



2023

## Prevalence of Chronic Endometritis in Unexplained Implantation Failure

Hossamuddin Hussein Kamel

*1Department of Obstetrics & Gynecology, Faculty of Medicine - Al-Azhar University, Egypt*

Shokry Abdul-Azeem El-Awady El-Shershaby

*Department of Obstetrics & Gynecology, International Islamic Center for Population Studies and Research, Al-Azhar University, Egypt*

Asem Anwar Abdou Moussa

*Department of Obstetrics & Gynecology, Faculty of Medicine - Al-Azhar University, Egypt*

Ibrahim Hassan Mohammad Youssef

*Department of Pathology, Faculty of Medicine - Al-Azhar University, Egypt*

Mohammad El-Sayed El-Saadany Mahmoud

*Department of Obstetrics & Gynecology, Faculty of Medicine - Al-Azhar University, Egypt,*  
dr\_elsadany@yahoo.com

Follow this and additional works at: <https://aimj.researchcommons.org/journal>



Part of the [Medical Sciences Commons](#), [Obstetrics and Gynecology Commons](#), and the [Surgery Commons](#)

### How to Cite This Article

Kamel, Hossamuddin Hussein; El-Shershaby, Shokry Abdul-Azeem El-Awady; Moussa, Asem Anwar Abdou; Youssef, Ibrahim Hassan Mohammad; and Mahmoud, Mohammad El-Sayed El-Saadany (2023) "Prevalence of Chronic Endometritis in Unexplained Implantation Failure," *Al-Azhar International Medical Journal*: Vol. 4: Iss. 2, Article 19.

DOI: <https://doi.org/10.58675/2682-339X.1673>

This Original Article is brought to you for free and open access by Al-Azhar International Medical Journal. It has been accepted for inclusion in Al-Azhar International Medical Journal by an authorized editor of Al-Azhar International Medical Journal. For more information, please contact [dryasserhelmy@gmail.com](mailto:dryasserhelmy@gmail.com).

# Prevalence of Chronic Endometritis in Unexplained Implantation Failures

Hossamuddin Hussein Kamel <sup>a</sup>, Shokry Abdul-Azeem El-Awady El-Shershaby <sup>c</sup>,  
Asem Anwar Abdou Moussa <sup>a</sup>, Ibrahim Hassan Mohammad Youssef <sup>b</sup>,  
Mohammad El-Sayed El-Saadany Mahmoud <sup>a,\*</sup>

<sup>a</sup> Department of Obstetrics and Gynecology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

<sup>b</sup> Department of Pathology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

<sup>c</sup> ART Unit, International Islamic Center for Population Studies and Research, Al-Azhar University, Cairo, Egypt

## Abstract

**Background:** The actual load of chronic endometritis (CE) in the general population and implantation failure are still ill-defined.

**Aim:** The aim of the study was to assess the incidence of CE at hysteroscopy and histology, in cases with implantation failure at Intracytoplasmic Sperm Injection (ICSI).

**Patients and methods:** The International Islamic Center for Population Studies and Research at Al-Azhar University performed this prospective observational cross-sectional research from 2017 to 2022. The study was conducted on 150 women with one unexplained implantation failure or more at ICSI.

**Results:** Histopathological examination confirmed the diagnosis of CE in 55/66 cases suspected to have CE by hysteroscopy (true positive), while 11 cases were found to be free from CE (false positive). However, histopathological examination confirmed the absence of CE in 82/84 negative cases by hysteroscopy (true negative), while only two cases were found to have CE (false negative). In our study, hysteroscopy is the trustworthy CE diagnostic method for CE in unexplained implantation failure with sensitivity, specificity, accuracy, positive predictive value, and negative predictive value such as 96.5, 88.17, 91.3, 83.3, and 97.6%, respectively.

**Conclusion:** According to this research, hysteroscopy is a useful diagnostic tool in women with unexplained implantation failure as regards CE diagnosis. However, endometrial samples should be obtained during hysteroscopy to increase the diagnostic accuracy.

