scientific reports

Check for updates

OPEN

Risk factors of chronic endometritis in women who have undergone hysteroscopy: a prospective nested case–control study

Yun Gao[1,2], Gufeng Xu[1,2], Min Yang[1], Kaiting Chen[1] & Yue Wang[1]✉

There is limited research on risk factors for chronic endometritis regarding reproductive history and clinical symptoms. Thus, this nested case–control study identified risk factors for chronic endometritis in women who have undergone hysteroscopy. Endometrial tissue sections were obtained from 502 women with intrauterine disorders who underwent hysteroscopy. Chronic endometritis was diagnosed via CD138 immunostaining. The women were divided into two groups: 271 women without chronic endometritis and 231 women with chronic endometritis. The prevalence of chronic endometritis was 46%. Univariate logistic regression revealed that prolonged menstruation and intermenstrual bleeding were associated with chronic endometritis, and subsequent multivariate logistic regression analyses showed that these were further independently associated. With univariable logistic regression, the gravidity and abortion history were correlated with chronic endometritis; however, no significant correlation was found with the adjusted odds ratio (OR) of 0.74 (95% confidence interval [CI] 0.46–1.19) or 0.76 (95% CI 0.58–1.11), respectively. No significant correlation was found between caesarean section history and the rates of chronic endometritis. No significant difference was found in all other variables between the three groups with > 5, ≤ 5 plasma cells and in a unknown group. Prolonged menstruation and intermenstrual bleeding were risk factors associated with chronic endometritis. Chronic endometritis should be considered and CD138 immunohistochemical examination should be recommended in women with these symptoms.

Keywords Chronic endometritis, CD138, Prolonged menstruation, Intermenstrual bleeding

Chronic endometritis (CE), known as persistent inflammation of the uterine endometrium, is commonly neglected in clinical practice because of the absence of specific symptoms or characteristic ultrasound appearances[1,2]. In most cases, it has no symptoms or only mild ones, including abnormal uterine bleeding (AUB), pelvic discomfort, abnormal leukorrhea, or dyspareunia. Therefore, its prevalence in the general population remains unclear. The latest data mention prevalence rates between 15.6%[3] and 24.4%[4].The gold standard for diagnosing CE is the histological evidence of plasma cell infiltration in the endometrial stroma[5]. In the current study, CE was diagnosed when there was at least one plasma cell in each of the 10 non-overlapping random stromal sites. Although no agreement on the histological diagnosis standard of CE has been reached, most studies consider at least one plasma cell in the endometrial stroma sufficient to diagnose CE[5–9]. CE does not localize focally but spreads to encompass the whole endometrial stroma; hence, the absence of plasma cells in 10 non-overlapping random areas of the endometrium suggests that there were no plasma cells in the total endometrial stromal region. The latest research by McQueen et al.[24] compared different numbers of plasma cells as diagnostic criteria for CE. This study proposed that CE may be defined as the presence of one or more plasma cells per 10 HPFs detected via CD138 staining in the setting of endometrial stromal changes. This definition would serve to maximize the sensitivity and specificity while limiting false positives.

Currently, mounting research demonstrates that CE may adversely affect pregnancy outcomes or even be a considerable cause of recurrent implantation failure or recurrent pregnancy loss. CE was diagnosed in approximately 14–67.5% of patients who had recurrent implantation failure and 9.3–67.6% of patients who had recurrent pregnancy loss, which were higher than the overall prevalence rates[10]. Although clinical examination and

[1]Department of Ambulatory Surgery, Women's Hospital, Zhejiang University School of Medicine, No.1 Xueshi Road, Hangzhou 31000, China. [2]These authors contributed equally: Yun Gao and Gufeng Xu. ✉email: misswangyue@zju.edu.cn

transvaginal ultrasonography are nonspecific for CE, timely diagnosis and subsequent therapy with antibiotics can increase the likelihood of pregnancy and live birth[11–13].

Currently, multiple intrauterine polyps[14,15], endometriosis[2,16], and fibroids[17] are recognized risk factors for CE. However, there is limited research on the risk factors for CE with regard to reproductive history and clinical symptoms. Thus, in this study, we aimed to fill these gaps by analyzing the prevalence of CE and its associated risk factors regarding patient history and symptoms in patients with intrauterine disorders who underwent hysteroscopy.

