Impact of antibiotic therapy on the rate of negative test results for chronic endometritis: a prospective randomized control trial

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Objective: To compare the rates of negative test results for chronic endometritis (CE) between subjects who did and did not receive antibiotic treatment.
Design: Prospective, single-blind randomized controlled trial.
Setting: Tertiary hysteroscopic center in a university teaching hospital.
Patient(s): A total of 132 women with CE confirmed with immunohistochemical study with CD138 epitope.
Intervention(s): Women randomized to antibiotic therapy received oral levofloxacin 500 mg and tinidazole 1,000 mg daily for 14 days. Women randomized to the control group did not receive any treatment. A repeated endometrial biopsy was performed 4 to 8 weeks after the initial biopsy to determine whether CE was still present.
Main Outcome Measure(s): The rate of negative test results for CE (from positive to negative).
Result(s): The CE rate of negative test results in the treatment group (89.3%) after one course of antibiotic treatment was significantly higher than that in the control group (12.7%). Among subjects who attempted pregnancy, there was no significant difference in ongoing pregnancy rates and miscarriage rates between the treatment arm (43.2%, 5.4%) and the control arm (25.7%, 14.3%). Among subjects randomized, there was also no significant difference in ongoing pregnancy rates and miscarriage rates between the treatment arm (27.1%, 3.4%) and the control arm (16.4%, 9.1%).
Conclusion: A course of broad-spectrum oral antibiotic therapy for 14 days is effective in the treatment of CE in >89.8% of cases. However, it is not yet clear whether treatment improved pregnancy outcomes.
Clinical Trial Identification Number: NCT02648698. (Fertil Steril® 2021;115:1549–56. ©2020 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Antibiotic, CD138, chronic endometritis, rate of negative test results

Chronic endometritis (CE) is a condition characterized by the presence of plasma cells in the endometrial stroma (1). CE may be associated with abnormal uterine bleeding, intrauterine pathologic features such as polyps or fibroids, and a variety of reproductive failures including infertility, recurrent implantation failure (RIF), and recurrent pregnancy loss (2–8). In women with reproductive failure, the reported prevalence of CE may be as high as 41% (2).

CE is often treated with antibiotics on the assumption that it is caused by an underlying infection. The response of CE to antibiotic therapy has been examined in several cohort studies (7–11). The cure rate, as determined by reduction of plasma cell density in a repeated endometrial biopsy specimen after antibiotic therapy, was found to be 75.4% (8), 99% (11), and 100% (7).

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The impact of antibiotic therapy on clinical outcome among subjects with CE has also been examined in several cohort studies. Cicinelli et al. (8) conducted a retrospective study which showed that after antibiotic therapy, the pregnancy rate and live birth rate (LBR) in women who become CE negative was higher than in those who remained CE positive after antibiotic treatment (65.2% vs. 33.0%, 60.8% vs, 13.3%, respectively). In another study involving women with RIF, Kitaya et al. (11) reported that the LBR in the first embryo transfer (ET) cycle and cumulative three ET cycles in the cured CE group after antibiotic treatment (32.8% and 38.8%, respectively) was significantly higher than in the non-CE group (22.1% and 27.9%, respectively). McQueen et al. (7) observed that the cumulative LBR was 88% (21/24) in the treated CE group vs. 74% (180/244) in the group without CE. In the CE group, the LBR for those before treatment was 7% (7/98) vs. 56% (28/50) after treatment.

Despite the apparently encouraging clinical data from the above observational cohort studies suggesting that antibiotic treatment was effective in curing CE and improving the reproductive outcome, the impact of antibiotic therapy has not yet been formally examined in any randomized controlled trial (RCT). In this report, we describe the findings of a prospective RCT designed to compare the rate of negative test results for CE in women who received antibiotic therapy with spontaneous cure conversion in those who did not receive antibiotic therapy, using the rate of negative test results based on measurement of plasma cell density as the primary endpoint.