**Keywords:** Chronic endometritis, In-vitro fertilization, Unexplained implantation failure

## 1. Introduction

Uterine anatomic anomalies, thrombophilia, nonreceptive endometrium, and immunological variables are some of the maternal reasons for implantation failures.<sup>1</sup>

Ultrasound and Hysterosalpingography (HSG) cannot identify chronic endometritis (CE), a subtle condition that is often asymptomatic or only accompanied by modest abnormalities. The gold standard for the diagnosis is histological detection

of plasma cells in the endometrial stroma; however, even this method might miss the diagnosis because of the common presence of leukocytes in the endometrium, particularly before menstruation.<sup>2</sup>

In 30.3% of patients who had had recurrent ICSI implantation failure, CE was found.<sup>3</sup> In contrast, Kasius et al.<sup>2</sup> revealed that the results of ICSI cycles' reproductive processes were not adversely impacted by CE.

The aim of the research was to evaluate the effects of CE on implantation failure at ICSI through its

Accepted 7 September 2022.

Available online 15 May 2023

\* Corresponding author at: Department of Obstetrics and Gynecology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt.  
E-mail address: [dr\\_elsadany@yahoo.com](mailto:dr_elsadany@yahoo.com) (M.E.-S.E.-S. Mahmoud).

<https://doi.org/10.58675/2682-339X.1673>

2682-339X/© 2023 The author. Published by Al-Azhar University, Faculty of Medicine. This is an open access article under the CC BY-SA 4.0 license (<https://creativecommons.org/licenses/by-sa/4.0/>).

prevalence at hysteroscopy and histology, in cases with implantation failure.

## 2. Patients and methods

The International Islamic Center for Population Studies and Research at Al-Azhar University performed this prospective observational cross-sectional research from 2017 to 2022.

The research included 150 women who had ICSI and had at least one unexplained implantation failure due to infertility.

### 2.1. Inclusion criteria

Age less than 40 years, documented history of excellent quality embryos transplanted in one or more prior ICSI cycles without evidence of implantation, absence of any abnormalities at transvaginal ultrasound and at HSG.

### 2.2. Exclusion criteria

Day 3 Follicle Stimulating Hormone (FSH) of more than 10 mUI/ml, BMI (kilograms per square meter) greater than 30 kg/m<sup>2</sup>, a history of clinically recurring miscarriages, surgery for endometriosis or myoma, ovarian endometriomas, corticosteroid use, or other medical procedures known to suppress the immune system, chromosomal rearrangements in either parent, antiphospholipid syndrome, thrombophilia needing anticoagulant medication, unwillingness to provide informed consent, and any known clinical autoimmune or other chronic general disorders.

After informed written consent, all patients included in this study have been subjected to the following:

History taking, clinical evaluation, and investigations: Investigational studies included (a) routine laboratory investigation: complete blood count, prothrombin time and activity, liver function, kidney function, blood sugar, etc. (b) Basic investigations for male and female infertility including Transvaginal Sonography (TVS) and folliculometry, HSG, hormonal profile of the lady, FSH, Luteinizing Hormone (LH), E2, Thyroid-Stimulating Hormone (TSH), prolactin and AMH, and semen analysis for the husband.

Diagnostic hysteroscopy and an endometrial biopsy: patients who met the requirements for inclusion were referred for hysteroscopy. While the cycle was in the proliferative stage, it was performed under general anesthesia (between days 6 and 12). A

sample of the endometrium was obtained and submitted for histopathology analysis.