Results

A total of 549 women were included in this study. After surgery, 37 women were excluded because of insufficient endometrial specimens, and 10 women were excluded due to receiving antibiotic treatment in the 3-month period before the procedure. Finally, 502 cases were included in the statistical analysis. Based on CD138 immunohistochemical results, they were divided into two groups: the non-CE group (NCE, n = 271) and CE group (CE, n = 231) (Fig. 1). The positive rate of CE was 46%. There were 65 patients with > 5 CD138-positive plasma cells, 119 patients with ≤ 5 CD138-positive plasma cells, and 47 patients who were reported as positive, though the number of CD138-positive plasma cells was not recorded.

The baseline characteristics of the two groups are shown in Table 1. Except for a significant difference in gravidity ($p = 0.031$), abortion history ($p = 0.018$), reason for hysteroscopy ($p < 0.001$) and prolonged menstruation ($p = 0.025$) between the two groups, the differences in all other variables were not statistically significant ($p > 0.05$).

Table 2 presents the univariate and multivariate logistic regression models used to assess the risk factors associated with CE. Gravidity, parity, abortion history, caesarean section history, prolonged menstruation, and intermenstrual bleeding were included in the univariate and multivariate analyses. The findings revealed that prolonged menstruation and intermenstrual bleeding were associated with CE, and subsequent multivariate logistic regression analysis showed that these were independently associated with CE. There was no significant correlation between caesarean section history and the rates of CE. Univariate logistic regression demonstrated that gravidity and abortion history were associated with CE. However, no significant correlation was found between gravidity, abortion history, and CE, with adjusted OR of 0.74. There was no significant difference in sampling phase between the two groups consistently (OR 0.95[0.62–1.46], OR 0.95[0.61–1.47]).

Table 3 illustrates no significant statistical difference in all other variables between the three groups with > 5, ≤ 5 plasma cells and in a unknown group.

Discussion

In the present study, prolonged menstruation and intermenstrual bleeding were correlated with CE prevalence (OR 1.72, 95% CI 1.07–2.78; OR 1.47, 95% CI 0.97–2.23, respectively) and also independently correlated with CE, which was consistent with several earlier reports[4,18]. Chen et al.[18] performed a study that included 93 women who were divided into two groups based on CD138 immunohistochemistry results: CE (n = 26) and non-CE (n = 67). They found that prolonged menstrual bleeding, abortion history, and fallopian tube obstruction were independent risk factors for CE. Song et al.[4] found that the incidence of CE in the AUB group (40.7%) was considerably higher than the overall prevalence (24%) in 1551 premenopausal women who underwent hysteroscopy. However, these studies either did not investigate the correlation between AUB and CE or had smaller sample sizes. Our study included patients undergoing hysteroscopic surgery, with their characteristics serving as potential confounders in our results due to varying reasons for surgery. We attempted to minimize these effects by adjusting for these confounding factors. The results of our study strongly suggest a correlation between prolonged menstruation, intermenstrual bleeding, and CE, and these should be considered as risk factors for CE. This finding carries significant clinical implications in light of the adverse effects of CE on pregnancy outcomes. To ensure timely diagnosis and treatment, for women experiencing prolonged menstruation or intermenstrual bleeding, it is essential to consider whether CE is associated and CD138 immunohistochemical examination should be taken after hysteroscopy.

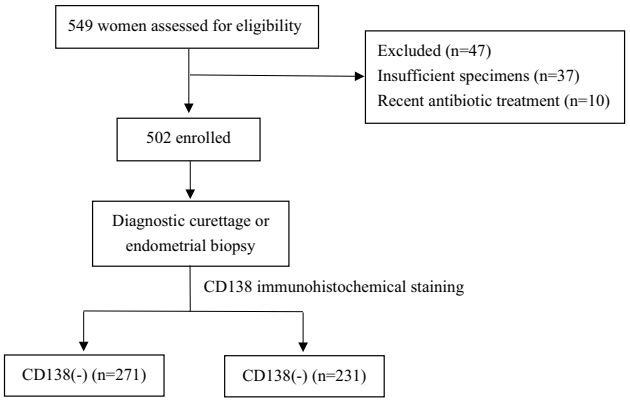

Figure 1. Flow diagram.