MATERIALS AND METHODS

Subjects

This RCT was conducted in the Hysteroscopic Centre, Fuxing Hospital, Capital Medical University, a national training center for hysteroscopy in China between 2016 and 2018. During the study, women who were referred to the center for hysteroscopy for investigation of reproductive failure including infertility, recurrent miscarriage, or RIF, and also for abnormal menstruation, underwent endometrial biopsy with specimens obtained for histologic examination, including CD138 immunohistochemical staining as a routine procedure. The inclusion criteria for patient participation in this study included CD138 immunohistochemical staining of endometrial specimen showing presence of ≥ 1 plasma cells per 10 HPF, which confirmed CE according to published criteria (2, 12, 13); premenopausal condition; no evidence of endometrial hyperplasia or malignancy or structural uterine pathologic features; agreement to have a second endometrial biopsy approximately 4 weeks after the initial endometrial biopsy; and written informed consent obtained. The exclusion criteria included receipt of steroid hormone therapy within 1 month of recruitment, allergy or suspected allergy to the chosen antibiotic therapy, development any concurrent infection, and receipt of any antibiotic therapy during the study other than the one prescribed according to the study protocol.

Ethical approval was obtained from the Institutional Review Board of Fuxing Hospital on December 21, 2015 (IRB Review Approval Notice Number:2015FXHEC–KY050). In recruiting women into the RCT, we explained to all subjects that there was no conclusive evidence that treatment with antibiotics improve outcome and that there was a chance that the condition might resolve on its own. We also explained that upon completion of their participation, subjects who still had positive test results for CE could opt for antibiotic treatment or a further course of it. The study was registered in the ClinicalTrials.gov Protocol Registration System (ClinicalTrials.gov identifier: NCT02648698).

Sample Size Calculation

Assuming that the spontaneous CD138 rate of negative test results (from positive to negative) was 25% and that the antibiotic therapy would yield a 60% rate of negative test results, the total number of subjects required in each arm of the RCT would be 37, accepting a type 1 error of 0.05 and a type 2 error of 0.1, and assuming a dropout rate of 20%, 45 subjects would need to be recruited into either arm. Hence, a total of 90 subjects who fulfilled the inclusion criteria would be required.

Randomization

Women who had histologic confirmation of CE in an endometrial biopsy specimen and who fulfilled the inclusion criteria were randomized into the antibiotic group and control group in a 1:1 ratio by use of a computer-generated randomization list and sealed opaque envelopes prepared by the first author. The patients were not blinded to the antibiotic treatment. The pathologist who performed the histologic evaluation was blinded to the treatment (Fig. 1).

