Original article
Ginecol Obstet Mex 2024; 92 (3): 85-93.

https://doi.org/10.24245/gom.v92i3.8811

Prevalence of chronic endometritis in infertile women by evaluative hysteroscopy and endometrial biopsy with CD138.

Prevalencia de endometritis crónica en mujeres infértiles establecida mediante histeroscopia y biopsia endometrial con CD138

Álvaro Ramos-Reyes[1], Álvaro Martín Ramos Alvarado,[2] Demi Estefanía Domínguez Valdes,[3] Arturo Martínez Muñoz,[4] Juan Francisco Nuncio Zamora[5]

Abstract

OBJECTIVE: To determine the prevalence of chronic endometritis in patients with infertility by evaluative hysteroscopy and endometrial biopsy, with histological analysis of the endometrium, and identification of plasma cells by immunohistochemistry with positive CD138.

MATERIALS AND METHODS: Observational, retrospective study performed from March 2016 to November 2021 at the Center for Assisted Reproduction of Saltillo (CREAS), Coahuila, Mexico, with patients who consulted for infertility. Chronic endometritis was diagnosed by hysteroscopy and endometrial biopsy with CD138 immunohistochemistry. The prevalence and diagnostic accuracy of hysteroscopy and endometrial biopsy were analyzed. The association between specific hysteroscopic features and chronic endometritis confirmed by CD138-positive endometrial biopsy was also investigated.

RESULTS: The prevalence of chronic endometritis by CD138-positive endometrial biopsy in the 170 patients studied was 36% (n = 62), and by hysteroscopy 48.8% (n = 83), the latter with a sensitivity of 48.3%, specificity of 50.9%, positive and negative predictive values of 36.1 and 63.2%, respectively. In relation to hysteroscopic features, endometrial hyperemia had a statistically significant relationship with the prevalence of chronic endometritis (p-value = 0.008; OR = 0.357; 95%CI: 0.14-0.81), and with ≥ 2 features suggestive of chronic endometritis (p-value = 0.015; OR = 3.63; 95%CI: 1.15-12.69).

CONCLUSIONS: It is important to exclude chronic endometritis in the diagnostic process of infertile patients. It is crucial to use diagnostic tools such as hysteroscopy, and to confirm the diagnosis by endometrial biopsy with positive CD138 immunohistochemistry, in order to guide treatment.

KEYWORDS: Chronic endometritis; Diagnostic hysteroscopy; Endometrial biopsy with CD138; Infertility.

Resumen

OBJETIVO: Determinar, mediante histeroscopia de evaluación y biopsia de endometrio, con análisis histológico endometrial e identificación de células plasmáticas con inmunohisdtoquímica con CD138 positiva, la prevalencia de endometritis crónica en pacientes infértiles.

MATERIALES Y MÉTODOS: Estudio observacional, retrospectivo, efectuado de marzo de 2016 a noviembre del 2021 en el Centro de Reproducción Asistida de Saltillo (CREAS), Coahuila, México, en pacientes que consultaron por infertilidad. El diagnóstico de endometritis crónica se estableció mediante histeroscopia y biopsia de

[1] Fourth year Obstetrics and Gynecology resident, Tecnológico de Monterrey's Medical Specializations Multicenter Program, Nuevo Leon, Mexico.
[2] Reproduction Biologist, Medical Director of Assisted Reproduction Center (CREAS), Saltillo, Coahuila, Mexico.
[3] Third year Obstetrics and Gynecology resident, Tecnológico de Monterrey's Medical Specializations Multicenter Program, Nuevo Leon, Mexico.
[4] Reproduction Biologist, Medical Subdirector of Assisted Reproduction Center (CREAS), Saltillo, Coahuila, Mexico.
[5] Anatomopathologist, chief of Pathological Anatomy Department, La Concepción Hospital Center, Saltillo, Coahuila, Mexico.

