



The Therapeutic Effects of Levofloxacin vs. Azithromycin + Ceftriaxone Regimens for the Treatment of Women's Pelvic Inflammatory Disease; a Randomized Clinical Trial

Mohammad Eslami vaghar¹, Armita Valmohammadi Emamchaei², Seyed Mohammad Masoud Shushtarian^{3*}

¹Department of Gynecology, Faculty of Medicine, Tehran Medical Science, Islamic Azad University, Tehran, Iran

²Faculty of Medicine, Tehran Medical Science, Islamic Azad University, Tehran, Iran

³Department of Biophysics and Biochemistry Faculty of Advance Science and Technology, Tehran Medical Science, Islamic Azad University, Tehran, Iran

Article Info

Received: August 25, 2026

Accepted: September 02, 2026

Published: September 14, 2026

***Corresponding author:** Seyed Mohammad Masoud Shushtarian, Department of Biophysics and Biochemistry Faculty of Advance Science and Technology, Tehran Medical Science, Islamic Azad University, Tehran, Iran.

Citation: Mohammad E vaghar, Armita V Emamchaei, Masoud Shushtarian SM. (2026) "The Therapeutic Effects of Levofloxacin vs. Azithromycin + Ceftriaxone Regimens for the Treatment of Women's Pelvic Inflammatory Disease; a Randomized Clinical Trial". Archives of Clinical Surgery, 1(1); DOI: 10.61148/ACS/004

Copyright: © 2026. Seyed Mohammad Masoud Shushtarian. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract:

Background and objectives: Pelvic inflammatory disease (PID) is a common cause of referral to gynecology clinics and on-time and effective treatment is required for preventing complications. Considering the controversies on the treatment strategies, this study aimed to compare the therapeutic effects of levofloxacin vs. azithromycin + ceftriaxone in treatment of PID.

Materials and methods: Eighty women who referred to the gynecology clinic at Amir-Al-Momenin Hospital (2021-2020) and were diagnosed with PID were randomly divided into: Group A, 40 patients treated with levofloxacin 400 mg twice daily for two weeks, and group B, 40 patients on ceftriaxone regimen (intramuscular 250 mg intramuscularly) + Azithromycin (500 mg single dose, repeated one week later). We asked patients to return to the clinic after 15 days to evaluate the pelvic pain, pain during two-handed physical examination, cervicitis, and vaginal discharge. Adverse effects, including nausea/vomiting, diarrhea, and dyspepsia were also asked from the patient during the follow-up visit. The groups were compared using SPSS v. 26.

Results: All patients had pelvic pain, pain during examination, vaginal discharge, and cervicitis; after treatment 5, 11, 15, and 11 in group A and 1, 1, 3, and 1 patient in group B; the change in each group and the difference between the groups were significant ($P < 0.001$). Considering the adverse effects, 19/80 had nausea/vomiting, 18/80 diarrhea, 12/80 dyspepsia, most of whom were in group A vs. B (16 vs. 3, 12 vs. 6, and 10 vs. 2, respectively; $P < 0.05$).

Conclusion: The azithromycin + ceftriaxone regimen had better results both in terms of improving patients' symptoms and in terms of adverse effects.

Keywords: pelvic inflammatory disease; azithromycin; ceftriaxone; levofloxacin

Introduction

Gynecological infections, affecting the female's reproductive tract, are among the most common causes of referral of women to medical centers. Pelvic inflammatory disease (PID) is a clinical syndrome, mainly caused by sexually transmitted organisms, such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, which climb up the genital organs and affect the ovaries, fallopian tubes, endometrium, peritoneum, and adjacent pelvic structures of young women (age 15-25 years), causing major to minor symptoms, including pelvic pain, fever, dyspareunia, abnormal vaginal

bleeding, vaginal discharge and frequency of urination (1). Diagnosis is mainly based on clinical symptoms, bimanual examination, and Papanicolaou; however, many patients remained undiagnosed, in whom long-term complications, including infertility, ectopic pregnancy, and chronic pain can occur; therefore on-time diagnosis and appropriate treatment is essential to prevent these complications (2).