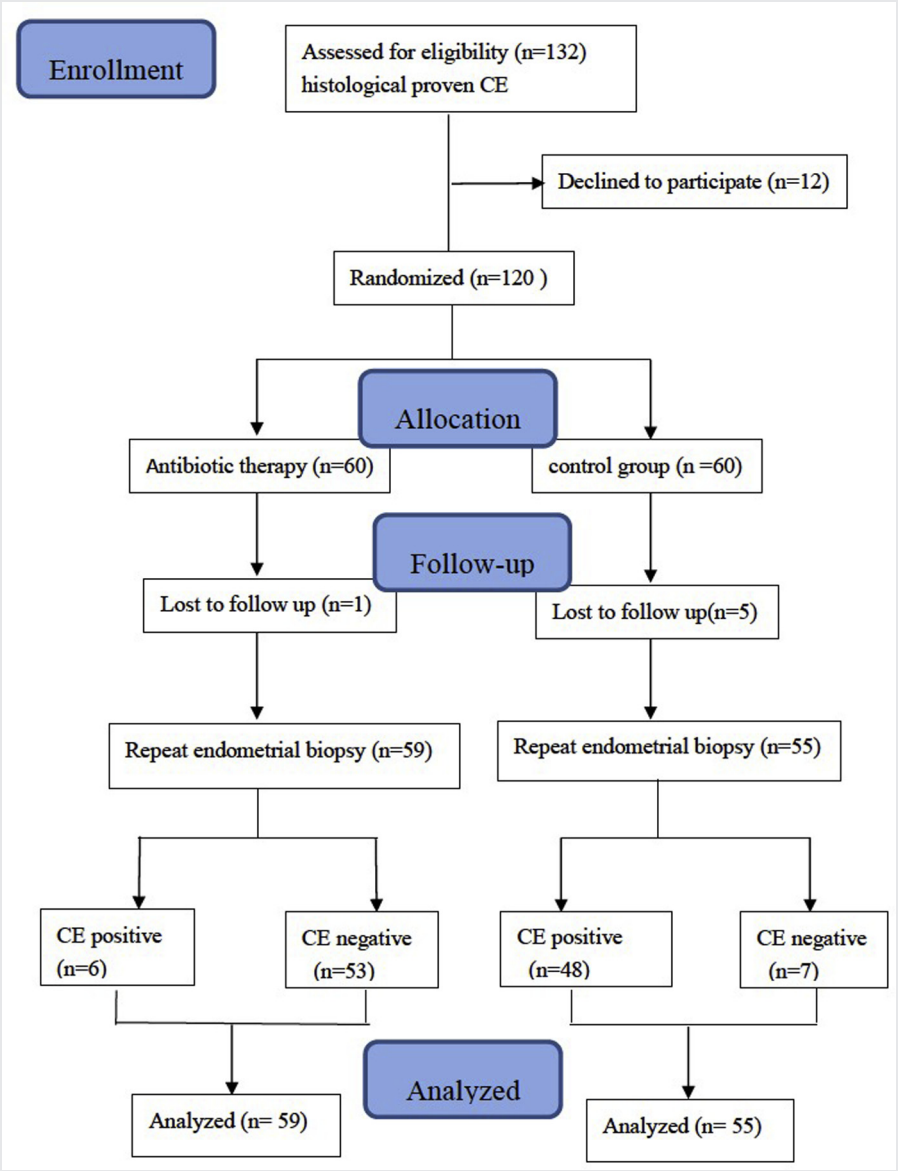
Hysteroscopy and Endometrial Biopsy

All subjects underwent hysteroscopy in their follicular stage. Hysteroscopy was performed with a 3-mm 30° rigid hysteroscope (Olympus) with an outer diameter of 4.5 mm by one of two experienced specialists who were blinded to the results of histologic assessment regarding CE. Normal saline solution was used to distend the uterine cavity at 100 mm Hg pressure. After hysteroscopy, an endometrial biopsy specimen was obtained with the use of a metal curette from the upper uterine cavity.

Histology and Immunohistochemistry

Endometrial samples were fixed in formalin and later embedded in paraffin for routine histologic analysis and immunohistochemistry. Five-micrometer sections were cut and incubated with mouse antihuman monoclonal CD138 antibody. The clone of anti-CD138 monoclonal antibody used in our study was MI15 Cell Marque (Biocare Medical). CD138-positive plasma cells were identified in the stroma. At least 50 high-power fields were examined per specimen. The biopsy specimens were graded as negative for CE if <1 plasma cell was identified per 10 HPF and positive when ≥ 1 plasma cell was identified per 10 HPF, according to published criteria (2, 12, 13). Mild CE was defined as plasma cell count <10 per 10 HPF and severe CE as plasma cell count ≥ 10 per 10 HPF. All endometrial biopsy specimens were examined by a single consultant histopathologist.

FIGURE 1



Subject participation, recruitment, randomization, and follow-up.

Song. Treatment of chronic endometritis. Fertil Steril 2020.

Antibiotic Therapy

Women who were randomized to the treatment group (group 1) were given oral levofloxacin 500 mg and tinidazole 1,000 mg daily for 14 days. Women who were randomized to the control group did not receive any antibiotic.

Second-Look Hysteroscopy and Endometrial Biopsy

All the hysteroscopies were performed in the follicular phase of the menstrual cycle. Recruitment and randomization took place within 2 to 4 weeks of the initial hysteroscopy when the results of the histologic analysis were discussed. For women randomized to the treatment arm, antibiotic therapy was commenced, and repeated hysteroscopy and biopsy for histopathologic CD138 immunohistochemical examination was scheduled 2 to 4 weeks after completion of antibiotic therapy. For women in the control arm, the second hysteroscopy and biopsy were scheduled to take place in the follicular phase of the following one or two cycles. At the second-look hysteroscopy, features of CE such as endometrial micropolyps, endometrial hyperemia, and edema were documented.