Received: May 2023
Accepted: February 2024

Correspondence
Álvaro Ramos Reyes
alvaroramos.2210@gmail.com

This article should be cited as: Ramos-Reyes A, Ramos-Alvarado A, Domínguez-Valdes DE, Martínez-Muñoz A, Nuncio-Zamora JF. Prevalencia de endometritis crónica en mujeres infértiles mediante histeroscopia y biopsia endometrial con CD138. Ginecol Obstet Mex 2024; 92 (3): 85-93.

endometrio con inmunohistoquímica CD138. Se analizaron la prevalencia y precisión diagnóstica de la histeroscopia y la biopsia de endometrio. Además, la relación entre las características histeroscópicas específicas y la endometritis crónica confirmada por biopsia con CD138 positiva.

RESULTADOS: La prevalencia de endometritis crónica por biopsia de endometrio CD138 positiva en las 170 pacientes estudiadas fue de 36% (n = 62) y por histeroscopia del 48.8% (n = 83), esta última con una sensibilidad del 48.3%, especificidad del 50.9%, valor predictivo positivo y negativo del 36.1 y 63.2%, respectivamente. En relación con las características histeroscópicas, la hiperemia endometrial tuvo una relación estadísticamente significativa con la prevalencia de endometritis crónica (p-value = 0.008; RM = 0.357; IC95%: 0.14-0.81) y con ≥ 2 características sugerentes de endometritis crónica (p-value = 0.015; RM = 3.63; IC95%: 1.15-12.69).

CONCLUSIONES: En el procedimiento diagnóstico de la paciente infértil es importante descartar la endometritis crónica. Para ello es decisivo recurrir a herramientas diagnósticas, como la histeroscopia y confirmar el diagnóstico con una biopsia de endometrio con inmunohistoquímica CD138 positiva para que de esta manera pueda dirigirse el tratamiento.

PALABRAS CLAVE: Endometritis crónica; histeroscopia diagnóstica; biopsia de endometrio con CD138; Infertilidad.

BACKGROUND

The endometrium is part of the reproductive system where the blastocyst is implanted. The participating factors in this process are variable and can be disturbed by multiple conditions.[1] Damaging processes to the endometrium, and their repercussion on infertility are an ever-growing research field. One of these conditions is chronic endometritis, which is a persistent inflammatory disease of the endometrial mucosa, characterized by the coexistence of plasma cells (B-cell subpopulations) in the endometrial stroma.[2] The symptoms of this disease are very heterogenous because among the different clinical manifestations are abnormal uterine hemorrhage, chronic pelvic pain, and leucorrhea. Despite this, there isn't a unified diagnostic criterion for the physical or ultrasound exploration that allows the identification of relevant data to confirm diagnosis.

Among the different diagnostic methods available are: 1) hysteroscopy, 2) histology, 3) microbial culture, and 4) endometrium molecular biology. The disadvantage is that there are controversial outcomes, even in the same patient.[3] The first two methods are the ones with more research about them, and also the ones most frequently used in clinical practice. With hysteroscopy it is possible to obtain images of endometrium lesions that can suggest the diagnosis of chronic endometritis. However, only a biopsy of the endometrium with CD138 immunohistochemistry staining (or syndecan-1) and plasma cell identification, unlike staining only with hematoxylin-eosin, allows for a correlation between histology-hysteroscopy findings to provide the certainty of the disease.[4]

Endometrium B-cells (uterine lymphocyte subpopulations) from the basal layer are usually no more than 2% of the total human healthy endometrium cells.[5] In chronic endometritis, a large

https://doi.org/10.24245/gom.v92i3.8811

number of plasma cells infiltrates the functional and basal layers of the endometrium.[6] The antigen CD138 is a transmembrane sulfate heparin proteoglycan that expresses relatively specifically in plasma cells; that's why it is used as its marker, and its expression is useful for the diagnosis of chronic endometritis.[7] It can be identified by using the monoclonal antibody of CD138 by immunohistochemistry.[8] Also, as a marker, it tends to yield high specificity and sensibility, besides reducing inter- and intra-observer variability.[9] There still isn't any established consensus about the number of necessary plasma cells to diagnose chronic endometritis.[10]

The objective of the present study was to determine the prevalence of chronic endometritis in patients with infertility evaluated by hysteroscopy and endometrium biopsy, with endometrium histology and immunohistochemistry for the identification of plasma cells with positive CD138.

