http://www.cjmb.org doi 10.34172/cjmb.2024.3014

Open Access Original Article

Crescent Journal of Medical and Biological Sciences
Vol. 11, No. 3, July 2024, 135–140
eISSN 2148-9696

Comparative Prophylactic Efficacy of Azithromycin and Doxycycline in Hysterosalpingography-Induced Infections: A Randomized Double-Blind Clinical Trial

Nazila Najdi[1], Fatemeh Saf[2], Maryam Shokrpour[1], Zahra Hajmohammadhoseini[1*], Behzad Khansarinejad[3], Amir Almasi-hashyani[4], Maryam Mohsenikia[1]

Abstract

Objectives: Doxycycline is commonly prescribed as the primary prophylactic treatment for women undergoing hysterosalpingography (HSG). This study aimed to compare the prophylactic effectiveness and safety of azithromycin and doxycycline in terms of treating infections caused by HSG.

Materials and Methods: This double-blind randomized clinical trial enrolled 107 women referred to Amiralmomenin Hospital in Arak, Iran, for HSG. After evaluation based on inclusion and exclusion criteria, the participants were randomly allocated to either the doxycycline or azithromycin group. The primary outcome was the incidence of adverse effects. The patients were also followed up to determine PCR test results for the clearance of chlamydia infection.

Results: The cumulative incidence of side effects was 1.85% in the doxycycline group, with adverse effects observed in only one patient. Conversely, no adverse effects were reported in the azithromycin group ($P = 0.505$). In the doxycycline group, one patient (1.85%) tested positive in the PCR test, while no positive PCR tests were recorded in the azithromycin group. Neither group exhibited cases of fever or required additional treatments. The results of statistical analyses did not reveal any statistically significant differences between the compared groups ($P > 0.05$).

Conclusions: A single dose of azithromycin could be considered interchangeable with a 1-week course of doxycycline as antibiotic prophylaxis in women undergoing HSG, as it provides similar effectiveness and safety.

Keywords: Azithromycin, Doxycycline, Pelvic inflammatory disease, Antibiotic prophylaxis

Introduction

Infertility poses a significant global public health challenge, impacting various aspects of individuals' lives (1). Investigating the causes of infertility involves employing different diagnostic approaches, among which hysterosalpingography (HSG) plays a crucial role (2). This procedure offers a valuable overview of the overall health status of reproductive organs, aids in identifying the root causes of infertility, diagnoses intrauterine adhesions, polyps, and fibroids, and assists in devising appropriate treatment plans (3,4).

HSG is generally regarded as a safe diagnostic approach, although it may present minor adverse effects such as mild pain, infection, or light bleeding (5,6). In rare cases, however, it has the potential to lead to more serious complications, including pelvic infections (7). These events are more likely to occur in women with a history of previous infections, such as chlamydia (7). HSG as a transcervical approach has the potential to introduce microorganisms from the vagina and endocervix to the upper female genital tract, thereby increasing the probability of developing pelvic inflammatory disease (PID) (8).

Doxycycline, an antibiotic, is recommended as a prophylactic measure to reduce the probability of PID in women undergoing HSG (9). Previous studies have reported high efficacy for doxycycline, indicating its potential to ultimately prevent the incidence of PID in these women (7,8). However, doxycycline is not exempt from adverse effects and can lead to photosensitivity and gastritis. Furthermore, it is contraindicated for pregnant women due to concerns about its harmful effects on fetal development, the risk of liver toxicity, and its impact on maternal health (9). Azithromycin is considered a safer alternative with fewer adverse effects for treating infections like chlamydia (10). Previous studies have demonstrated promising outcomes for azithromycin compared to doxycycline in this regard (11,12). Additionally, azithromycin has no contraindication during pregnancy, making it a viable option for use in pregnant women (10). Despite the significance of the issue, there is limited evidence directly comparing the effectiveness

Received 10 February 2024, **Accepted** 8 June 2024, **Available online** 15 July 2024

[1]Department of Obstetrics and Gynecology, School of Medicine, Arak University of Medical Sciences, Arak, Iran. [2]Department of Radiology, School of Medicine, Arak University of Medical Sciences, Arak, Iran. [3]Molecular and Medicine Research Center, Department of Microbiology and Immunology, School of Medicine, Arak University of Medical Sciences, Arak, Iran. [4]Department of Epidemiology, School of Health, Arak University of Medical Sciences, Arak, Iran.