Statistical Methods

Comparison of results between the two groups was made by an independent-sample *t*-test for continuous variables and contingency table analysis for categoric variables. A *P* value

of $<.05$ was considered to be significant. The relative risk of various outcome measures was calculated. All statistical tests were two-sided. Statistical analysis was performed with SPSS for PC version 21 (2016).

RESULTS

A total of 132 subjects were randomized (Fig. 1). Eighteen subjects dropped out of the study for the following reasons: 12 declined participation despite initial consent, and 6 did not attend for second hysteroscopy and endometrial biopsy. At the end, 59 subjects in the treatment group and 55 subjects in the control group completed the study according to the protocol, and these 114 cases were included in the final analysis. The recruitment was conducted from July 2016 to July 2018, and the follow-up was completed in December 2018, after which the trial was stopped.

The demographic characteristics of the two groups are compared in Table 1. The age, body mass index, parity, and number of miscarriages were not significant different between the two groups. The findings of the second-look hysteroscopy are summarized in Supplementary Table 1. The presence of one or more features suggestive of CE in the control group was 32.7% (8/55), compared with 15% (9/59) in the antibiotic group; nevertheless, the difference was not significantly different ($P=.46$).

The CE rate of negative test results (from positive to negative) in the treatment group (53/59, 89.8%) after one course of antibiotic treatment was significantly ($P<.001$) higher than that in the control group (7/55,12.7%) (RR=7.06; 95% CI, 3.51–14.72) (Figure 2). By use of an intention-to-treat analysis, the CE rate of negative test results in the antibiotic treatment group (54/60, 90%) was significantly ($P<.001$) higher that in the control group (12/60, 20%) (RR=7.71; 95% CI, 3.83–15.56).

The relationship between the CE rate of negative test results and plasma cell count is analyzed in Table 2. Both the spontaneous and treatment-related rates of negative test results in women with plasma cell counts $<10/10$ HPF (mild group) (17.5% and 97.7%, respectively) was significantly ($P<.001$ and $P<.001$ respectively) higher than in those with plasma cell counts ≥ 10 per 10 HPF (severe group) (0% and 68.8%, respectively).

There were no adverse reactions to the antibiotic treatment and no complications resulting from hysteroscopy including significant bleeding, infection, or fluid absorption during the study. Among 48 women in the control group whose test results were still positive for CE at the end of their participation, 18 opted for a course of antibiotic treatment.

The reproductive outcome at the 12-month follow-up among women who attempted to conceive after completion of treatment is shown in Table 2. Among those who wished to conceive, there was no difference ($P=.46$) in conception rates between the treatment arm (48.6%) and the control arm (40%). Among subjects who attempted pregnancy, there was no significant difference ($P=.12$, $P=.38$) in ongoing pregnancy rates and miscarriage rates between the treatment arm (43.2%, 5.4%) and the control arm (25.7%, 14.3%) (RR=1.69, RR=0.38, respectively). Among subjects randomized, there was also no significant difference ($P=.16$, $P=.38$) in ongoing pregnancy rates and miscarriage rates between the treatment arm (27.1%, 3.4%) and the control arm (16.4%, 9.1%) (RR=1.66, RR=0.37, respectively).

DISCUSSION

In this study, we found that the CE cure rate after a 2-week course of antibiotics was 89.8% compared with a spontaneous cure rate of 12.7%.

CE is a condition characterized by the presence of plasma cells in the endometrial stroma (1), often assumed to be a consequence of an underlying chronic infection. There are several areas of controversy relating to the study of CE. First, regarding diagnosis, the result of traditional microbiologic

TABLE 1

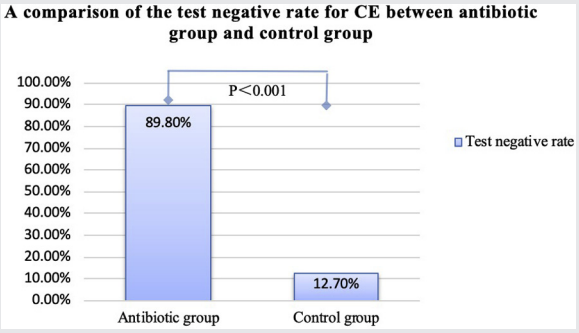
Demographic and clinical features of two groups of subjects with chronic endometriosis.