Mild-to-moderate disease can be treated in out-patient setting, while patients with severe symptoms such as nausea, vomiting, and peritoneal irritation benefit from inpatient treatments. Several antibiotic regimens are suggested for outpatient treatment of PID and several studies have compared the efficacy of different antibiotic regimens; some trials showed no difference between parenteral cefoxitin and doxycycline vs. intramuscular (IM) cefoxitin (outpatient) plus oral doxycycline in microbiologic or clinical cure or long term reproductive health outcomes (3, 4). An important issue to be noticed is the adherence rate, which differ between antibiotics, considering their adverse effects and problems it causes for the patients; poor adherence to doxycycline or tetracycline has been reported frequently (5). Accordingly, some guidelines suggest administration of intravenous (IV) or IM antibiotics, until clinical improvement (for at least 24 hours) (6).

The current US and European guideline also differ in their antibiotic regimens; Ceftriaxone IM single dose plus oral doxycycline once daily. As the second regimen, cefoxitin IM single and oral doxycycline is recommended as regimen 2, and other third-generation cephalosporin plus doxycycline is suggested as regimen 3 in the US guideline and oral ofloxacin plus metronidazole in the European guideline. For the alternative outpatient management, oral levofloxacin is recommended by the US guideline (500 mg daily for two weeks) with or without metronidazole and in the European guideline, IM ceftriaxone is recommended plus azithromycin (single dose), followed by a second dose of azithromycin after a week (7). In resistant and recurrent cases, the sexual partner(s) should be evaluated for infection with *Neisseria gonorrhoeae* and *Chlamydia* and positive cases should be treated.

Considering the gastrointestinal side effects of co-amoxiclav, and risk of oral intolerance or contra-indications of doxycycline (like breastfeeding women), erythromycin or azithromycin is preferred. Also, considering the antibiotic resistance, increasing every year, new generations of antibiotics are preferred. Levofloxacin is also effective against a wide range of aerobic and anaerobic Gram-negative and Gram-positive bacteria and exerts its bactericidal effect by inhibiting DNA ligase. Therefore, the alternative regimens appear to be the most appropriate. However, to date, no comprehensive studies have been conducted to compare their efficacy and ensure the physician which antibiotic to prescribe, when a patient is diagnosed with PID. Therefore, the present study aimed to compare the therapeutic effects of levofloxacin vs. azithromycin + ceftriaxone in treatment of PID.

Materials And Methods

Study design

In this randomized clinical trial (RCT), approved by the Ethics

Committee of Islamic Azad University, Tehran, Iran, all women who referred to the gynecology clinic at Amir-Al-Momenin Hospital (2021-2020) and were diagnosed with PID by the gynecologist were considered as the study population. Women younger than 25 years, who had pelvic pain and discomfort for less than 30 days, pelvic organ tenderness on bimanual examination, mucopurulent discharge or cervicitis, normal abdominal and pelvic ultrasound results and normal urine test were included into the study, after they received complete explanation about the research objectives and signed the written informed consent form. Any pregnant women, or those with any abnormality in ultrasound (including fallopian tube or ovarian abscess, endometriosis, appendicitis, diverticulitis, hemorrhagic ovarian cyst, and ovarian torsion), those having an IUD, or sensitivity to the antibiotics prescribed were not included into the study. The sample size was calculated at 40 in each group, considering the alpha error at 0.05 and $\beta=0.2$ (study power of 80%), using the following equation:

$$n = \frac{2(Z_{1-\alpha/2})^2 [P(1-P)]}{d^2} \quad n = \frac{(1.96 + 0.84)^2 0.25}{(0.5)^2} = 40$$

The eligible participants were selected among the referrals, considering the inclusion criteria (mentioned above) and randomly divided into two groups:

- Group A, 40 patients treated with levofloxacin 400 mg twice daily for two weeks
- Group B, 40 patients on ceftriaxone regimen (250 mg IM) + Azithromycin (500 mg single dose, repeated one week later).

We asked patients to return to the clinic after 15 days to evaluate the pelvic pain, pain during bimanual examination, cervicitis, and vaginal discharge. Also, adverse effects, including nausea/vomiting, diarrhea, dyspepsia, allergies, fever, skin rashes, granulocytopenia, and hemolytic anemia were also asked from the patient during the follow-up visit.