*Corresponding Author: Zahra Hajmohammadhoseini, Tel: +989186951372; Email: zahrahmh@gmail.com

Key Messages

- The study aims to fill gaps in knowledge by directly comparing the efficacy and safety of azithromycin and doxycycline as prophylactic treatments for infections following HSG. Focusing on their impact in preventing chlamydia infections and assessing side effects specific to this clinical procedure, it addresses the need for safer prophylactic alternatives, particularly for pregnant women undergoing fertility assessments. This research offers potentially significant implications for improving clinical practices in gynecology.

of azithromycin versus doxycycline, specifically in the treatment of infections induced by HSG. Therefore, the primary aim of the current study was to evaluate the prophylactic effectiveness and safety of azithromycin compared to doxycycline in terms of treating infections caused by HSG.

Materials and Methods

Study Design and Population

The current study was a double-blind randomized clinical trial that enrolled women referred to Amiralmomenin Hospital in Arak, Iran, for HSG. The study participants underwent evaluations based on inclusion and exclusion criteria before being randomly allocated to either the doxycycline or azithromycin group. The participants in each group were administered their assigned treatment before undergoing HSG. Subsequently, the investigated outcomes were compared between the doxycycline and azithromycin groups 2 weeks after the HSG procedure was conducted.

Inclusion and Exclusion Criteria

The inclusion criteria comprised individuals aged between 18 and 55 who were candidates for HSG, had no history of PID within 2 months before the HSG, lacked a history of gynecological surgery or other transcervical procedures, and had not used multiple antibiotics within 2 months prior to the HSG procedure. Additionally, individuals with a history of allergic reactions to azithromycin or doxycycline were excluded from the study. Cases that expressed reluctance to continue with the study were also excluded.

Study Interventions

The patients in the azithromycin group were given a single dose of 1g of azithromycin immediately before the HSG procedure. Conversely, the patients in the doxycycline group received 100 mg of doxycycline twice a day for a duration of 5 days prior to the HSG procedure (13,14).

Outcomes

The incidence of adverse effects was the primary outcome in the current study. The evaluation of side effects in the patients included assessing for gastritis, photophobia, diarrhea, nausea, vomiting, and an increased risk of sunburn. The patients were followed actively during the next 2 weeks after HSG to ascertain the investigated outcomes.

Two weeks following the HSG procedure, the patients from both groups underwent examinations for fever (temperature exceeding 38 °C) and symptoms such as vaginal discharge, suprapubic, or epigastric pain. Furthermore, the patients from both groups were screened for chlamydia using PCR analysis of cervical secretions and underwent physical examinations to detect female infections, including cervical motion tenderness (CMT+) and the presence of purulent discharge. We additionally evaluated the necessity for further treatment and documented any instances requiring additional medical intervention.

Randomization and Concealment

We utilized a balanced block randomization method to assign the participants to two distinct groups. Initially, we created six blocks labeled A and B (e.g., AABB), numbered from 1 to 6. Employing random number generator software with the block method, we generated the necessary randomization sequence to accommodate the sample size for both groups. Each AB block determined the intervention statuses for four participants. This randomization process was repeated 28 times for all the participants. Group A represented the doxycycline intervention, while group B represented the azithromycin intervention, with the respective intervention types indicated on each letter. Each participant was assigned a unique number from 1 to 110, receiving an 8-digit code comprising both numbers and letters. We meticulously documented these interventions on paper and placed them in sealed envelopes provided to the research group. Upon enrolling each participant, we disclosed the specific envelope code to be opened and repeated this process consistently until all the participants were enrolled. Throughout the enrollment period, we diligently implemented routine quality control measures to uphold the integrity of the randomization process and prevent any deviations from the established protocol.

Blinding

The current study was conducted as a double-blind trial, ensuring that both patients and physicians remained unaware of the interventions. To facilitate blinding, the patients in the azithromycin group received a single dose of 1g of azithromycin along with a placebo designed to match the size, dose, and duration of doxycycline. Conversely, the patients in the doxycycline group underwent a similar blinding process, but in reverse. They were administered 100 mg of doxycycline for 5 days along with a placebo mimicking azithromycin. This approach maintained blindness regarding the specific interventions received by each group.