### 2.3. Diagnostic hysteroscopy

A 4-mm-diameter diagnosis sheath with an atraumatic tip on a rigid hysteroscope (Karl Storz Endoscopy, Tuttlingen, Germany) was used. The uterine cavity was light with a high-intensity cold light source and fiber-optic wire. To employ the lowest pressure necessary to sufficiently distend the uterine cavity, normal saline (0.9%) was used as the distention medium, with the pressure being maintained between 100 and 120 mm Hg. According to previously published research, micropolyps (<1 mm in size), stromal edema, and localized or diffuse hyperemia were used to make the diagnosis of CE.<sup>4,5</sup>

### 2.4. Histological examination of an endometrial sample

For histological analysis, endometrial tissues were first fixed in neutral formalin and then embedded in paraffin. A senior pathologist evaluated 5 µm sections that had been stained with hematoxylin-eosin but not told about previous hysteroscopic examinations. The existence of superficial stromal edema, elevated stromal density, and pleomorphic stromal inflammatory infiltration dominated by lymphocytes and plasma cells have all been used to make the histological diagnosis of CE.<sup>6</sup>

### 2.5. Ethical considerations

Al-Azhar University Faculty of Medicine's Ethics Committee gave its approval to this work. All patients provided their written, signed permission. There are adequate provisions to maintain the privacy of participants and the confidentiality of data.

### 2.6. Sample size calculation

The sample size was calculated by the IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp with an  $\alpha$ -error of 0.05, 80% power, and 80% confidence interval. The prevalence of the disease was 66%, which was in agreement with a previous study that had the same objective and research question.<sup>7</sup> Also, the design effect was one and the population size was 100 000 during the calculation. So, the sample size was 148 cases.

## 2.7. Statistical analysis

The SPSS Windows version 28 program was used in this study to analyze the data. For univariable analysis, the data were expressed in numbers and percentages for qualitative data, while in quantitative parametric data after testing of normality using skewness score, kurtosis score, and the normality graphs as the histogram and box plot; the mean  $\pm$  SD was used for normal parametric data, while the median and interquartile range were used for the nonparametric one. For bivariate analysis and for hypothesis testing  $\chi^2$ -test was used for nonparametric value relationships to determine the level of significance when more than 25% of the cells in tables with more than two groups have a count of less than 5. The Monte–Carlo test is used as a correction for the  $\chi^2$ -test, and Fischer's exact test was used within the two groups. However, *t*-test, analysis of variance, and Pearson's correlation test were also used for quantitative data significance. The statistical significance correlation is reached if the *P* value is less than 0.05. The study included a measure of sensitivity for hysteroscopy in the diagnosis of chronic endometritis. Sensitivity: probability that a test result was positive when the disease is present (true positive rate, expressed as a percentage). Sensitivity=(true positive)/(true positive)+(false negative). Specificity: The likelihood that a test would come back negative if the illness were not present (true negative rate, expressed as a percentage). Specificity=(true negative)/(true negative)+(false positive). Positive predictive value (PPV) refers to the likelihood that a disease will be present when a test is positive (expressed as a percentage of true positive cases to all positive). PPV=(true positive)/(true positive)+(false positive). When a test results in a negative result, the likelihood that the illness is absent is known as negative predictive value (NPV) (given as a ratio of all negative subjects to actual negative subjects). NPV=(true negative)/(true negative)+(false negative). Significant association results if the *P* value is less than 0.05.

## 3. Results

The 150 women who participated in this cross-sectional research had experienced one or more unexplained implantation failures. The final results are as follows.

**Table 1** shows that 59.3% of cases are at or below 30 years old. Mean  $\pm$  SD is 30.56  $\pm$  4.33 years.

**Table 2** shows that 69.3% of cases have primary infertility.

**Table 3** shows that 46% of cases had implantation failure once, while 54% of cases experienced at least two unexplained implantation failures [repeated implantation failure (RIF)].

**Table 4** shows that there is a strong, statistically highly substantial connection between the presence of CE and unexplained implantation failure (*P* = 0.000). Among cases with histopathologically confirmed CE (*n* = 57), 23 cases and 34 cases experienced single implantation failure and RIF, respectively. However, out of the cases without CE (*n* = 93), 46 and 47 cases gave a documented history of single implantation failure and RIF, respectively.

**Table 5** shows that there is no significant difference among cases with or without endometritis according to residence.

**Table 6** shows that there is no significant difference among cases with or without CE as regards the type of infertility.

**Fig. 1** shows that 64 cases have hyperemia during hysteroscopy, which represents 96.9% of hysteroscopically diagnosed cases as having CE (64/66). However, biopsies from these cases are also positive for CE in only 53 cases (53/57).