Variables	No chronic endometritis (n = 271)	Chronic endometritis (n = 231)	p-value
Age (year)	37.4 ± 8.5	36.0 ± 7.7	0.070
BMI (kg/m^2)	21.9 ± 3.1	21.9 ± 3.2	0.909
Gravidity			
0	53 (19.6%)	64 (27.7%)	0.031
≥ 1	218 (80.4%)	167 (72.3%)	
Parity			
0	95 (35.1%)	82 (35.5%)	0.918
≥ 1	176 (64.9%)	149 (64.5%)	
Abortion history			
Yes	152 (56.1%)	105 (45.5%)	0.018
No	119 (43.9%)	126 (54.5%)	
Caesarean section history			
Yes	76 (28.0%)	55 (23.8%)	0.282
No	195 (72.0%)	176 (76.2%)	
Sampling phase			
Proliferative	193 (71.2%)	175 (75.8%)	0.070
Secretory	57 (21.0%)	49 (21.2%)	
Undetermined	21 (7.7%)	7 (3.0%)	
No. CD138+			
0	271 (100.0%)	0 (0.0%)	< 0.001
≤ 5	0 (0.0%)	119 (51.5%)	
> 5	0 (0.0%)	65 (28.1%)	
Not specified	0 (0.0%)	47 (9.4%)	
Reason for hysteroscopy			
Uterine polyps	186 (68.6%)	186 (80.5%)	< 0.001
Intrauterine adhesion	43 (15.9%)	6 (2.6%)	
Cervical polyps	12 (4.4%)	12 (5.2%)	
Others[a]	30 (11.1%)	27 (11.7%)	
Prolonged menstruation			
Yes	35 (12.9%)	47 (20.3%)	0.025
No	236 (87.1%)	184 (79.7%)	
Intermenstrual bleeding			
Yes	54 (19.9%)	62 (26.8%)	0.067
No	217 (80.1%)	169 (73.2%)	

Table 1. Baseline characteristics. [a]Others: submucous myoma, uterine septum, pregnancy residue, and endometrial hyperplasia.

AUB may cause flora imbalances in the female reproductive tract, such as a decreased proportion of anaerobic *Lactobacillus* species, which may result in CE[19]. The association between CE diagnosis and the reproductive tract microbiome warrants further investigation. Furthermore, in this study, we found there was no significant difference in all other variables between the three groups with > 5, ≤ 5 plasma cells and in a unknown group, including prolonged menstruation (p = 0.595) and intermenstrual bleeding (p = 0.790). There was no significant difference in clinical variables between different degrees of CE. Future studies with a large sample and refined design are warranted to investigate this topic.

In our prospective analysis, a history of abortion, caesarean delivery, and gravidity were not identified as risk factors for CE. This was consistent with the study by Kitaya et al.[5] who found that caesarean delivery, abortion, miscarriage, or preterm delivery was not correlated with CE. However, this is still controversial since abortion[18] and caesarean history[19] were found to be possible risk factors for CE in other studies. Chen et al.[18] found that a history of abortion (p = 0.029; OR 3.194; 95% CI 1.125–9.073) was an independent risk factor for CE in 93 patients who were planning to undergo assisted conception treatment. Additionally, Yang et al.[19] found a lower *Lactobacillus*-dominating percentage and disrupted microbial flora in the caesarean section groups, which may be closely connected with CE and poor pregnancy outcomes in patients with post-caesarean section scar diverticulum. Further large-sample studies are required in the future.

In the present study, the prevalence of CE was 46%, which was higher than its prevalence in the general population in other studies[3,4]. All patients underwent hysteroscopy for intrauterine abnormalities, including endometrial polyps, cervical polyps, intrauterine adhesions, and submucosal fibroids. Most of these intrauterine diseases were linked to a notably higher prevalence of CE; the prevalence of CE in patients with endometrial and cervical polyps were both 50% (186/372, 12/24), and the prevalence of CE in other intrauterine diseases

	Univariate analysis OR (95% CI)	Multivariate analysis[a] OR (95% CI)
Gravidity		
0	Ref	Ref
≥ 1	0.63 (0.42–0.96)	0.74 (0.46–1.19)
Parity		
0	Ref	Ref
≥ 1	0.98 (0.68–1.42)	1.24 (0.79–1.96)
Sampling phase		
Proliferative	Ref	Ref
Secretory	0.95 (0.62–1.46)	0.95 (0.61–1.47)
Abortion history		
No	Ref	Ref
Yes	0.65 (0.46–0.93)	0.76 (0.58–1.11)
Caesarean section history		
No	Ref	Ref
Yes	0.80 (0.54–1.20)	0.77 (0.50–1.20)
Prolonged menstruation		
No	Ref	Ref
Yes	1.72 (1.07–2.78)	2.00 (1.21–3.29)
Intermenstrual bleeding		
No	Ref	Ref
Yes	1.47 (0.97–2.23)	1.58 (1.02–2.44)