MATERIALS AND METHODS

Observational, retrospective study carried out from March 2016 to November 2021, at the Assisted Reproduction Center (CREAS) with patients who consulted for infertility. All the patients, as part of the chronic endometritis diagnostic protocol, had a hysteroscopy done for evaluation, and an endometrium biopsy was also taken, for immunohistochemistry and plasma cell identification (CD138). *Exclusion criteria*: patients with any type of uterine bleeding, or menstruation, pregnancy, vaginal or cervical active infection, and those who were on antibiotic treatment.

Hysteroscopy

It was performed in the proliferative phase, with anesthesia-sedation, or with local cervical anesthesia. It was an outpatient procedure, with a uterine cavity distension physiological solution, and a hysteroscopy (Karl Storz Hopkins II), with a 30° telescope, from 2.9 mm to 30 cm. During the study, different data of the endometrium cavity condition were recorded with hysteroscopic vision by close observation of the anterior, posterior, and side walls, and the ostium and cervical conduct. An endometrium biopsy for pathologic anatomy was taken with a Pipelle cannula.

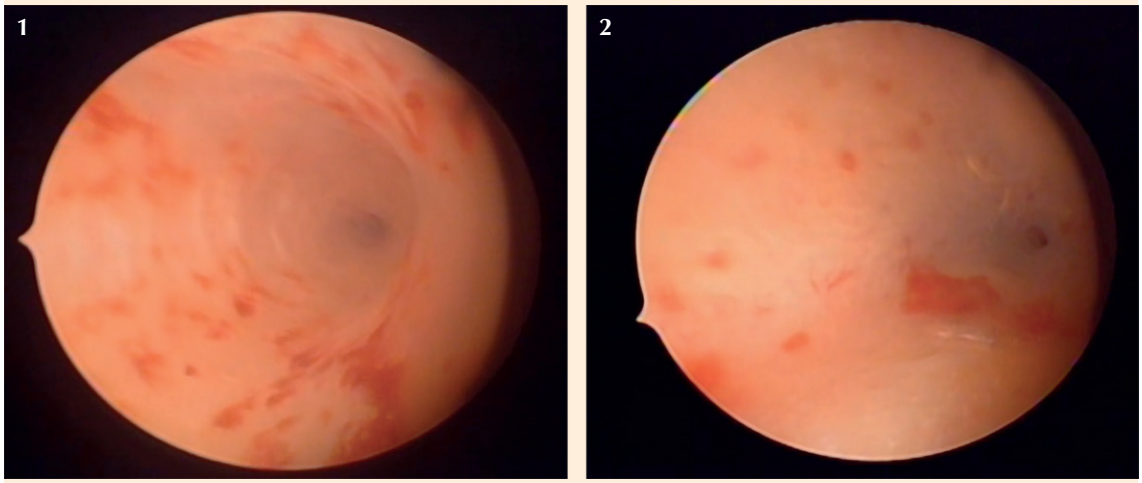
The characteristics of positive chronic endometritis by hysteroscopy, similar to those used in recent studies[11,12] were: 1) endometrium hyperemia: focal or diffuse hyperemic lesions (**Figures 1 to 5**); 2) micropolyps (**Figure 6**), and 3) raspberry-like lesions. **Figure 7**