Sample Size

To calculate the sample size, given a 20% prevalence of chlamydia in women undergoing HSG (compared to 3% in the general population) and aiming for an alpha level of 5% and a power of 80%, we estimated the sample size requirement of 55 individuals per group, totaling 110 participants overall (15, 16). Nevertheless, three patients were excluded from the study due to the severity of their condition, as advised by the hospital administration. Consequently, we successfully enrolled 107 patients for the study (Figure 1).

Statistical Analysis

The statistical analyses were conducted following an intention-to-treat approach. Continuous variables were summarized using mean and standard deviation (SD), supplemented by median and interquartile range (IQR) in cases where the distribution was skewed. Dichotomous variables were presented as frequencies and proportions. A comparison of the investigated outcomes was executed using the exact Fisher test. All the statistical analyses were carried out at a significance level of 0.05 using Stata software (Version 17.0, StataCorp, College Station, Texas, USA).

Results

Table 1 provides the baseline characteristics of the study participants, divided into the doxycycline and azithromycin groups. The mean (standard deviation) age for the patients in the doxycycline group was 32.1 (4.5) and 33.5 (5.1) for the patients in the azithromycin group. Primary infertility was observed in 70.4% and 64.2% of the patients in the doxycycline and azithromycin groups, respectively ($P > 0.05$). Additionally, 25.9% of the patients in the doxycycline group had a history of ectopic pregnancy, compared to 20.7% in the azithromycin group. Notably, no statistically significant differences were detected between the compared groups concerning baseline characteristics (Table 1).

We conducted a comparison of outcomes between the doxycycline and azithromycin groups. The cumulative incidence of side effects was 1.85% in the doxycycline group, where adverse effects were observed in only one patient. Conversely, no adverse effects were reported in the azithromycin group ($P = 0.505$). Among those in the doxycycline group, one patient (1.85%) tested positive in the PCR test, while no positive PCR tests were recorded in the azithromycin group. Neither group exhibited cases of fever or required additional treatments. Our analysis did not reveal any statistically significant differences between the compared groups ($P > 0.05$) (Table 2).

Discussion

The current study conducted a double-blind randomized clinical trial to compare the prophylactic effectiveness and safety of azithromycin versus doxycycline concerning HSG-induced infections in infertile women who underwent the procedure at the Infertility Center of