Table 2. Risk factors for chronic endometritis. Data were n (%). [a]For gravidity, parity, abortion history, sampling phase and caesarean section history, ORs were adjusted for prolonged menstruation, intermenstrual bleeding, age, and reason for hysteroscopy; for prolonged menstruation, ORs were adjusted for gravidity, intermenstrual bleeding, age, and reason for hysteroscopy; for intermenstrual bleeding, ORs were adjusted for gravidity, prolonged menstruation, age, and reason for hysteroscopy.

	≤ 5	> 5	Unspecified	p value
Gravidity ≥ 1	81 (68.1%)	54 (83.1%)	32 (68.1%)	0.072
Parity ≥ 1	77 (64.7%)	45 (69.2%)	27 (57.4%)	0.436
Sampling at secretory phase	25 (21.0%)	14 (21.5%)	10 (21.3%)	0.996
Abortion history	48 (40.3%)	36 (55.4%)	21 (44.7%)	0.146
Caesarean section history	28 (23.5%)	15 (23.1%)	12 (25.5%)	0.951
Prolonged menstruation	22 (18.5%)	13 (20.0%)	12 (25.5%)	0.595
Intermenstrual bleeding	32 (26.9%)	19 (29.2%)	11 (23.4%)	0.790

Table 3. Presence of risk factors stratified by number of plasma cells. p value was calculated with Chi-square test.

was 47.3% (27/57), which included submucosal fibroids, uterine septum, pregnancy residue and endometrial hyperplasia. These findings were consistent with those of recent studies, which found that endometrial polyps[14,15], uterine fibroids[17], and endometrial hyperplasia[4] were associated with a higher prevalence of CE. Moreover, women with endometriosis[2,16] or retained pregnancy tissue[20] after miscarriage have a greater prevalence of CE.

The prevalence of CE in patients with intrauterine adhesions was 12.2% (6/49), which was not markedly different from the reported prevalence in the general population. This was consistent with the study by Song et al.[4], who found that the prevalence of CE in patients with intrauterine adhesions was 17.6% (72/408), which was not significantly different from the overall prevalence of the entire sample. However, in more recent investigations, intrauterine adhesions have been linked to a higher prevalence of CE. Kuroda et al.[21] found that the presence of intrauterine adhesions increased the risk of developing CE by 8.85-fold. Liu et al.[22] reported that CE had a higher frequency (46%) in patients with moderate and severe intrauterine adhesions. Additionally, Chen et al.[23] found that the recurrence rate of intrauterine adhesions in women with CE (13/29, 44.8%) was substantially higher than that of those without CE (11/53, 20.8%). The size of the biopsy specimens may affect the accuracy of the immunohistochemistry staining, it is acknowledged that biopsies typically provides lesser tissue in comparison to endometrial curettage. Endometrial biopsies were taken from multiple sites to ensure adequate endometrial sampling in this study. In this study, endometrial samples were obtained via biopsy in patients with intrauterine

adhesions instead of diagnostic curettage to avoid additional damage to the endometrium, which may be a contributing factor for the lower CE incidence.

In addition to pathological diagnosis, according to Orestis[24] and Mahvash[25], hysteroscopy can be used to diagnose CE by detecting the presence of micropolyposis, stromal oedema, localized or diffuse hyperaemia and the 'strawberry aspect'. The negative diagnostic criterion is the absence of any of these hysteroscopic features observed during hysteroscopy. Orestis[24] included 2675 patients who underwent outpatient hysteroscopy to test the validity of these hysteroscopic features, the results suggested that in all subpopulations, micropolyposis combined with "strawberry aspect", stromal oedema and/or diffuse or focal hyperaemia are the most accurate hysteroscopic features of Chronic endometritis. In recent studies, it was found that a negative diagnostic hysteroscopy for the presence of CE was adequate to rule out CE, without the use of histologic confirmation[24,26,27]. Furthermore, Yang et al.[28] found that patients with negative of CE "signs" in hysteroscopy had greater IVF success compared to those with no residual plasma cells in CD138 immunohistochemistry. Therefore, the importance of hysteroscopy in the diagnosis of CE should be emphasized as an add-on technique for the diagnosis of CE, particularly as a useful tool for ruling out CE. Strict diagnostic criteria for hysteroscopy and immunopathology are vital and require further investigation.