Histology and immunohistochemistry

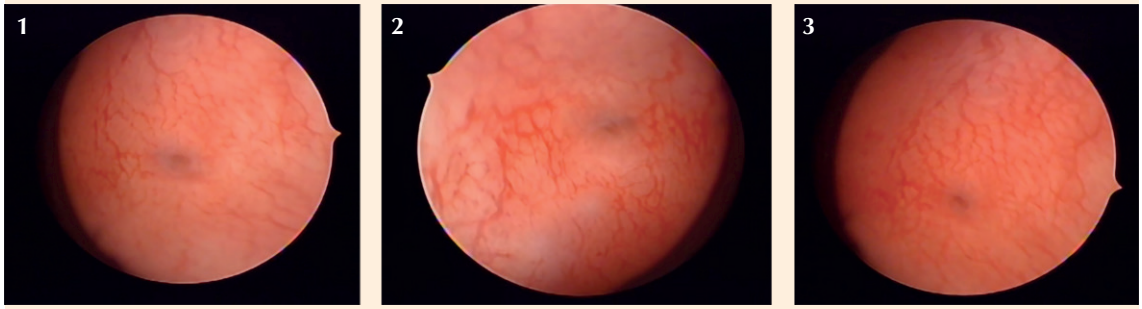
The endometrium samples were fixed in formaldehyde and stained with immunohistochemistry coloring for CD138 (syndecan-1). (**Figure 8**) The reactive used in the pathology lab is CD138/syndecan-1 (B-A38) Mouse Monoclonal Antibody, according to the supplier specifications (Merck) for a preparation similar to what's published in the literature.[13] Biopsies were considered negative for chronic endometritis when ≤ 2 plasma cells were identified in 10 high power fields, and positive when ≥ 3 plasma cells were identified in 10 high power fields of the ranges described.[10]

Statistical analysis

Sensibility, specificity, and predictive positive and negative values were determined, after specific hysteroscopic forms for the diagnosis of chronic endometritis. The results were compared with the $CD138^{+}$ endometrial biopsy (reference pattern). The relationship between hysteroscopic characteristics, infertility, and chronic endometritis was analyzed, according to the biopsy report, to verify the correlation with Fisher's exact bilateral test, and a level of significance of 95%. To group patients with similar hysteroscopic characteristics, five hysteroscopic groups were



Figures 1-2. Focalized hyperemic lesions.



Figures 3-5. Diffuse hyperemic lesions (augmented vascularity).

made. The statistical analysis was made with Excel and SPSS.

RESULTS

The results of 170 patients were obtained: 95 (55.8%) patients had primary infertility, and 75 (44.1%) had secondary infertility. The age average was 32.9 ± 4.5 years. The body mass index was 27.1 ± 4.9. The length of infertility was 3.3 ± 2.2 years.

The prevalence of chronic endometritis, with CD138+ immunohistochemistry diagnosis was 36.4% (n = 62). (**Table 1**) The chronic endometritis diagnosis, established by hysteroscopy, was

https://doi.org/10.24245/gom.v92i3.8811

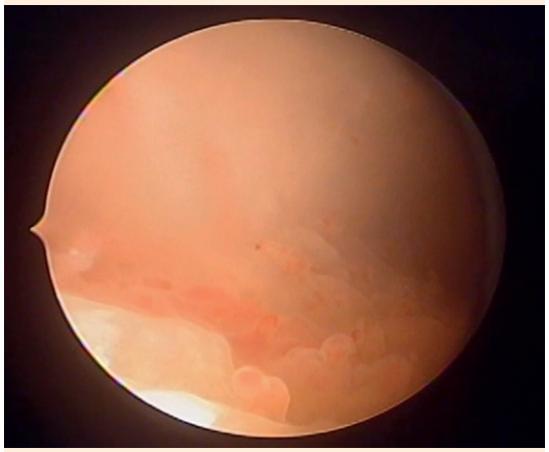


Figure 6. Micropolyps.