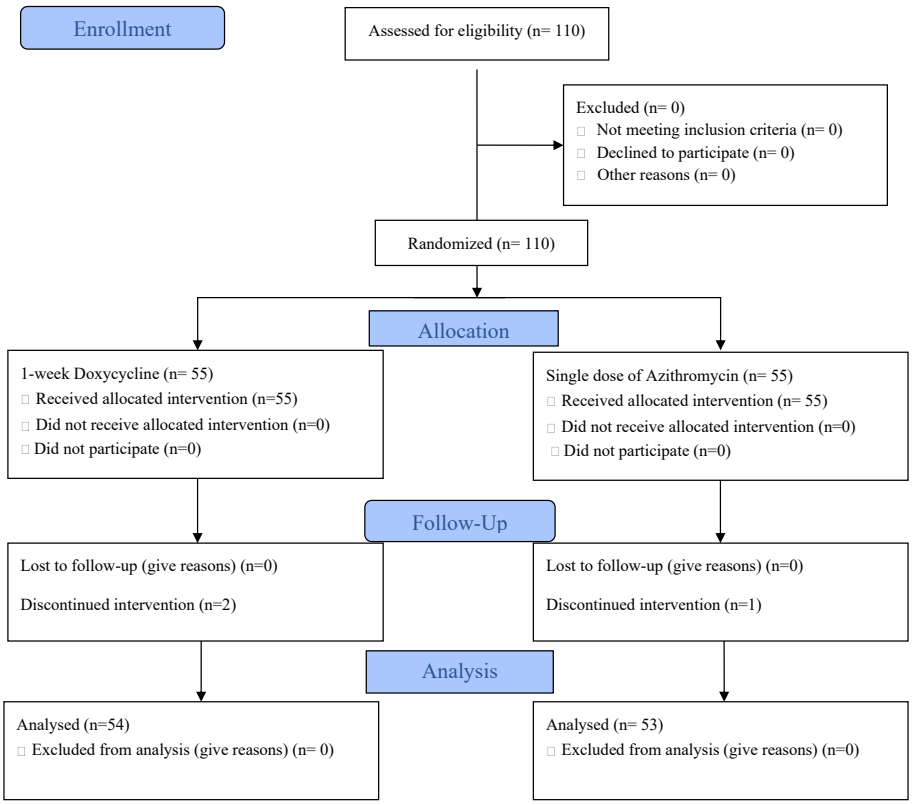

Figure 1. Flow Diagram of the Study.

Amiralmomenin Hospital, Iran, in 2023. Our study revealed that azithromycin had a similar prophylactic efficacy, as there was no difference in the cumulative incidence of infection among the participants; only one patient in the doxycycline group tested positive for chlamydia infection based on the results of PCR. In contrast, no patients in the azithromycin group reported positive PCR test results. Moreover, we noted one adverse effect in the doxycycline group, while no such reports were recorded in the azithromycin arm group. Based on this observation, it can be realized that azithromycin and doxycycline were quite comparable and provided similar results in terms of safety. Besides, no cases of fever or required additional treatments were reported during the follow-up in both compared groups.

The incidence rate of chlamydia infection in the study was less than 1%, a figure consistent with previous findings. Studies conducted in the US and European countries have reported that the incidence of PID after HSG is between 1.4% and 3.4% (17, 18). Li et al also reported a post-HSG PID incidence rate of 1.02% in patients who received either azithromycin or doxycycline (7). The disparity in the observed results could be attributed to differences in the outcomes of interest. While our assessment focused on PCR-positive results as an indication of non-clearance of chlamydia infection, previous studies primarily investigated the incidence of PID as their primary outcome (7,17,18).

Our findings, demonstrating the similar prophylactic efficacy of azithromycin and doxycycline following HSG, align with and are supported by previous studies. The findings from a Cochrane review indicated that both azithromycin and doxycycline exhibited comparable prophylactic effects for women using an intrauterine contraceptive device (IUD), reducing the probability of PID (19). However, it is important to note that the current study differed in terms of intervention, the prescribed antibiotic dosage, and the specific outcome of interest, distinguishing it from the findings reported in the Cochrane review (19). Also, Li et al demonstrated that doxycycline and first-generation cephalosporins could prevent the incidence of acute PID after HSG (7). An additional study that compared the efficacy of azithromycin versus doxycycline in clearing chlamydia for non-gonococcal urethritis demonstrated no significant difference between the compared groups in this regard (20). Conversely, a clinical trial conducted by Peuchant et al demonstrated the superiority of azithromycin over doxycycline in the treatment of chlamydia trachomatis infection in women with vaginal infection (21). They showed that a single dose of azithromycin could provide a better cure rate in such cases than a 1-week course of doxycycline (21).

The comparison of adverse events between doxycycline and azithromycin was an additional objective of the current study. The findings suggested that azithromycin might be as safe as doxycycline for infertile women undergoing HSG. These results align with those of Peuchant et al, demonstrating no significant difference in adverse events between the patients who received azithromycin and those treated with doxycycline (21).

This study was distinctive as it was among the few attempts to compare the effectiveness and safety of azithromycin versus doxycycline in women who underwent HSG. We conducted a randomized double-blind clinical trial to minimize potential biases. However,

Table 1. Baseline Characteristics of the Participants in the Azithromycin and Doxycycline Groups

Characteristics	Doxycycline (n=54)	Azithromycin (n=53)	*P* Value
Age (y), Mean (SD)	32.1(4.5)	33.5(5.1)	0.137[a]
Infertility type, n (%)			
Primary	38 (70.4%)	34 (64.2%)	
Secondary	16 (29.6%)	19 (35.8%)	0.243[b]
History of ectopic pregnancy, n (%)	14 (25.9%)	11 (20.7%)	0.289[b]

[a] Independent t-test; [b] Chi-square.