Characteristic	Treatment group (n = 59)	Control group (n = 55)	*P* value
Age (y)[a]	31.86 ± 4.7	31.93 ± 4.8	.94
BMI (kg/m^2)[a]	22.91 ± 3.4	22.28 ± 3.5	.33
Parity[a]	2.15 ± 0.9	2.15 ± 0.9	.97
Miscarriage[a]	1.59 ± 1.0	1.93 ± 1.0	.07
Presentation[b]			.74
Infertility	35	29	
Recurrent miscarriage	8	12	
AUB	9	8	
RIF	6	4	
Cervical incompetence	1	2	
Hysteroscopic CE features[b]			1.00
Hyperemia	21	20	
Micropolyp	2	1	
Interstitial edema	2	2	
None	34	32	

Note: Treatment group received antibiotic therapy; control group did not receive antibiotic therapy. No statistically significant differences were found between the treatment group and the control group. AUB = abnormal uterine bleeding, BMI = body mass index, CE = chronic endometriosis, RIF = recurrent implantation failure.
[a] Mean ± standard deviation, comparison by using independent-samples *t*-test.
[b] Comparison by using contingency table analysis.

Song. Treatment of chronic endometritis. Fertil Steril 2020.

FIGURE 2



Comparison of negative test result rates for chronic endometritis between antibiotic group and control group.

Song. Treatment of chronic endometritis. Fertil Steril 2020.

study is often negative (14) and therefore cannot be relied on to confirm the diagnosis. Hysteroscopic evaluation has been advocated by some investigators (15–18), but the diagnostic accuracy remains uncertain (12, 19). The majority of literature reports have based the diagnosis of the CE on the identification of plasma cells in the stroma of the endometrium by the use of immunohistochemistry using CD138 epitope (5, 13, 20–22), which so far remains the criterion standard for diagnosis. More recently, molecular microbiologic study or microbiome analysis of endometrial fluid or endometrial biopsy specimens has been reported as a more informative and accurate alternative (23–31), but its superiority over histologic assessment as the diagnostic method of choice has yet to be confirmed.

Another second area of controversy is the prevalence of CE in various gynecologic conditions. The reported prevalence of CE among different populations ranges from 9% to 56% in women with recurrent miscarriage (7, 19, 21, 32, 33) and from 14% to 57.3% in women with RIF (2, 8, 10, 11, 18, 19). The main underlying reason for the wide variation in reported prevalence relates to a lack of consensus in the diagnostic criteria used (2, 34).

Third, the treatment of CE is also controversial. Many investigators advocate the use of broad-spectrum antibiotic therapy for 2 weeks to treat the condition (7, 8, 35). Several antibiotics have been used, including doxycycline, metronidazole, ofloxacin, ciprofloxacin, amoxicillin/clavulanate, and ceftriaxone (7, 8, 10, 11). Many of the studies reported encouraging results, with cure rates ranging from 28% to 92.8% after one course of antibiotic treatment (3, 7, 8, 10, 11, 22, 36), but these reports were all based on cohort studies of a retrospective nature; so far there has not been any formal RCT to confirm the value of antibiotic treatment. In this RCT, we chose to use a combination of levofloxacin (500 mg/day) and tinidazole (1,000 mg/day) for 2 weeks based on the recommendation of an earlier study (7) and showed that this combination of antibiotics is effective in curing CE.

TABLE 2

Comparison of treatment-related and spontaneous conversion rate of CE (from positive to negative) according to severity of CE (mild or severe) between antibiotic group and control group and reproductive outcomes between two groups at 12-month follow-up.