Statistical analysis

The collected data were input into SPSS v. 26 (Released 2017. Armonk, NY: IBM Corp). Number of patients with the positive symptoms were compared in each group before and after the treatment and between the groups using Chi square test or Fisher's exact test. For the number of patients with adverse effects, the same tests were used. A P-value of <0.05 was considered significant.

Results

All patients had pelvic pain, pain during examination, vaginal discharge, and cervicitis; after treatment 5, 11, 15, and 11 in group A and 1, 1, 3, and 1 patient in group B; the change in each group was significant, as well as the difference between the two groups ($P<0.001$).

Table 1: The frequency of symptoms before and after the interventions

Groups	Group A		Group B		P-value*
	Before	After	Before	After	
Pelvic pain	40	5	40	1	<0.001
Pain during examination	40	11	40	1	<0.001
Vaginal discharge	40	15	40	3	<0.001
Cervicitis	40	11	40	1	<0.001

*The results of chi square test or Fisher's exact test

Considering complications, 19/80 had nausea/vomiting, 18/80 diarrhea, 12/80 dyspepsia, most of whom were in group A (16 vs. 3, 12 vs. 6, and 10 vs. 2, respectively).

Table 2: Comparing the rate of adverse effects between the groups

	Group A	Group B	P-value*
Nausea/vomiting	16	3	<0.001
Diarrhea	12	6	<0.001
Dyspepsia	10	3	<0.001

*The results of chi square test or Fisher's exact test

Discussion

The results of the present study showed that patients in group B, who received the alternative treatment of the European and center for disease control (CDC) guideline, were superior to group A, who received the alternative treatment of the US guideline, both in terms of treatment efficacy and adverse effects. For evaluating the treatment efficacy, we considered the number of patients who had symptoms after treatment, which included pelvic pain, pain during examination, vaginal discharge, and cervicitis. Improvement of the clinical symptoms, including pain and vaginal discharge, has been used for evaluation of the efficacy of PID treatment, as well. The bimanual examination can also confirm that the clinical criteria are present as an objective measurement (8).

According to the results of the present study, the IM administration of ceftriaxone plus two doses of azithromycin (one week apart) was more effective with less adverse effects than levofloxacin (twice daily for 2 weeks). This results may be related to the different efficacy of the antibiotics, in addition to different patient adherence to treatment; as taking two pills a day for two weeks is difficult for the patients and results in poorer adherence to treatment. While IM administration in the other regimen is under the supervision and the patient only has to take two other pills. The less number of medications used may be also the reason for the fewer complication rate.

Previous studies have also studied the efficacy of these antibiotic regimens for PID. Savaris and colleagues compared the efficacy of azithromycin plus ceftriaxone with doxycycline in a RCT and reported a cure rate of 98.2% in the azithromycin group,

significantly higher than doxycycline (85.7%) (9). The results of this study is consistent with the results of the present study considering azithromycin regimen, although the group compared differed, as we evaluated levofloxacin regimen in the other group. Moghtadaei and colleagues compared the efficacy of ceftriaxone plus ofloxacin 200 mg per day or azithromycin 1 g per week for two weeks and showed a higher clinical cure rate (70/78, 90%) for azithromycin vs. ofloxacin (50/60, 83.3%) (10). The results of this study also compared the superiority of this antibiotic regimen, ceftriaxone plus azithromycin, which is consistent with the results of the present study. The group compared with this treatment regimen was ofloxacin, which is also a quinolone, similar to levofloxacin, used in the present study; but, they added ceftriaxone to this group, as well, which we did not. Others have also shown the high cure rate of azithromycin for PID (used either as single treatment or combined with another antibiotic) (11, 12), which is in line with the results of the present study.

Azithromycin is a macrolide, effective for treating cervical *Chlamydia trachomatis* infections, including PID. Single-dose azithromycin has also been shown to be more compliant than multidose therapy for chlamydial infection. Accordingly, some have suggested the use of azithromycin alone for treatment of PID with a higher efficacy of single dose IV than oral administration (250 mg for 7 days) with clinical success rate of 94% (13). Another RCT also showed high cure rates of single dose azithromycin for *chlamydia*, *chlamydia* with *gonorrhea* and *gonorrhea* only (95.8, 84.2 and 98.2%, respectively), compared to doxycycline twice daily for 7 days (14). *In vitro* investigation also showed that azithromycin is at least 100-fold more active against *M. genitalium* than the quinolones or tetracyclines (15). In addition to the higher efficacy of the antibiotic, the ease of administration is another superiority, mentioned for azithromycin (16). These facts are possibly the underlying reasons of better results in group B of the present study. However, the patient's sensitivity to macrolids should be considered when administering this treatment regimen.