Table 2. Cumulative Incidence of Adverse Effects, Need for Other Treatments, Fever, and PCR Positive Test Results Among the Patients Treated in the Doxycycline and Azithromycin Groups

Characteristics	Doxycycline (n=54)	Azithromycin (n=53)	*P* Value[a]
Side effects, n (%)	1 (1.85%)	0 (0.0%)	0.505
Requiring additional treatments, n (%)	0 (0.0%)	0 (0.0%)	1.00
Fever, n (%)	0 (0.0%)	0 (0.0%)	1.00
PCR positive test results, n (%)	1 (1.85%)	0 (0.0%)	0.505

[a] Fisher exact test.

our findings should be interpreted in light of certain limitations. Firstly, we did not collect data on PID; patients were only followed for 2 weeks to assess the clearance of chlamydia infection via PCR tests. Additionally, our single-center setting constrained our ability to recruit a larger sample size, potentially reducing the study's power. Further research through multicenter studies with larger sample sizes is warranted. Moreover, adding a control group with only a placebo could provide better insights regarding the effectiveness of prophylactic treatments after HSG.

Conclusions

In summary, both azithromycin and doxycycline exhibited similar effectiveness in clearing the chlamydia infection induced by HSG. Furthermore, both treatment approaches displayed a favorable safety profile with a low incidence of adverse events. A single dose of azithromycin could be considered interchangeable with a 1-week course of doxycycline as antibiotic prophylaxis in women undergoing HSG.

Authors' Contribution

Conceptualization: Zahra Hajmohammadhoseini.
Data curation: Fatemeh Safi, Maryam Shokrpour.
Formal analysis: Amir Almasi-Hashyani.
Investigation: Maryam Mohsenikia, Zahra Hajmohammadhoseini, Behzad Khansarinejad.
Methodology: Zahra Hajmohammadhoseini.
Project administration: Zahra Hajmohammadhoseini.
Resources: Zahra Hajmohammadhoseini.
Software: Amir Almasi-Hashyani.
Supervision: Fatemeh Safi, Maryam Shokrpour.
Validation: Amir Almasi-Hashyani.
Writing–original draft: Nazila Najdi.
Writing–review & editing: Fatemeh Safi, Maryam Shokrpour, Zahra Hajmohammadhoseini, Behzad Khansarinejad, Amir Almasi-hashyani, Maryam Mohsenikia.

Availability of Data and Materials

The supporting data is available through the corresponding author.

Conflict of Interests

All authors declare that they have no conflict of interest.

Ethical Issues

The study obtained ethical approval from the Arak University of Medical Sciences Ethics and Review Board, designated with the ethics code IR.ARAKMU.REC.1401.161. All the patients received comprehensive information about the study protocol, and informed consent was obtained from each participant before enrollment in the study. The trial was registered in the Iranian Registry of Clinical Trials under the code IRCT20191104045328N15.

Acknowledgements

We extend our gratitude to all our colleagues at Amiramlmomin Hospital and Arak University of Medical Sciences for their support.