Variable	Antibiotic group (n = 59)	Control group (n = 55)	*P* value (exact value)	Relative risk (95% CI)
CE conversion rate from positive to negative				
All cases	53/59	7/55	<.001	7.06 (3.51–14.18)
Mild CE	42/43	7/40	<.001	5.58 (2.84–10.96)
Severe CE	11/16	0/15	<.001	>10[a]
Reproductive outcome				
Lost to follow-up	3	5	.64	0.56 (0.14–2.23)
No desire to conceive (n)	19	15	.67	1.13 (0.65–1.98)
Attempted to conceive (n)	37	35	.67	0.94 (0.73–1.23)
Conception rate among those wishing to conceive (%)	48.6% (18/37)	40% (14/35)	.46	1.22 (0.72–2.05)
Miscarriage rate (per conception)	11.1% (2/18)	35.7% (5/14)	.20	0.31 (0.71–1.37)
Ongoing pregnancy rate per attempting pregnancy[b]	43.2% (16/37)	25.7% (9/35)	.12	1.68 (0.86–3.30)
Ongoing pregnancy rate per subject randomized[b]	27.1% (16/59)	16.4% (9/55)	.17	1.66 (0.80–3.44)
Miscarriage rate per attempting pregnancy	5.4% (2/37)	14.3% (5/35)	.38	0.38 (0.08–1.83)
Miscarriage rate per subject randomized	3.4% (2/59)	9.1% (5/55)	.38	0.37 (0.08–1.84)

Note: CE = chronic endometriosis, LB = live birth.
[a] Not possible to compute because of nil occurrence in control group.
[b] Including one LB in antibiotic arm.

Song. Treatment of chronic endometritis. Fertil Steril 2020.

Our observation in the control group also provided information on the spontaneous cure or resolution rate of CE, which was approximately 13% (7/55).

A possible limitation of our study is that patients were not blinded to the antibiotic treatment. Although we originally planned to conduct a double-blinded RCT trial, we encountered organizational difficulties that necessitated conversion to an open-labeled RCT. Nevertheless, the pathologist who assessed the biopsy specimens for features of CE was blinded to the treatment. A further limitation of our study relates to the inclusion of subjects with different presentations, which necessitated the choice of a laboratory-based primary endpoint, which was the cure rate based on a repeat of the test used to make the diagnosis, instead of a clinical endpoint such as pregnancy, miscarriage, or live birth. We had anticipated that the choice of a clinical primary endpoint, although more relevant to clinical practice, would require a much larger sample size with a more homogenous population. Nevertheless, the finding in the present study provides the scientific basis and justification to proceed with a further RCT with a clinically oriented primary endpoint.

It is concluded that a course of broad-spectrum oral antibiotic therapy for 14 days is effective in the treatment of CE in >89.8% of cases. However, it is not yet clear whether treatment improves pregnancy outcomes.

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Impacto del tratamiento antibiótico en la tasa de resultado negativo para endometritis crónica: un estudio prospectivo controlado aleatorizado.

Objetivo: Comparar las tasas de resultados negativos para endometritis crónica (CE) entre sujetos que recibieron y no recibieron tratamiento antibiótico.

Diseño: Ensayo ciego prospectivo controlado aleatorizado

Escenario: Centro de histeroscopia de tercer nivel en un hospital universitario

Paciente(s): Un total de 132 mujeres con CE confirmada por estudio inmunohistoquímico con epítope CD 138.

Intervención(es): Las mujeres en el grupo de tratamiento antibiótico recibieron levofloxacina 500 mg y tinidazol 1000 mg diarios por vía oral durante 14 días. Las mujeres aleatorizadas en el grupo control no recibieron ningún tratamiento. Se realizó biopsia endometrial de 4 a 8 semanas después de la biopsia inicial para determinar si la CE estaba todavía presente.

Medida(s) de Resultado Principal: tasa de resultado negativo para CE (de positivo a negativo).

Resultado(s): La tasa de resultado negativo para CE en el grupo tratamiento (89.3%) luego de un curso de tratamiento antibiótico fue significativamente mayor que en el grupo control (12.7%). Entre los sujetos que buscaban embarazo, no hubo diferencia significativa en la tasa de gestación evolutiva ni en la tasa de aborto entre la el grupo de tratamiento (43.2%, 5.4%) y el grupo control (25.7%, 14.3%). Entre los sujetos aleatorizados, tampoco hubo diferencia significativa en la tasa de gestación evolutiva y la tasa de aborto entre el grupo de tratamiento (27.1%, 3.4%) y el grupo control (16.4%, 9.1%).

Conclusión: Un curso de tratamiento antibiótico oral de amplio espectro durante 14 días es efectivo en el tratamiento de CE en >89.8% de los casos. Sin embargo, no está claro aún si el tratamiento mejora los resultados gestacionales.