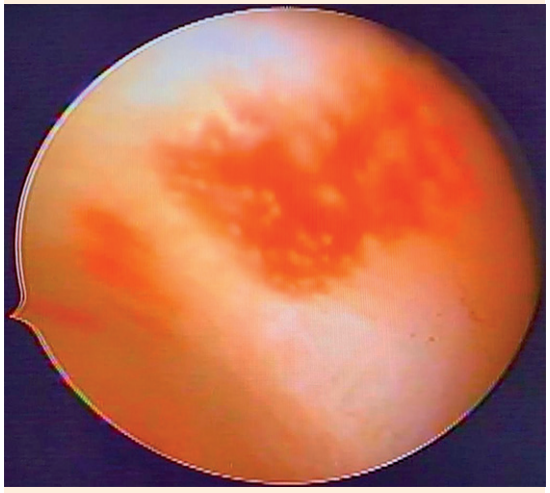


Figure 7. Raspberry-like lesion.

suspected in 83 (48.8%) of the 170 patients, based on the mentioned diagnostic criteria. Thirty (36.1%) of these patients were confirmed with the CD138+ endometrial biopsy report. The hysteroscopy had normal uterine cavity findings in 87 cases (51.1%); however, in 32 (36.7%) cases,

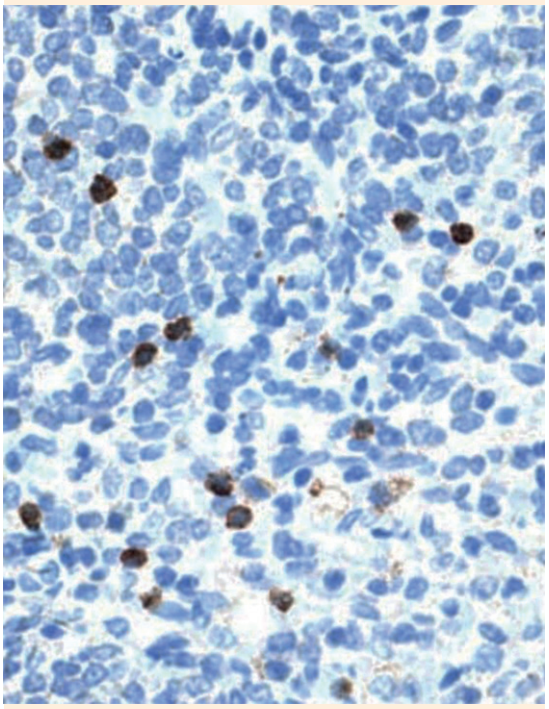


Figure 8. Endometrial biopsy with CD138+ plasma cells (10 cells x 10 high power fields).

chronic endometritis was diagnosed based on the CD138+ biopsy. **Table 2**

The chronic endometritis diagnosis by hysteroscopy, in correlation with the results obtained by CD138+ endometrial biopsy was: sensibility 48.3%, specificity 50.9%, positive predictive value 36.1%, and negative predictive value 63.2%.

The hysteroscopic characteristic findings and their incidences were: polyps in 12.9% (n = 22), hyperemia in 28.2% (n = 48), septate uterus in 8.8% (n = 15), micropolyps in 9.4% (n = 11), unilateral tubal ostium stenosis in 20% (n = 34), raspberry-like lesions in 4.1% (n = 7), and fibroids in 2.3% (n = 4).

Table 1. Demographic data and prevalence of chronic endometritis

	Total population	Primary infertility	Secondary infertility
Patients	170	95 (55.8%)	75 (44.1%)
Age (mean ± standard deviation)	32.9 ± 4.5	32.8 ± 4.1	33.4 ± 4.9
BMI	27.1 ± 4.9	26.9 ± 5.1	27.3 ± 4.7
Length of infertility (years)	3.3 ± 2.2	3.3 ± 2.2	3.29 ± 2.3
Prevalence (CD138+)	62 (36.4%)	35 (36.8%)	27 (36.0%)

Table 2. Chronic endometritis. Hysteroscopic-histologic correlation (CD138)

