknown. In this group, each woman initially received antibiotic treatment for cervicitis and recurrent hemorrhage: doxycycline of 100 mg x 2 for

10 days after a diagnostic work-up. However, as symptoms persisted, after one month each woman received again the same antibiotic treatment alone for 10 days.

Clinical improvement of cervicitis and normalization of Pap smear were evaluated at the end of the treatment for both groups. A normal Pap smear was classified as P1 or P2. P1 indicated that no abnormal cervical cells were found, while P2 meant that several cells appear slightly different from normal. In contrast, P3 to P5 were categorized as abnormal results. P3 indicated that the cervical cells were somewhat abnormal, P4 signified that the cells were more abnormal than P3 and P5 indicated highly abnormal cells, which may suggest the presence of cervical cancer. In our study, only subtypes P1, P2 and P3 were noticed.

The clinical research undertaken satisfies all national and international ethical and moral requirements, including the Helsinki Convention. Personal data was handled and processed following the General Data Protection Regulation's (GDPR) guidelines (EU 2018/1725). Ethical approval was given by the Research Ethics Committee of the Rea Maternity Hospital, in Athens, Greece (Reference Number: 61/2020-10/01/2020).

Statistical analysis

The statistical analysis of the study was performed using SPSS Statistics (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, USA) and the z-test was used to calculate the p-value. A statistically significant result was considered if the p-value was < 0.05 . A t-test for independent samples and Levene's test for equality of variances were also used to examine the differences between the groups, regarding the normalization of Pap test and improvement in cervicitis by using different treatment procedures. $\square$

RESULTS

Case group

In the case group, two of the 23 female patients were excluded because they did not complete the treatment. Thus, 21 women remained, out of whom four subjects (19%) had no children and 17 women (80.9%) had children: 12 subjects had one child (57.1%), four patients (19%)

had two children and one woman (4.8%) had three children. Most participants demonstrated improvement and were successfully treated using the "sandwich" method, where cryotherapy was combined with antibiotic therapy, compared to antibiotics alone. Clinical improvement in cervicitis was observed in 18 women (85.7%), with normalization of Pap smear results in 16 women (76.2%) (Table 1). For the five women (23.8%) whose chronic cervicitis and cervical hemorrhage did not resolve after the initial treatment, a follow-up Pap smear was conducted six months post-procedure (Figure 5). However, it should be noted that the incidental finding of cervicitis on Pap smear does not require antibiotic treatment in most cases. In those cases, two additional courses of antibiotics were administered at a one-month interval, leading to a complete cure in three women (after a total of three rounds of antibiotics following cryosurgery). The remaining two women underwent a second round of cryo-

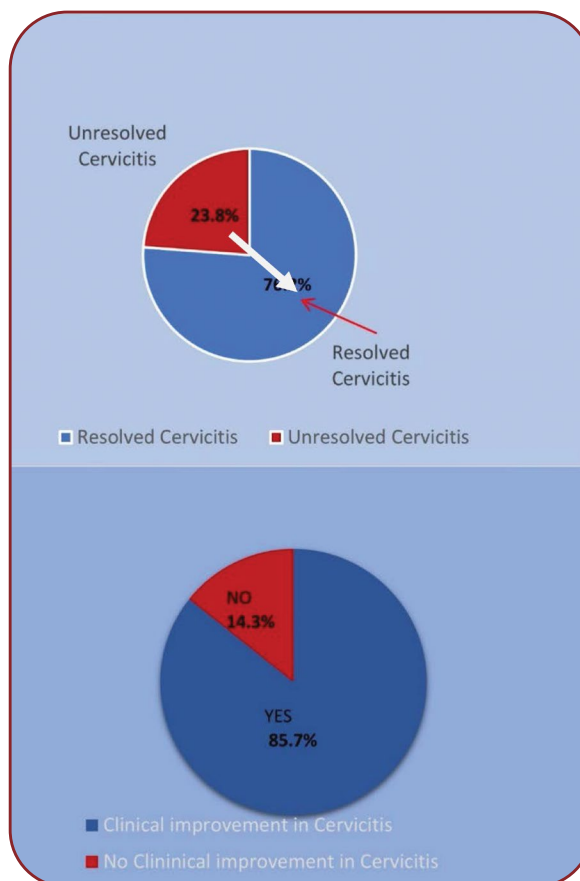


FIGURE 5. Percentage analysis of improvement in cervicitis and percentages of resolved and unresolved cervicitis after "sandwich" technique

therapy after one year, which effectively treated chronic cervicitis and recurrent cervical hemorrhage in both. No serious side effects, such as infection, hemorrhage, or fever, were observed. Four women reported mild abdominal pain, which was managed with simple medication paracetamol and resolved within a few days. Treatment was less successful in women with higher parity, as it failed in all four women with two children and the one woman with three children. Overall, our study showed that the “sandwich” technique achieved a success rate of 76.2% after a single session for treating recurrent cervicitis and cervical hemorrhage.