In recent studies, it has been found that CE can interfere with normal implantation by decreasing receptivity of the endometrium and modifying the beneficial pattern of uterine contractility[29]. The recommended treatment for CE is 100 mg doxycycline for two weeks, and adequate response to antibiotic therapy may significantly improve reproductive outcomes[29–31]. Furthermore, a recent systematic review and meta-analysis revealed that various degrees of CE severity may exert a different effect on in vitro fertilization (IVF) outcomes. Negative effects of CE on IVF outcome may be restricted to severe disease (≥ 5 plasma cells/HPF), whereas mild CE (1–4 plasma cells/HPF) may be non-harmful for embryo implantation[32].However, further randomized controlled trials on IVF patients are still necessary, and strict diagnostic criteria for immunopathology are vital and require further investigation.

This study is not without limitations. First, the follow-up period of our study was too short to observe subsequent pregnancy outcomes in CE patients with the desire for future pregnancy. Second, although the sample size was larger than that in some previous studies, we believe that a larger sample size would enhance the power of this study. Third, our study included patients with intrauterine disorders; hence, their characteristics may serve as potential confounders in our results due to varying reasons for surgery, and our conclusions may not be applicable to the general population. Fourth, endometrial samples were obtained via different method in patients with intrauterine adhesions, which may be a contributing factor.

In conclusion, prolonged menstruation and intermenstrual bleeding were identified as risk factors for CE in women who have undergone hysteroscopy in this nested case–control study. The prevalence of CE in these women was higher than its prevalence in the general population. Considering the unsatisfactory reproductive outcomes in women with CE, CD138 immunohistochemical examination should be considered in women with prolonged menstruation or intermenstrual bleeding. Prospective randomized controlled trials in the future are required to investigate the effectiveness of antibiotic treatment and pregnancy outcomes following antibiotic treatment.

Methods

Study design

This prospective nested case–control study was conducted at the Women's Hospital, Zhejiang University School of Medicine, China. All patients who underwent hysteroscopy at our Day Surgery Center were recruited into the hysteroscopy cohort. Patients were excluded after surgery if endometrial specimens could not be obtained or if they received antibiotic treatment in the 3-month period prior to the procedure. The recruitment period for the hysteroscopy cohort was between May 31, 2022, and July 31, 2022. The diagnosis of CE was based on the presence of one or more plasma cells in 10 non-overlapping random stromal areas. The cell was regarded to be a CD138 + plasma cell if it displayed complete, unambiguous, brown staining with intact cell membranes after CD138 immunohistochemical staining. Based on histologic diagnosis, patients were categorized into two groups, which were defined as patients with CE and patients without CE.

This study was approved by the hospital's institutional review board (IRB-20220173-R). All participants provided written informed consent, and the study was conducted in conformity with the principles of the Declaration of Helsinki.

Patient information

Baseline patient data, including age, body mass index, gravidity, parity, abortion history, reason for hysteroscopy, caesarean section history, and symptoms (prolonged menstruation and intermenstrual bleeding) were obtained upon admission.

Hysteroscopic procedure

All the patients underwent hysteroscopic surgery via 10 mm, 30° forward-oblique hysteroscopy with a unipolar/bipolar electrosurgical loop, except for patients with intrauterine adhesion, who accepted a 4 mm, 30° fore-oblique viewing scope with cold scissors. To prime the cervix, 40 mg of phloroglucinol was administered intravenously 30 min prior to surgery. During surgery, prudent dilatation of the cervix was maintained by using Hegar dilators if necessary, and 5% glycine or 0.9% saline solution was used as an irrigating fluid. No preoperative treatment was used.