N =170	Biopsy CD138+	Biopsy CD138 -
Hysteroscopy with positive clinical data for CE N = 83	30 (36.1%)	53 (63.8%)
Hysteroscopy with negative clinical data for CE N = 87	32 (36.7%)	55 (63.2%)

After the analysis made to the 5 hysteroscopic groups, (**Table 3**) hyperemia was found (group 2) to have a statistically significant relation with chronic endometritis prevalence, confirmed by CD138+ endometrial biopsy (p value = 0.008; OR = 0.357; CI95%: 0.14-0.81), and the coexistence of ≥ characteristics among hyperemia, micropolyps, and raspberry-like lesions (group 5, p value = 0.015; OR = 3.63; CI95%: 1.15-12.69). **Table 4**

DISCUSSION

The diagnostic value of hysteroscopy in the present study had 48.3% sensibility, and 50.9% specificity, positive predictive value of 36.1%,

Table 3. Hysteroscopic findings and CD138+ according to age, gestation, type of infertility, and subjacent pathology

	Group 1: Without chronic endometritis	Group 2: Endometrial hyperemia	Group 3: Endometrial micropolyps	Group 4: Raspberry-like lesions	Group 5: Two or more characteristics	CD 138+
Age group						
≤30	16 (18.3%)	22 (45.9%)	3 (27.2%)	0 (0%)	8 (47.1%)	21 (33.9%)
>30	71 (81.7%)	26 (54.1%)	8 (72.8%)	7 (100%)	9 (52.9%)	41 (66.1%)
Gestation						
0	42 (48.2%)	29 (60.4%)	9 (81.8%)	5 (71.4%)	10 (58.9%)	35 (56.4%)
1	22 (25.3%)	9 (18.8%)	1 (9.1%)	1 (14.3%)	4 (23.5%)	11 (17.8%)
≥2	23 (26.5%)	10 (20.8%)	1 (9.1%)	1 (14.3%)	3 (17.6%)	16 (25.8%)
Type of infertility						
Primary	43 (49.4%)	29 (60.4%)	9 (81.8%)	4 (57.1%)	10 (58.9%)	35 (56.4%)
Secondary	44 (50.6%)	19 (39.6%)	2 (18.2%)	3 (42.9%)	7 (41.1%)	27 (43.6%)

https://doi.org/10.24245/gom.v92i3.8811

Table 4. Correlation between hysteroscopic findings, subjacent pathology, and chronic endometritis (CD138+)

Variable	p-value	OR	CI (95%)	p-value <0.05
Hysteroscopic group				
Group 1	1	1.03	0.52-2.01	NO
Group 2	0.008	0.357	0.14-0.81	YES
Group 3	0.21	2.19	0.53-9.53	NO
Group 4	0.21	1.32	0.18-8.09	NO
Group 5	0.015	3.63	1.15-12.69	YES
Type of infertility				
Primary	1	1.04	0.52-2.05	NO
Secondary	1	1	0.51-1.97	NO

Group 1: without chronic endometritis; Group 2: hyperemia; Group 3: micropolyps; Group 4: raspberry-like lesions; Group 5: two or more characteristics.

and negative predictive value of 63.2%. These percentages are within the limits of statistical reports from other publications.

A retrospective study with 2675 patients reported a prevalence of chronic endometritis of 53.9%, with diagnostic criteria of stroma edema, diffuse or focal hyperemia, raspberry-like lesions, and micropolyps, similar to those of our sstudy.[14] The lack of consensus for the hysteroscopic characteristics of chronic endometritis is reflected in the literature because the range of sensibility and specificity goes from 35.2 to 91.8%, and 67.5 to 99.9%, respectively.[15,16,17] Another very similar retrospective study, with 1189 cases of hysteroscopy with CD138 biopsy, found a prevalence of chronic endometritis by hysteroscopy of 38.2%, with a sensibility of 59.3%, and specificity of 69.7%.[18] These results highlight the need of doing the CD138 endometrial biopsy to confirm diagnosis. The similitude of the results points to the promotion of the use of both tools for an adequate diagnosis of chronic endometritis.