Levofloxacin is a quinolone, used alone or in combination with metronidazole, for treatment of PID. In the present study, we used it as a single drug regimen and the results showed low cure rate and high adverse effects in group A. Possibly, the efficacy of its combination with metronidazole is higher, as the results of previous studies showed (17). In another study, ciprofloxacin was compared with levofloxacin and the results of expression of serum tumor necrosis factor – alpha and C-reactive protein showed appropriate curative effect for patients with PID (18), which is inconsistent with the results of the present study; although the compared group, as well as parameters considered for evaluating the response to treatment differed among studies. Reduced susceptibility of *N. gonorrhoeae* to quinolones in patients with PID may explain the lower efficacy of treatment in this group of our study (19). Another factor that may contribute to this low efficacy may be the low adherence to treatment, as taking two pills a day for 14 days is not easy for the patients; this has been previously suggested for doxycycline, indicating that women with PID who were prescribed doxycycline took an average of 70% of the total dose, and less than half took it twice daily as directed (5, 20).

It is important to notice that the adverse effects of antibiotics,

considered casual for the physicians, are factors that make the patient suffer during the treatment period; the resulting dissatisfaction can reduce the tolerability of the patient to the antibiotic and make the patient discontinue treatment or take it not based on the suggested protocol. In the present study, we evaluated all adverse effects, among which only nausea/vomiting, diarrhea, and dyspepsia were observed, more frequently in group A vs. group B. These adverse effects have been also reported in other studies for these antibiotics with higher rates for fluoroquinolones, compared to azithromycin (21, 22), although they have not considered PID as the indication.

In the present RCT, we investigated an issue, which has been addressed less frequently in the literature and the results can help the physicians in decision making for treatment of PID. However, this study also had some limitations. One of the limitations of the present study was related to the nonrandom inclusion of patients into the study and selection of patients from one medical center from one city, which minimizes the generalizability of the results to the whole study population and necessitates studying this issue in different populations. Another limitation was related to the possible effect of confounders on the results of the present study. Although we randomized the patients to the groups, some factors like the underlying infection may differ in the participants and influence the results; however, we did not evaluate the culture results before administering the antibiotic regimens and can therefore not comment about the efficacy of the antibiotics on different infections.

Conclusion

The results of the present study showed a higher effectiveness and lower adverse effects for the treatment regimen, recommended by the European guidelines and CDC, namely azithromycin + ceftriaxone regimen, compared to the regimen recommended by the US guidelines, namely levofloxacin. These results suggest this treatment regimen an appropriate option for outpatient management of women with mild and uncomplicated PID. Further studies are required to investigate this issue in different subpopulations and a larger sample size, taking into account the limitations of the present study.

Acknowledgements

The authors of the present study sincerely thank ...