**Fig. 2** shows that 53 cases have stromal edema during hysteroscopy, which represents 80.3% of hysteroscopically diagnosed cases as having CE (53/

Table 1. Description of the whole sample cases according to age.

Age groups	N (%)
≤30 years	89 (59.3)
>30 years	61 (40.7)
Mean $\pm$ SD	30.56 $\pm$ 4.33 years
Minimum age	23 years old
Maximum age	39 years old

Table 2. Distribution of cases according to the type of infertility.

	Frequency	%
Infertility type		
Primary	104	69.3
Secondary	46	30.7
Total	150	100

Table 3. Number of implantation failures among the whole sample cases.

	N (%)
Failed implantation	
Single	69 (46)
Repeated	81 (54)
Total	150 (100)
Number of failed previous implantation (mean $\pm$ SD)	3.02 $\pm$ 1.34

Table 4. Relationship between implantation failure and chronic endometritis.

	Failed implantation		Total	$\chi^2$	P value
	Single (n)	Repeated (n)			
Chronic endometritis by biopsy					
Chronic endometritis	23	34	57	21.1	0.000
No chronic endometritis	46	47	93		
Total	69	81	150		

Table 5. Difference between cases according to residence.

	Residence		Total	$\chi^2$	P value
	Rural (n)	Urban (n)			
Chronic endometritis				0.88	0.758
Chronic endometritis	28	29	57		
No chronic endometritis	48	45	93		
Total	76	74	150		

Table 6. Relationship between chronic endometritis and type of infertility.

	Primary (n)	Secondary (n)	Total (n)	$\chi^2$	P value
Endometritis by biopsy				10.1	0.452
Chronic endometritis	39	18	57		
No chronic endometritis	65	28	93		
Total	104	46	150		

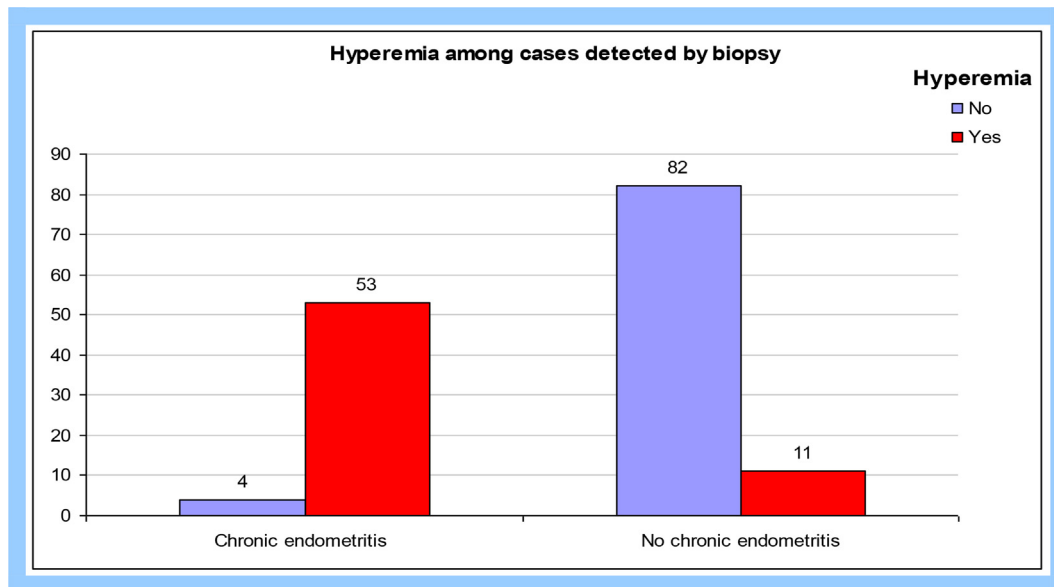


Fig. 1. Distribution of hyperemia as a finding by hysteroscopy among cases after histopathological examination.

66). Biopsies from all these cases are also positive for CE (53/57).