We found in this study that hyperemia, and ≥ 2 characteristics among hyperemia, micropolyps, and raspberry-like lesions, had a statistically significant relationship with the prevalence of chronic endometritis, confirmed by CD138+. The evidence raises controversy about the criterion for hyperemia in itself as a predictor of the disease, because there are studies that support, and studies that don't support the association.[19,20] However, the coexistence of ≥ 2 to 3 characteristics in multiple studies has been described as a highly suggesting criterion of confirmation by hysteroscopy.[11,12,14,18,21]

The limited diagnostic sensibility and specificity of hysteroscopy can be due to the learning curve and the experience of the operator, to be able to recognize the kind of lesion that represents a real alteration of the endometrium, together with the lack of consensus for the diagnostic criteria.

The application of the CD138+ marker as diagnostic criterion was considered positive when ≥ 3 plasma cells were found, and they were correlated with the hysteroscopic data. The decision can be seen as arbitrary as there are studies that diagnose the disease when there only is ≥ 1 plasma cells. However, in a recent systematic revision and meta-analysis, which included 12 studies, 6 different criteria were found, ranging from ≥ 1 to ≥ 5 plasma cells, in 1 to 10 high power fields to establish diagnosis.[22] Thus, the

need for a consensus for the diagnosis criteria for chronic endometritis with CD138+ is clear.

CONCLUSIONS

The diagnosis for chronic endometritis requires diagnostic hysteroscopy and endometrial biopsy with histology and CD138+ immunohistochemistry. While it's not possible with this study to determine if chronic endometritis plays a causal role in infertility, by demonstrating its prevalence in this group of patients it's possible to highlight the importance of researching this disease in infertility. It is necessary to establish a consensus for the different diagnostic tools, and of more research with a larger number of patients that allow for a precise diagnosis and treatment of the disease.