Financial Disclosure

The authors of the present study declare that

Funding/Support

The present study was financially supported by

References

1. de Britto LCV, Siqueira RDM, de Barros MLNM, Arrivabene KCS. Pelvic Inflammatory Disease: updates from diagnosis to treatment. *Brazilian Journal of Health Review*. 2023;6(5):23011-8.
2. Curry A, Williams T, Penny ML. Pelvic inflammatory disease: diagnosis, management, and prevention. *American family physician*. 2019;100(6):357-64.
3. Ness RB, Soper DE, Holley RL, Peipert J, Randall H, Sweet RL, et al. Effectiveness of inpatient and outpatient treatment strategies for women with pelvic inflammatory disease: results from the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) Randomized Trial. *American journal of obstetrics and gynecology*. 2002;186(5):929-37.
4. Ness R, Trautmann G, Richter H, Randall H, Peipert J, Nelson D. Effectiveness of treatment strategies of some women with pelvic inflammatory disease: A randomized trial (vol 106, pg 573, 2005). *OBSTETRICS AND GYNECOLOGY*. 2006;107(6):1423-5.
5. Dunbar-Jacob J, Sereika SM, Foley SM, Bass DC, Ness RB. Adherence to oral therapies in pelvic inflammatory disease. *Journal of Women's Health*. 2004;13(3):285-91.
6. Mitchell C, Prabhu M. Pelvic inflammatory disease: current concepts in pathogenesis, diagnosis and treatment. *Infectious Disease Clinics*. 2013;27(4):793-809.
7. Duarte R, Fuhrich D, Ross JD. A review of antibiotic therapy for pelvic inflammatory disease. *International Journal of Antimicrobial Agents*. 2015;46(3):272-7.
8. Mealey K, Braverman PK, Koenigs LM. Why a pelvic exam is needed to diagnose cervicitis and pelvic inflammatory disease. *Annals of Emergency Medicine*. 2019;73(4):424-5.
9. Savaris RF, Teixeira LM, Torres TG, Edelweiss MIA, Moncada J, Schachter J. Comparing ceftriaxone plus azithromycin or doxycycline for pelvic inflammatory disease: a randomized controlled trial. *Obstetrics & Gynecology*. 2007;110(1):53-60.
10. Moghtadaei P, Sardari F, Esmaeilian S. Comparison of ceftriaxone plus weekly azithromycin or daily ofloxacin for outpatient treatment of pelvic inflammatory disease: a randomized clinical trial. *Journal of Family and Reproductive Health*. 2008:87-94.
11. Malhotra M, Sharma J, Batra S, Arora R, Sharma S. Ciprofloxacin-tinidazole combination, fluconazole-azithromycin-secnidazole-kit and doxycycline-metronidazole combination therapy in syndromic management of pelvic inflammatory disease: a prospective randomized controlled trial. *Indian journal of medical sciences*. 2003;57(12):549-55.
12. Bevan C, Ridgway G, Rothermel C. Efficacy and safety of azithromycin as monotherapy or combined with metronidazole compared with two standard multidrug regimens for the treatment of acute pelvic inflammatory disease. *Journal of International Medical Research*. 2003;31(1):45-54.
13. Mikamo H, Iwasaku K, Yamagishi Y, Matsumizu M, Nagashima M. Efficacy and safety of intravenous azithromycin followed by oral azithromycin for the treatment of acute pelvic inflammatory disease and perihepatitis in Japanese women. *Journal of Infection and Chemotherapy*. 2014;20(7):429-35.
14. Rustomjee R, Kharsany A, Connolly C, Karim SA. A randomized controlled trial of azithromycin versus doxycycline/ciprofloxacin for the syndromic management of sexually transmitted infections in a resource-poor setting.

- Journal of Antimicrobial Chemotherapy. 2002;49(5):875-8.
15. Unemo M, Jensen JS. Antimicrobial-resistant sexually transmitted infections: gonorrhoea and Mycoplasma genitalium. *Nature Reviews Urology*. 2017;14(3):139-52.
 16. Jaiyeoba O, Lazenby G, Soper DE. Recommendations and rationale for the treatment of pelvic inflammatory disease. *Expert review of anti-infective therapy*. 2011;9(1):61-70.
 17. Judlin P, Thiebaugeorges O. Levofloxacin plus metronidazole in uncomplicated pelvic inflammatory disease: a preliminary study. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2009;145(2):177-9.
 18. Zou H, Zhang W, Wang M, Li Z. Effects of levofloxacin hydrochloride and ciprofloxacin on pelvic inflammation and risk factors related to their effects. *International Journal of Clinical and Experimental Medicine*. 2019;12(9):11754-61.
 19. Takei M, Yamaguchi Y, Fukuda H, Yasuda M, Deguchi T. Cultivation of *Neisseria gonorrhoeae* in liquid media and determination of its in vitro susceptibilities to quinolones. *Journal of clinical microbiology*. 2005;43(9):4321-7.
 20. Piyadigamage A, Wilson J. Improvement in the clinical cure rate of outpatient management of pelvic inflammatory disease following a change in therapy. *Sexually transmitted infections*. 2005;81(3):233-5.
 21. Lode H. Safety and tolerability of commonly prescribed oral antibiotics for the treatment of respiratory tract infections. *The American journal of medicine*. 2010;123(4):S26-S38.
 22. Lavanya S. Randomized comparative study of levofloxacin based triple therapy with standard triple therapy for helicobacter pylori eradication: Rajiv Gandhi University of Health Sciences (India); 2007.