TABLE 1. Characteristics of case-control groups

	N	Percentage (%)
Case group – cryotherapy and antibiotics	21	
Number of children:		
None	4	19
One	12	57.1
Two	4	19
Three	1	4.8
Pathological agent found		
<i>Chlamydia</i>	3	14.2
<i>Streptococcus</i>	2	9.5
<i>Escherichia coli</i>	1	4.7
Unknown/unspecified	16	76.1
Clinical improvement after intervention	18	85.7
Normalization of Pap smear	16	76.2
Control group – antibiotics alone	27	
Number of children:		
None	5	18.5
One	10	37
Two	9	33.3
Three	3	11.1
Pathological agent found		
<i>Chlamydia</i>	4	14.8
<i>Streptococcus</i>	2	7.4
<i>Escherichia coli</i>	2	7.4
Unknown/unspecified	19	70.3
Clinical improvement after intervention	16	59.3
Normalization of Pap smear	13	48.1

Control group

In the control group comprising 28 women, one patient was lost to follow-up and. Out of the remaining 27 patients, five subjects (18.5%) had no children, while 22 (81.5%) had children: 10 women (37%) had one child, nine subjects (33.3%) had two children and three women (11.1%) had three children. Sixteen of the 27 participants (59.3%) in the control group had clinical improvement in cervicitis after the intervention with antibiotics alone, while 13 subjects (48.1%) had normalization of Pap smear (Table 1).

Comparison between groups

The p-value was calculated with the z-test for two proportions to compare the two percentages and see whether the difference between them was statistically significant. The z-score was compared to the critical value ($z_{critical} = 1.96$) for 0.05. The comparison of the two groups found that $z\text{-score} = 1.99 > 1.96$. The difference in percentages (85.7% versus 59.3%, $p = 0.045$) was statistically significant. Regarding the normalization of Pap smear applying the z-test for the comparison of the two groups (case-control), we found that $z\text{-score} = 1.971 > 1.96$. The difference in percentages (76.2% versus 48.1%, $p = 0.0048$) was statistically significant. Therefore, there is a statistically significant difference between the two groups, and in particular, the “sandwich” technique achieved a success rate of 76.2% ($p = 0.048$) after a single session for treating recurrent cervicitis and cervical hemorrhage (normalization in Pap smear) and an 85.7% ($p = 0.04$) success rate in clinical improvement after intervention.

A t-test for independent sample sizes unveiled similar results. More precisely, the 21 patients in the case group who underwent a combined cryotherapy and antibiotic treatment, compared to the 27 patients in the control group,

TABLE 2. Comparison between groups results for clinical treatment success and normalization of Pap smear

	Levene's test for equality of variances		Independent samples test			95% confidence interval of the difference	
	F	p-value	t-test	df	p-value	Lower	Upper
Clinical improvement after intervention	20.037	<0.001	-2.045	46	0.047	-0.52490	-0.00420
Normalization of Pap smear	9.601	0.003	-2.012	46	0.046	-0.56090	-0.00529

df = degrees of freedom.

demonstrated statistically significant improvements in managing chronic and hemorrhagic cervicitis [$t(46) = -2.045$, $p = 0.047$]. Furthermore, it was found that after the two interventions, normalization of Pap smear in the case group fluctuated significantly at higher levels ($n = 16$, 76.2%) than the control group ($n = 13$, 48.1%) [$t(46) = -2.012$, $p = 0.046$] (Table 2). $\square$

DISCUSSION

This study aimed to compare standard antibiotic treatment with a combination of antibiotics and cryocoagulation in managing chronic and hemorrhagic cervicitis. The results demonstrated that the "sandwich" technique achieved a 76.2% success rate ($p < 0.005$) after a single session, as evidenced by Pap smear normalization. Furthermore, clinical improvement was observed in 95.7% of cases ($p < 0.05$) following the intervention. This treatment approach, consisting of initial antibiotic therapy, cryosurgery and a subsequent prophylactic course of antibiotics, shows promise as an effective strategy for managing chronic cervicitis and recurrent cervical hemorrhage.