REFERENCES

1. Parry JP, Isaacson KB. Hysteroscopy and why macroscopic uterine factors matter for fertility. Fertil Steril 2019; 112 (2): 203-210. doi:10.1016/J.FERTNSTERT.2019.06.031
2. Buzzaccarini G, Vitagliano A, Andrisani A, et al. Chronic endometritis and altered embryo implantation: a unified pathophysiological theory from a literature systematic review. J Assist Reprod Genet 2020; 37 (12): 2897-911. doi:10.1007/S10815-020-01955-8
3. Moreno I, Cicinelli E, Garcia-Grau I, et al. The diagnosis of chronic endometritis in infertile asymptomatic women: a comparative study of histology, microbial cultures, hysteroscopy, and molecular microbiology. Am J Obstet Gynecol 2018; 218 (6): 602.e1-602.e16. doi:10.1016/j.ajog.2018.02.012
4. Bayer-Garner IB, Korourian S. Plasma cells in chronic endometritis are easily identified when stained with syndecan-1. Mod Pathol 2001; 14 (9): 877-79. doi:10.1038/MODPATHOL.3880405
5. Shen M, O'Donnell E, Leon G, et al. The role of endometrial B cells in normal endometrium and benign female reproductive pathologies: a systematic review. Hum Reprod 2021; 2022 (1). https://doi.org/10.1093/hropen/hoab043
6. Kitaya K, Takeuchi T, Mizuta S, Matsubayashi H, Ishikawa T. Endometritis: new time, new concepts. Fertil Steril 2018; 110 (3): 344-50. doi:10.1016/j.fertnstert.2018.04.012
7. Fan X, Li X, Li Y, et al. Endometrial CD138 count appears to be a negative prognostic indicator for patients who have experienced previous embryo transfer failure. Fertil Steril 2019; 112 (6): 1103-1111. doi:10.1016/J.FERTNSTERT.2019.08.006
8. Bayer-Camer IB, Nickell JA, Korourian S. Routine syndecan-1 immunohistochemistry aids in the diagnosis of chronic endometritis. Arch Pathol Lab Med 2004; 128 (9): 1000-1003. doi:10.5858/2004-128-1000-RSIAIT
9. Kitaya K, Yasuo T. Inter-observer and intra-observer variability in immunohistochemical detection of endometrial stromal plasmacytes in chronic endometritis. Exp Ther Med 2013; 5 (2): 485-88. doi:10.3892/ETM.2012.824
10. Murtinger M, Wirleitner B, Spitzer D, Bralo H, Miglar S, Schuff M. Diagnosing chronic endometritis: when simplification fails to clarify. Hum Reprod Open 2022; 2022 (3). doi:10.1093/HROPEN/HOAC023
11. Cicinelli E, Vitagliano A, Kumar A, et al. Unified diagnostic criteria for chronic endometritis at fluid hysteroscopy: proposal and reliability evaluation through an international randomized-controlled observer study. Fertil Steril 2019; 112 (1): 162-173.e2. doi:10.1016/j.fertnstert.2019.03.004
12. Liu HL, Song J, Zhang FF, et al. A new hysteroscopic scoring system for diagnosing chronic endometritis. J Minim Invasive Gynecol 2020; 27 (5): 1127-1132. doi:10.1016/J.JMIG.2019.08.035
13. Fan X, Li X, Li Y, et al. Endometrial CD138 count appears to be a negative prognostic indicator for patients who have experienced previous embryo transfer failure. Fertil Steril 2019; 112 (6): 1103-111. doi:10.1016/J.FERTNSTERT.2019.08.006
14. 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 2021; 50 (9). doi:10.1016/J.JOGOH.2021.102182
15. Bouet PE, El Hachem H, Monceau E, Gariépy G, Kadoch IJ, Sylvestre C. Chronic endometritis in women with recurrent pregnancy loss and recurrent implantation failure: Prevalence and role of office hysteroscopy and immunohistochemistry in diagnosis. Fertil Steril 2016; 105 (1): 106-110. doi:10.1016/j.fertnstert.2015.09.025
16. Yang R, Du X, Wang Y, Song X, Yang Y, Qiao J. The hysteroscopy and histological diagnosis and treatment value of chronic endometritis in recurrent implantation failure patients. Arch Gynecol Obstet 2014; 289 (6): 1363-69. doi:10.1007/S00404-013-3131-2
17. Cicinelli E, Resta L, Nicoletti R, et al. Detection of chronic endometritis at fluid hysteroscopy. J Minim Invasive Gynecol 2005; 12 (6): 514-18. doi:10.1016/J.JMIG.2005.07.394
18. Song D, Li TC, Zhang Y, et al. Correlation between hysteroscopy findings and chronic endometritis. Fertil Steril 2019; 111 (4): 772-79. doi:10.1016/j.fertnstert.2018.12.007
19. Abdel Moneim ME, Abdel Latif AA, Shehata MS, Latif Ghanem IA. Accuracy of office hysteroscopy in the diagnosis of chronic endometritis. Clin Exp Obstet Gynecol 2022; 49 (2): 44. doi:10.31083/J.CEOG4902044/2709-0094-49-2-044.PDF

https://doi.org/10.24245/gom.v92i3.8811

20. Wang S, Li F, Zhang W, Sui X, Hao C. Investigation of the relationship between chronic endometritis manifestations under hysteroscope and CD138 expression. Appl bionics Biomech 2022; 2022. doi:10.1155/2022/8323017

21. Zolghadri J, Momtahan M, Aminian K, Ghaffarpasand F, Tavana Z. The value of hysteroscopy in diagnosis of chronic endometritis in patients with unexplained recurrent spontaneous abortion. Eur J Obstet Gynecol Reprod Biol 2011; 155 (2): 217-220. doi:10.1016/j.ejogrb.2010.12.010

22. Huang W, Liu B, He Y, 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 2020; 140: 103146. doi:10.1016/J.JRI.2020.103146