Sample collection and CD138 immunostaining

Endometrium was collected via diagnostic curettage or endometrial biopsy prior to the surgical procedure. For fixation, tissue was submerged immediately in 10% neutral formaldehyde. The tissue was dehydrated using an ethanol gradient and then cleaned with xylene. After the tissue had been embedded using paraffin, serial slices of 4 μm were cut from it. The presence of plasma cells, as indicated by CD138 immunohistochemical staining, was considered a positive CE diagnosis[5,33]. In brief, mouse monoclonal antibody clone GR106 against human Syndecan-1 (Gene Technology, Shanghai) was incubated on slides for an entire night at 4 °C. The secondary rabbit anti-mouse horseradish peroxidase-labeled antibody ab97046 (Abcam, UK) was then applied to the slides and incubated for an additional hour. CD138 + plasma cells were counted under a light microscope (400-fold magnification, a high-powered field; HPF). The diagnosis of chronic endometritis was confirmed about 7 days post-surgery.

Statistical analysis

IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Data for each group are presented as the mean (standard deviation), and proportions are presented as percentages. Univariate logistic regression models were constructed to determine the risk factors for CE. Odds ratios (ORs) and their 95% confidence intervals were calculated. A p-value of < 0.05 or confidence intervals that did not cross 1 were considered statistically significant. Multivariable logistic regression models were constructed to adjust for confounders. For gravidity, parity, abortion history, and caesarean section history, ORs were adjusted for prolonged menstruation, intermenstrual bleeding, age, and reason for hysteroscopy. For prolonged menstruation, ORs were adjusted for gravidity, intermenstrual bleeding, age, and reason for hysteroscopy; and for intermenstrual bleeding, ORs were adjusted for gravidity, prolonged menstruation, age, and reason for hysteroscopy.

Ethics approval and consent to participate

This study was approved by Institutional Review Boards of Women's Hospital Zhejiang University School of Medicine (IRB-20220173-R). All participants provided written informed consent.

Data availability

We have placed the database upon Mendeley Data (https://doi.org/10.17632/7y72w6sxph.1) and provided in section Availability of data and materials.

Received: 7 December 2023; Accepted: 31 July 2024
Published online: 05 August 2024