Doxycycline effectively targets most pathogens responsible for cervicitis and is therefore considered the first-line empiric antibiotic therapy for its treatment. Additionally, it should be noted that the treatment with doxycycline is efficacious in chlamydial infection and it should be preferred for cases with suspected gonorrhea coinfection. Our study showed that doxycycline was effective even alone in control group and combined in the case group, which lead both groups to significant clinical improvements of cervicitis that was caused by several pathological agents, including *Chlamydia*. In a study that compared the efficacy of a three-day course of doxycycline to a standard seven-day course for treating uncomplicated *Chlamydia* cervicitis, Reedy *et al* (14) found that doxycycline therapeutic regimens were effective, as doxycycline is effective towards *Chlamydia*. While in a study by Schwebke *et al* (2002), in which 51 women with cervicitis and bacterial vaginosis were assigned to receive doxycycline or ofloxacin, along with either intravaginal metronidazole or a placebo, results showed that those who received metronidazole showed a higher resolution rate of cervicitis at two and four weeks. Additionally,

women whose bacterial vaginosis resolved were more likely to see improvement in cervicitis at two weeks, regardless of their treatment.

In confirmed cases of gonorrhea, ceftriaxone 150 mg is given as a single intramuscular injection in most cases. However, in cases of gonorrhea without chlamydial infection, doxycycline is not an appropriate alternative (15, 16). When antibiotics fail to resolve the initial condition, a second diagnostic work-up can be offered to check for possible *C. trachomatis* and *N. gonorrhea* persistent infection. When antibiotics fail to resolve the condition, "destructive" methods could be used after full informed consent of the woman. In general, in chronic cervicitis with mucopurulent discharge, cauterization of the bleeding points with silver nitrate or the use of a laser can successfully reduce symptomatology (15).

Considering cryosurgery as a similar method, it may offer an effective alternative. Our study demonstrated that combining cryotherapy with doxycycline significantly led to higher normalization of Pap smear and enhanced the clinical management of chronic and hemorrhagic cervicitis compared to doxycycline treatment alone. Cervical ectopy can be associated with chronic or recurrent symptoms of cervicitis like leucorrhea and post-coital bleeding, and many of these cases have associated cervical ectropion, the extension of endocervical columnar epithelium onto the ectocervix (12). Differential diagnosis from ectropion may be necessary in certain cases of cervicitis because ectropion does not need to be treated in most instances. Furthermore, in the rare occurrence of excessive mucous discharge or spotting in ectropion, there is no evidence to guide the choice of treatment. In all cases, treatment should be chosen very carefully. Cryotherapy is regarded as one of the most effective treatment options for cervical ectropion (17). However, it can lead to significant and unpleasant vaginal discharge, may take several weeks for healing to be completed, and can potentially cause cervical stenosis (18). For cryotherapy, some suggestions could be extrapolated from other cervical pathology (18, 19). In general, no severe adverse effects have been reported from this procedure (2, 4, 12). These considerations were verified from a few studies, such as the double-blind clinical trial by Agah *et al.* (2), who concluded that cryotherapy, is a safe and effective therapy, offering a rapid and cost-effective

solution for treating symptomatic cervical ectropion, providing reassurance in its use. More precisely, they found that symptoms like vaginal discharge ($p = 0.006$), itching ($p < 0.001$), dyspareunia ($p = 0.005$), post-coital bleeding ($p = 0.023$) and pelvic pain ($p = 0.009$) showed favorable significant improvements with cryotherapy. Moreover, Çekmez *et al* (4), showed that success rate of cryotherapy was highest in patients with abundant leucorrhea and lowest in patients with pelvic pain and recurrent cervicitis. In a randomized controlled trial that investigated the differences of receiving 400 mg of vaginal effervescent tranexamic acid tablets for 10 days with cryotherapy, Farzaneh *et al* (20) observed that 97.72% and 93.18% of the patients respectively showed improvement in clinicals symptomatology of cervical ectropion. However, there was no significant difference in clinical improvement between the two treatment methods. Similarly, Zhang *et al* (21), demonstrated that CO₂ cryotherapy, when combined with Kushen gel for treating chronic cervicitis, showed significant clinical efficacy and had few adverse reactions. These studies are crucial for effective cervicitis management, emphasizing the clinical value of combined therapies rather than relying solely on antibiotics or cryotherapy.

The present study has both strengths and limitations. The combination of antibiotic treatment followed by cryosurgery and then another prophylactic course of antibiotics presents a promising approach for managing chronic cervicitis and recurrent hemorrhagic cervicitis, and thus it is considered a strength of our clinical study. In contrast, small sample size, absence of

fertility data for each patient and lack of longer-term follow-up, may be considered limitations of our study.

CONCLUSION

Human papilloma virus (HPV) infection plays a significant role in the development of cervical abnormalities, making it essential to differentiate between benign infections and pre-neoplastic lesions. Since persistent high-risk HPV infections can lead to cervical intraepithelial neoplasia (CIN) and, ultimately, cervical cancer, a thorough differential diagnosis is crucial. This distinction ensures appropriate clinical management, preventing unnecessary interventions for transient infections while enabling timely treatment for lesions with malignant potential. A combined approach involving antibiotic treatment, followed by cryosurgery and then a prophylactic course of antibiotics – the so-called “sandwich” technique – has shown promise in managing chronic cervicitis and recurrent hemorrhagic cervicitis. However, longer-term follow-up studies are necessary to confirm their efficacy. While concerns regarding antibiotic resistance due to prolonged treatment remain valid, this technique offers a highly effective treatment option with excellent success rates and minimal short- and long-term side effects. Given its potential benefits, greater awareness and adoption of the “sandwich” technique among gynecologists should be encouraged. □

Conflicts of interest: none declared.