Fig. 3 shows that 39 cases have endometrial micropolys during hysteroscopy, which represents 59% of hysteroscopically diagnosed cases as having

CE (39/66). Biopsies from all these cases are also positive for CE (39/57).

Table 7 shows hysteroscopy is a trustworthy CE diagnostic method in unexplained implantation failures with sensitivity, specificity, accuracy,

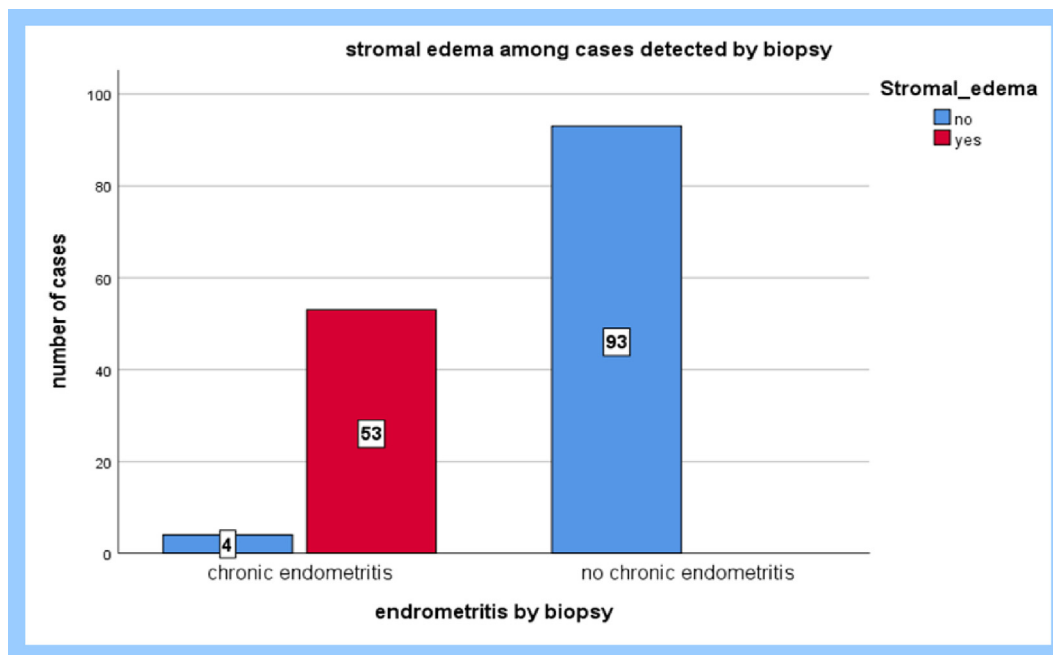


Fig. 2. Distribution of stromal edema as a finding by hysteroscopy among cases, after histopathological examination.