References

1. World Health Organization (WHO). 1 in 6 People Globally Affected by Infertility: WHO; 2023. Available from: https://www.who.int/news/item/04-04-2023-1-in-6-people-globally-affected-by-infertility. Accessed December 11, 2023.
2. Schankath AC, Fasching N, Urech-Ruh C, Hohl MK, Kubik-Huch RA. Hysterosalpingography in the workup of female infertility: indications, technique and diagnostic findings. Insights Imaging. 2012;3(5):475-483. doi:10.1007/s13244-012-0183-y
3. Role of Hysterolaparoscopy in Evaluation of Infertility–A One Year Prospective Observational Study. ProQuest [Internet]. Available from: https://www.proquest.com/openview/9471e4921add854e76b0062ff890f3f5/1?pq-origsite=gscholar&cbl=2026366&diss=y. Accessed December 11, 2023.
4. Diagnostic Laparoscopy in the Evaluation of Female Factor Infertility. ProQuest [Internet]. Available from: https://www.proquest.com/openview/28e0ec62bc371004a6914a8c43dbf8c1/1?pq-origsite=gscholar&cbl=2026366&diss=y. Accessed December 11, 2023.
5. Mayer C, Deedwania P. Hysterosalpingogram. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2023. Available from: http://www.ncbi.nlm.nih.gov/books/NBK572146/. Accessed December 11, 2023.
6. Roest I, Rosielle K, van Welie N, et al. Safety of oil-based contrast medium for hysterosalpingography: a systematic review. Reprod Biomed Online. 2021;42(6):1119-1129. doi:10.1016/j.rbmo.2021.03.014
7. Li HM, Sung FC, Li SC, et al. The effect of antibiotic prophylaxis for acute pelvic inflammatory disease after hysterosalpingography: a retrospective cohort study. Curr Med Res Opin. 2018;34(7):1271-1276. doi:10.1080/03007995.2017.1417243
8. Pereira N, Hutchinson AP, Lekovich JP, Hobeika E, Elias RT. Antibiotic prophylaxis for gynecologic procedures prior to and during the utilization of assisted reproductive technologies: a systematic review. J Pathog. 2016;2016:4698314. doi:10.1155/2016/4698314
9. Nelson ML, Levy SB. The history of the tetracyclines. Ann N Y Acad Sci. 2011;1241:17-32. doi:10.1111/j.1749-6632.2011.06354.x
10. Bakheit AH, Al-Hadiya BM, Abd-Elgalil AA. Azithromycin. Profiles Drug Subst Excip Relat Methodol. 2014;39:1-40. doi:10.1016/b978-0-12-800173-8.00001-5
11. Jabs C, Giroux M, Minion J, Karreman E, Faires M. Evaluation of adjunctive azithromycin prophylaxis in women undergoing cesarean delivery in a setting with low baseline incidence of surgical site infection. J Obstet Gynaecol Can. 2021;43(9):1062-1068.e2. doi:10.1016/j.jogc.2020.12.016
12. Kong FY, Tabrizi SN, Law M, et al. Azithromycin versus doxycycline for the treatment of genital Chlamydia infection: a meta-analysis of randomized controlled trials. Clin Infect Dis. 2014;59(2):193-205. doi:10.1093/cid/ciu220
13. Speroff's Clinical Gynecologic Endocrinology and Infertility [Internet]. Available from: https://www.wolterskluwer.com/en/solutions/ovid/speroffs-clinical-gynecologic-endocrinology-and-infertility-711. Accessed December 11, 2023.
14. Berek & Novak's Gynecology [Internet]. Available from: https://shop.lww.com/Berek---Novak-s-Gynecology/p/9781496380333. Accessed December 11, 2023.
15. Chlamydia [Internet]. Available from: https://www.who.int/news-room/fact-sheets/detail/chlamydia. Accessed December 11, 2023.
16. Huai P, Li F, Chu T, Liu D, Liu J, Zhang F. Prevalence of genital Chlamydia trachomatis infection in the general population: a meta-analysis. BMC Infect Dis. 2020;20(1):589. doi:10.1186/s12879-020-05307-w
17. Prevention of Acute Pelvic Inflammatory Disease After Hysterosalpingography: Efficacy of Doxycycline Prophylaxis. [Internet]. Available from: https://reference.medscape.com/medline/abstract/6638106. Accessed December 11, 2023.
18. Møller BR, Allen J, Toft B, Hansen KB, Taylor-Robinson D. Pelvic inflammatory disease after hysterosalpingography associated with Chlamydia trachomatis and Mycoplasma hominis. Br J Obstet Gynaecol. 1984;91(12):1181-1187. doi:10.1111/j.1471-0528.1984.tb04734.x
19. Grimes DA, Schulz KF. Antibiotic prophylaxis for intrauterine

contraceptive device insertion. Cochrane Database Syst Rev. 2001(2):CD001327. doi:10.1002/14651858.cd001327
20. Manhart LE, Gillespie CW, Lowens MS, et al. Standard treatment regimens for nongonococcal urethritis have similar but declining cure rates: a randomized controlled trial. Clin Infect Dis. 2013;56(7):934-942. doi:10.1093/cid/cis1022
21. Peuchant O, Lhomme E, Martinet P, et al. Doxycycline versus azithromycin for the treatment of anorectal Chlamydia trachomatis infection in women concurrent with vaginal infection (CHLAZIDOXY study): a multicentre, open-label, randomised, controlled, superiority trial. Lancet Infect Dis. 2022;22(8):1221-1230. doi:10.1016/s1473-3099(22)00148-7