References

1. Kitaya, K., Takeuchi, T., Mizuta, S., Matsubayashi, H. & Ishikawa, T. Endometritis: New time, new concepts. *Fertil. Steril.* **110**(3), 344–350. https://doi.org/10.1016/j.fertnstert.2018.04.012 (2018) (**Epub 2018/07/02**).
2. Cicinelli, E. *et al.* Higher prevalence of chronic endometritis in women with endometriosis: A possible etiopathogenetic link. *Fertil. Steril.* **108**(2), 289–951. https://doi.org/10.1016/j.fertnstert.2017.05.016 (2017) (**Epub 2017/06/19**).
3. Adegboyega, P. A., Pei, Y. & McLarty, J. Relationship between eosinophils and chronic endometritis. *Hum. Pathol.* **41**(1), 33–37. https://doi.org/10.1016/j.humpath.2009.07.008 (2010) (**Epub 2009/10/06**).
4. Song, D. *et al.* Prevalence and confounders of chronic endometritis in premenopausal women with abnormal bleeding or reproductive failure. *Reprod. Biomed. Online.* **36**(1), 78–83. https://doi.org/10.1016/j.rbmo.2017.09.008 (2018) (**Epub 2017/11/08**).
5. Kitaya, K. *et al.* Chronic endometritis: Potential cause of infertility and obstetric and neonatal complications. *Am. J. Reprod. Immunol.* **75**(1), 13–22. https://doi.org/10.1111/aji.12438 (2016) (**Epub 2015/10/20**).
6. Crum, C. P., Egawa, K., Fenoglio, C. M. & Richart, R. M. Chronic endometritis: The role of immunohistochemistry in the detection of plasma cells. *Am. J. Obstet. Gynecol.* **147**(7), 812–815. https://doi.org/10.1016/0002-9378(83)90045-5 (1983).
7. McQueen, D. B. *et al.* Redefining chronic endometritis: The importance of endometrial stromal changes. *Fertil. Steril.* **116**(3), 855–861. https://doi.org/10.1016/j.fertnstert.2021.04.036 (2021) (**Epub 2021/06/15**).
8. Kasius, J. C. *et al.* The reliability of the histological diagnosis of endometritis in asymptomatic IVF cases: A multicenter observer study. *Hum. Reprod.* **27**(1), 153–158. https://doi.org/10.1093/humrep/der341 (2012) (**Epub 2011/10/26**).
9. Chisholm, C. & Lopez, L. *Arch. Pathol. Lab. Med.* **135**(10), 1357–1362. https://doi.org/10.5858/arpa.2010-0156-RS.Review (2011).
10. Huang, W. *et al.* Variation of diagnostic criteria in women with chronic endometritis and its effect on reproductive outcomes: A systematic review and meta-analysis. *J. Reprod. Immunol.* **140**, 103146. https://doi.org/10.1016/j.jri.2020.103146 (2020) (**Epub 2020/05/23**).
11. Xiong, Y. *et al.* Impact of oral antibiotic treatment for chronic endometritis on pregnancy outcomes in the following frozen-thawed embryo transfer cycles of infertile women: A cohort study of 640 embryo transfer cycles. *Fertil. Steril.* **116**(2), 413–421. https://doi.org/10.1016/j.fertnstert.2021.03.036 (2021) (**Epub 2021/05/01**).
12. Mitter, V. R. *et al.* Treatment following hysteroscopy and endometrial diagnostic biopsy increases the chance for live birth in women with chronic endometritis. *Am. J. Reprod. Immunol.* **86**(5), e13482. https://doi.org/10.1111/aji.13482 (2021) (**Epub 2021/07/05**).
13. Zhang, Y. *et al.* Confirmation of chronic endometritis in repeated implantation failure and success outcome in IVF-ET after intrauterine delivery of the combined administration of antibiotic and dexamethasone. *Am. J. Reprod. Immunol.* **82**(5), e13177. https://doi.org/10.1111/aji.13177 (2019) (**Epub 2019/08/03**).
14. Peng, J. *et al.* Endometrial polyp is associated with a higher prevalence of chronic endometritis in infertile women. *Int. J. Gynaecol. Obstet.* https://doi.org/10.1002/ijgo.14207 (2022).
15. Guo, L. *et al.* Multiple endometrial polyps is associated with higher risk of chronic endometritis in reproductive-aged women. *J. Obstet. Gynaecol. Res.* **47**(1), 389–396. https://doi.org/10.1111/jog.14541 (2021) (**Epub 2020/12/11**).
16. Takebayashi, A. *et al.* The association between endometriosis and chronic endometritis. *PLoS One.* **9**(2), e88354. https://doi.org/10.1371/journal.pone.0088354 (2014) (**Epub 2014/02/22**).
17. Kabodmehri, R. *et al.* The association between chronic endometritis and uterine fibroids. *J. Fam. Med. Prim. Care.* **11**(2), 653–659. https://doi.org/10.4103/jfmpc.jfmpc_1470_21 (2022) (**Epub 2022/04/02**).
18. Chen, Y. Q., Fang, R. L., Luo, Y. N. & Luo, C. Q. Analysis of the diagnostic value of CD138 for chronic endometritis, the risk factors for the pathogenesis of chronic endometritis and the effect of chronic endometritis on pregnancy: A cohort study. *BMC Womens Health.* **16**(1), 60. https://doi.org/10.1186/s12905-016-0341-3 (2016) (**Epub 2016/09/07**).