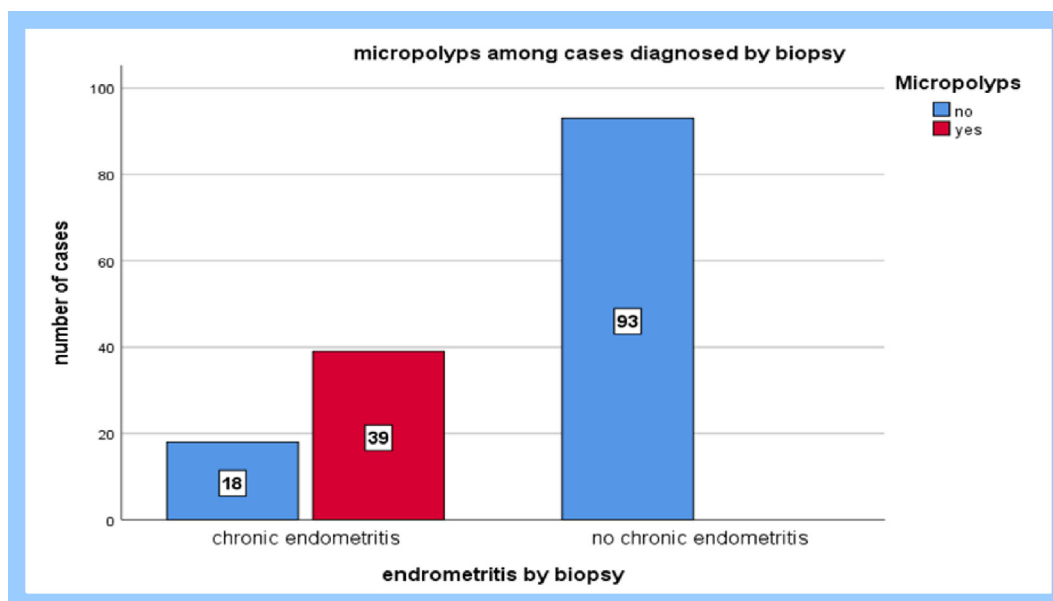


Fig. 3. Distribution of micropolyps as a finding by hysteroscopy among cases, after histopathological examination.

PPV, and NPV of 96.5, 88.17, 91.3, 83.3, and 97.6% respectively.

#### 4. Discussion

This cross-sectional, observational research was carried out at Al-Azhar University's ART division of the International Islamic Center for Population Studies and Research. It used hysteroscopy and

endometrial biopsy to look for CE in inexplicable implantation failure. We included 150 infertile females with a documented history of one or more unexplained implantation failures.

In our research, median and SD age is  $30.5 \pm 4.33$  years. The mean BMI of the included cases was  $25.4 \pm 3.53$  kg/m<sup>2</sup>, as ladies with a BMI of more than 30 kg/m<sup>2</sup> were not included.

Table 7. Describe the degree of sensitivity and specificity of hysteroscopy in comparison with the biopsy histological examination which is the gold standardized test applied in our study.

	By biopsy		Total
	No chronic endometritis	Chronic endometritis	
Hysteroscopy			
No chronic endometritis	82 (TN)	2 (FN)	84
Chronic endometritis	11 (FP)	55 (TP)	66
Total	93	57	150
Sensitivity (%)		96.5	
Specificity (%)		88.17	
Accuracy (%)		91.3	
PPV (%)		83.3	
NPV (%)		97.6	

FN, false negative cases; FP, false positive cases; NPV, negative predictive value; PPV, positive predictive value; TN, true negative cases; TP, true positive cases.

Although 44% of our sample cases are diagnosed by hysteroscopy as having CE (66/150), the prevalence of CE in our study by histopathological examination is 38% (57/150). There was no significant difference among cases with or without CE according to residence, level of education, or type of infertility. The current research, however, showed that there is a strong, statistically highly substantial relationship between CE and unexplained implantation failure ( $P = 0.000$ ). Among cases with histopathologically confirmed CE ( $n = 57$ ), 23 cases and 34 cases experienced single implantation failure and RIF, respectively. However, out of the cases without CE ( $n = 93$ ), 46 and 47 cases have single implantation failure and RIF, respectively.

We agree with Espinós et al.<sup>8</sup> who advised to test for CE in cases of RIF. Kitaya et al.<sup>9</sup> found the incidence of CE in RIF as 33.7%.

Kimura et al.<sup>10</sup> reported that the incidence of CE ranges from 2.8 to 56.8% in infertile women and from 14 to 67.5% in women with RIF.

Also, we agree with Agrawal et al.<sup>11</sup> who found that 33.3% of infertile women using ART have CE.

In our study, histopathological examination confirmed the diagnosis of CE in 55/66 cases suspected to have CE by hysteroscopy (true positive), while 11 cases were found to be free of CE (false positive). However, histopathological examination confirmed the absence of CE in 82/84 negative cases by hysteroscopy (true negative), while only two cases were found to have CE (false negative). In the current research, hysteroscopy has sensitivity, specificity, accuracy, PPV, and NPV as 96.5, 88.17, 91.3, 83.3, and 97.6%, respectively, in the diagnosis of CE.

Previous studies have reported that by enabling the identification of micropolyps (<1 mm in size), stromal edema, and localized or diffuse hyperemia,

hysteroscopy may aid in CE detection.<sup>4,5,12</sup> All of these signs were reported by our study.