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REFERENCES

1. **Centers for Disease Control and Prevention.** Sexually Transmitted Infections Treatment Guidelines. *Morbidity and Mortality Weekly Report*. 2021, Jul 23.
2. **Agah J, Sharifzadeh M, Hosseinzadeh A.** Cryotherapy as a Method for Relieving Symptoms of Cervical Ectopy: A Randomized Clinical Trial. *Oman Med J* 2019;34:322-326.
3. **Zhang L, Zhou Y, Liu J, et al.** CO₂ Cryotherapy Combined with Kushen Gel for the Treatment of Chronic Cervicitis: A Real-World Study. *Clin Exp Obstet Gynecol* 2024;51:141.
4. **Çekmez Y, Şanlıkan F, Göçmen A, et al.** Is Cryotherapy Friend or Foe for Symptomatic Cervical Ectopy? *Medical Principles and Practice* 2016;25:8-11.
5. **Iatrakis G.** Chlamydial Infection of the Genital Tract. In: *Gynecology and Obstetrics*. Zevelekakis Editions. Athens. 2021.
6. **Peitsidis P, Kalmantis K, Peitsidou A, et al.** Chlamydial infection in female lower genital tract and its correlation with cervical smear abnormalities. *Bratislava Medical Journal* 2012;113:357-360.
7. **Kavga F, Bothou A, Nanou C, et al.** Quality of Life Among Natural Menopausal Women and Early Surgical Menopausal Women: A Study from Greece.

- Nurs Rep* 2024;14:3445-3453.
8. **Yildiz S, Alay I, Eren E, et al.** The impact of cryotherapy for symptomatic cervical ectropion on female sexual function and quality of life. *J Obstet Gynaecol (Lahore)* 2021;41:815-820.
9. **Weed JC, Curry SL, Duncan ID, et al.** Fertility after cryosurgery of the cervix. *Obstetr Gynecol* 1978;52:245-246.
10. **NHS.** Pregnancy, breastfeeding and fertility while taking doxycycline. 2022.
11. **Hou L, Fu Y, Zhao C, et al.** The research progress on the impact of antibiotics on the male reproductive system. *Environ Int* 2024;187:108670.
12. **Sharma DrS, Dixit DrA, Sharma DrAK, Tiwary DrV.** Cryotherapy: A Method for Relieving Symptoms of Cervical Ectopy. *Int J Clin Obstetr Gynaecol* 2020;4:28-30.
13. **Rokita W.** The importance of cryosurgery in gynecological practice. *Ginekol Pol* 2011;82:618-622.
14. **Reedy MB, Sulak PJ, Miller SL, et al.** Evaluation of 3-Day Course of Doxycycline for the Treatment of Uncomplicated Chlamydia trachomatis Cervicitis. *Infect Dis Obstet Gynecol* 1997;5:18-22.
15. **Powell AM NP.** Acute Cervicitis. In: *UpToDate*, Wolters Kluwer, 2024.
16. **Workowski KA, Bachmann LH, Chan PA, et al.** Sexually Transmitted Infections Treatment Guidelines, 2021. *MMWR Recommendations and Reports* 2021;70:1-187.
17. **Patel KD, Karnavat RD, Viramgama DG, Dalal RK.** Evaluation of efficacy and safety of cryotherapy in benign and premalignant cervical lesion. *Int J Reprod Contracept Obstet Gynecol* 2021;10:3066.
18. **Laufer MR.** Benign cervical lesions and congenital anomalies of the cervix. In: *UpToDate*, Wolters Kluwer, 2024.
19. **Taylor NP.** Cervical intraepithelial neoplasia: Ablative therapies. In: *UpToDate* 2024.
20. **Farzaneh H, Shabnam T, Hamideh G, et al.** Clinical Improvement, Disease recurrence, and Patient Satisfaction Following Treatment with Vaginal Effervescent Tablets of Tranexamic Acid and Cryotherapy in Patients with Symptomatic Cervical Ectropions: A Randomized Controlled Trial. *J Midwifery Reprod Health* 2023;11:3910-3918.
21. **Zhang F, Huang L, Wang W, et al.** Effect of intradialytic progressive resistance exercise on physical fitness and quality of life in maintenance haemodialysis patients. *Nurs Open* 2020;7:1945-1953.