19. Yang, X. *et al.* Microbial flora changes in cesarean section uterus and its possible correlation with inflammation. *Front. Med. (Lausanne).* **8**, 651938. https://doi.org/10.3389/fmed.2021.651938 (2021) (**Epub 2021/12/10**).
20. McQueen, D. B. *et al.* Retained pregnancy tissue after miscarriage is associated with high rate of chronic endometritis. *J. Obstet. Gynaecol.* https://doi.org/10.1080/01443615.2022.2100693 (2022) (**Epub 2022/08/04**).
21. Kuroda, K. *et al.* Prevalence of and risk factors for chronic endometritis in patients with intrauterine disorders after hysteroscopic surgery. *Fertil. Steril.* https://doi.org/10.1016/j.fertnstert.2022.05.029 (2022) (**Epub 2022/06/20**).
22. Liu, L., Yang, H., Guo, Y., Yang, G. & Chen, Y. The impact of chronic endometritis on endometrial fibrosis and reproductive prognosis in patients with moderate and severe intrauterine adhesions: A prospective cohort study. *Fertil. Steril.* **111**(5), 1002–1102. https://doi.org/10.1016/j.fertnstert.2019.01.006 (2019) (**Epub 2019/03/30**).
23. Chen, Y. *et al.* Prevalence and impact of chronic endometritis in patients with intrauterine adhesions: A prospective cohort study. *J. Minim. Invasive Gynecol.* **24**(1), 74–79. https://doi.org/10.1016/j.jmig.2016.09.022 (2017) (**Epub 2016/10/25**).
24. Tsonis, O., Gkrozou, F., Dimitriou, E. & Paschopoulos, M. Hysteroscopic detection of chronic endometritis: Evaluating proposed hysteroscopic features suggestive of chronic endometritis. *J. Gynecol. Obstet. Hum. Reprod.* **50**(9), 102182. https://doi.org/10.1016/j.jogoh.2021.102182 (2021) (**Epub 2021/06/11**).
25. Zargar, M., Ghafourian, M., Nikbakht, R., Mir Hosseini, V. & Moradi, C. P. Evaluating chronic endometritis in women with recurrent implantation failure and recurrent pregnancy loss by hysteroscopy and immunohistochemistry. *J. Minim. Invasive Gynecol.* **27**(1), 116–121. https://doi.org/10.1016/j.jmig.2019.02.016 (2020) (**Epub 2019/03/10**).
26. Gkrozou, F., Tsonis, O., Dimitriou, E. & Paschopoulos, M. In women with chronic or subclinical endometritis is hysteroscopy suitable for setting the diagnosis? A systematic review. *J. Obstet. Gynaecol. Res.* **46**(9), 1639–1650. https://doi.org/10.1111/jog.14360 (2020) (**Epub 2020/06/25**).
27. Cicinelli, E., Cicinelli, R. & Vitagliano, A. Consistent evidence on the detrimental role of severe chronic endometritis on in vitro fertilization outcome and the reproductive improvement after antibiotic therapy: On the other hand, mild chronic endometritis appears a more intricate matter. *Fertil. Steril.* **116**(2), 345–346. https://doi.org/10.1016/j.fertnstert.2021.06.022 (2021) (**Epub 2021/07/14**).
28. Yang, R. *et al.* The hysteroscopy and histological diagnosis and treatment value of chronic endometritis in recurrent implantation failure patients. *Arch. Gynecol. Obstet.* **289**(6), 1363–1369. https://doi.org/10.1007/s00404-013-3131-2 (2014) (**Epub 2014/01/08**).
29. Puente, E. *et al.* Chronic endometritis: Old problem, novel insights and future challenges. *Int. J. Fertil. Steril.* **13**(4), 250–256. https://doi.org/10.22074/ijfs.2020.5779 (2020).
30. Johnston-MacAnanny, E. B. *et al.* Chronic endometritis is a frequent finding in women with recurrent implantation failure after in vitro fertilization. *Fertil. Steril.* **93**(2), 437–441. https://doi.org/10.1016/j.fertnstert.2008.12.131 (2010) (**Epub 2009/02/17**).
31. Cicinelli, E. *et al.* Prevalence of chronic endometritis in repeated unexplained implantation failure and the IVF success rate after antibiotic therapy. *Hum. Reprod.* **30**(2), 323–330. https://doi.org/10.1093/humrep/deu292 (2015) (**Epub 2014/11/12**).
32. Vitagliano, A. *et al.* Chronic endometritis in infertile women: Impact of untreated disease, plasma cell count and antibiotic therapy on IVF outcome-a systematic review and meta-analysis. *Diagnostics (Basel).* https://doi.org/10.3390/diagnostics12092250 (2022).
33. Margulies, S. L. *et al.* The diagnostic criteria for chronic endometritis: A survey of pathologists. *Int. J. Gynecol. Pathol.* **40**(6), 556–562. https://doi.org/10.1097/PGP.0000000000000737 (2021) (**Epub 2020/12/17**).

Author contributions

Y.G. was responsible for design of the work, acquisition, analysis and interpretation of data, and drafting the manuscript. G.F.X. was responsible for design of the work, analysis of data, and revising the manuscript critically for crucial intellectual content. M.Y. and K.T.C. were responsible for analysis of data, revising it critically for important intellectual content. Y.W. was responsible for design of the work, acquisition, analysis and interpretation of data, and revising the manuscript critically for crucial intellectual content. All authors read and approved the final manuscript.

Funding

This work was supported by the Natural Science Foundation of Zhejiang Province under Grant LGF22H040011; the Health Commission of Zhejiang Province under Grant 2022KY857; and the Zhejiang Provincial Department of Education under Grant Y202146852.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to Y.W.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.