A recent study has found that to diagnose CE, hysteroscopy's sensitivity, specificity, PPV, and NPV were 86.36, 87.30, 70.37, and 94.82%, respectively.<sup>13</sup>

However, Song et al.<sup>14</sup> recommended that the recommended technique of diagnosis should still be the immunohistochemical examination of plasma cells from endometrial biopsies.<sup>14</sup>

#### 4.1. Conclusion

The study shows that women who report inexplicable implantation failure after ICSI often have CE, particularly those who have had recurrent failures. Besides, according to this research, hysteroscopy may help with CE diagnosis in women who have unexplained implantation failure. However, endometrial samples should be obtained during hysteroscopy to increase the diagnostic accuracy.

#### Conflicts of interest

None declared.

#### References

- Salim R, Ben-Shlomo I, Colodner R, Keness Y, Shalev E. Bacterial colonization of the uterine cervix and success rate in assisted reproduction: results of a prospective survey. *Hum Reprod.* 2002;17:337–340.
- Kasius JC, Fatemi HM, Bourgain C. The impact of chronic endometritis on reproductive outcome. *Fertil Steril.* 2011;96:1451–1456.
- Quaas A, Dokras A. Diagnosis and treatment of unexplained infertility. *Rev Obstet Gynecol.* 2008;1:69–76.
- Cicinelli E, Resta L, Nicoletti R, Tartagni M, Marinaccio M, Bulletti C. Detection of chronic endometritis at fluid hysteroscopy. *J Minim Invasive Gynecol.* 2005;12:514–518.
- Cicinelli E, Tinelli R, Colafoglio G, Saliani N, Pastore A. Tubercular endometritis: a rare condition reliably detectable with fluid hysteroscopy. *J Minim Invasive Gynecol.* 2008;15:752–754.
- Cicinelli E, De Ziegler D, Nicoletti R, Tinelli R, Saliani N, Resta L. Poor reliability of vaginal and endocervical cultures for evaluating microbiology of endometrial cavity in women with chronic endometritis. *Gynecol Obstet Invest.* 2009;68:108–115.
- Cicinelli E, Matteo M, Tinelli R, Lepera A, Alfonso R, Indraccolo U. Prevalence of chronic endometritis in repeated unexplained implantation failure and the IVF success rate after antibiotic therapy. *Hum Reprod.* 2015;30:323–330.
- Espinós JJ, Fabregues F, Fontes J, García-Velasco JA, Llácer J, Requena A. Impact of chronic endometritis in infertility: a SWOT analysis. *Reprod Biomed Online.* 2021;42:939–951.
- Kitaya K, Matsubayashi H, Takaya Y, Nishiyama R, Yamaguchi K, Takeuchi T. Live birth rate following oral antibiotic treatment for chronic endometritis in infertile women with repeated implantation failure. *Am J Reprod Immunol.* 2017;78, e12719.
- Kimura F, Takebayashi A, Ishida M, Nakamura A, Kitazawa J, Morimune A. Chronic endometritis and its effect on reproduction. *J Obstet Gynaecol Res.* 2019;45:951–960.
- Agrawal H, Reddy N, Vembu R, Pandurangi M, Nagireddy S. Effect of antibiotic treatment for chronic endometritis on art cycle outcome. *Fertil Steril.* 2021;116:e312.

12. Kumar A, Kumar A. Hysteroscopic markers in chronic endometritis. *J Minim Invasive Gynecol.* 2017;24:1069–1070.
13. Zargar M, Ghafourian M, Nikbakht R, Mir Hosseini V, Moradi Choghakabodi P. Evaluating chronic endometritis in women with recurrent implantation failure and recurrent pregnancy loss by hysteroscopy and immunohistochemistry. *J Minim Invasive Gynecol.* 2020;27:116–121.
14. Song D, Li TC, Zhang Y, Feng X, Xia E, Huang X. Correlation between hysteroscopy findings and chronic endometritis. *Fertil Steril.* 2019;111:772–779.