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Correlation between hysteroscopy finding and chronic Endometritis in Unexplained Primary Infertility

Abd Elsamie A. Abd Elsamie[1], Mohammed S. Bakry[1], Sameh S. Abou-Beih[2], Medhat A. Ibrahim[1*]

1 Department of obstetrics and gynecology, Faculty of Medicine, Fayoum University, Fayoum, Egypt.

2 Department of pathology, Faculty of Medicine, Fayoum University, Fayoum, Egypt.

* Correspondence: Medhat A. Ibrahim, dr_dido5@yahoo.com; Tel.: (002) 01060469962

Abstract

Introduction: One of the most common conditions in a fertility clinic is unexplained infertility. Only recently, chronic endometritis (CE) has been linked to embryonic transplantation failure and infertility.

Aim of the study: To evaluate the role of hysteroscopy in the diagnosis of chronic endometritis (CE) and to determine the correlation between hysteroscopic and histologic findings of CE in patients with unexplained primary infertility.

Subjects and methods: The present study was conducted on 25 female patients under the age of 40 years attending the infertility clinic at Mataria teaching hospital complaining of unexplained primary infertility during the period from May 2018 to April 2019. Patients underwent office hysteroscopy (for evaluation of CE by visualized hysteroscopic features of CE as endometrial hyperemia), endometrial interstitial edema, micro-polyps, and visualized endometrial biopsies were obtained.

Results: We found that 21 patients (84 %) had chronic endometritis by endometrial biopsies taken after being stained with CD138. The diagnostic accuracy of hysteroscopy in the diagnosis of CE in our study was 52%. The hysteroscopy sensitivity was 48%, the specificity was 75%, the positive predictive was 91%, and the negative predictive was 21%.

Conclusion: Chronic endometritis should be considered in the workup of unexplained primary infertility. Hysteroscopy is a useful procedure with high diagnostic accuracy in chronic endometritis screening in asymptomatic infertile women however, endometrial biopsy should be complemented for the CE diagnosis.

Keywords: Hysteroscopy; chronic endometritis; primary infertility.

1. Introduction

Infertility is the inability to achieve a clinical pregnancy after 12 months of frequent unprotected sexual intercourse or more [1]. Diagnosis of unexplained infertility might be achieved without a specific medical cause following infertility work-up, including semen analysis in males and ovulation and fallopian tube assessment in females [2].

In fertility clinics, one of the most common conditions is unexplained infertility [3-4]. Despite the improvement of diagnostic tools in reproductive medicine, infertility remains unexplained in up to 25% of cases [5].

Recently, chronic endometritis (CE) was linked to embryonic transplantation failure and infertility [6]. Chronic endometritis is a persistent inflammation of the uterine endometrial lining. It is thought to be related to irregular uterine bleeding, recurrent abortion, and infertility [7-8].

Most CE cases show no symptoms or only mild ones. Due to the time-consuming microscopic examinations required to diagnose CE, gynecologists and pathologists often pay little clinical attention to CE, the mild clinical manifestations of the disease, and its benign nature. Nevertheless, the association between CE and infertility-related conditions, such as frequent failure of implantation and recurrent miscarriage, has recently emerged as an area of inquiry [6].

Chronic endometritis was found to be present in 12–46% of endometrial biopsies in infertile patients [9-10]. In these cases, early diagnosis and treatment significantly improve pregnancy rates [11].

However, it was found that it is too difficult to treat chronic endometritis. Most diagnostic tests are usually asymptomatic and not easily identified. The gold standard remains the histological examination of endometrial biopsy. Abnormal levels of lymphocytes, leukocytic infiltration of both glands and stroma, and eosinophils or macrophages may be associated with chronic inflammation [12-13]. Though, the existence of plasma cells in the endometrial stroma is the only widely recognized histological criterion for chronic endometritis diagnosis [14].

Several conditions may interfere with the search for plasma cells, such as mononuclear inflammatory cell infiltrates, stromal cell proliferation, plasmacytoid presence of stromal cells, or a marked decidual reaction in the late endometrial secretion [13, 15].

In general, chronic endometritis is a condition that is asymptomatic and, therefore, hard to diagnose. There is a debate on the effect of chronic endometritis on fertility. This research clarifies the usefulness and the true impact of an endometrial biopsy in patients suffering from primary unexplained infertility.

The current study aimed to evaluate the role of hysteroscopy in CE diagnosis. Besides the determination of the correlation between hysteroscopic and histologic findings of CE in patients with unexplained primary infertility.

2. Subjects and methods

2.1. Subjects

The present study was conducted on 25 patients <40 years of age who reported for fertility therapy, after being diagnosed

with unexplained primary infertility at Mataria teaching hospital in collaboration with the department of obstetrics and gynecology, Faculty of Medicine, Fayoum University. The current study was carried out from May 2018 through April 2019.

2.2. Inclusion criteria

After taking the medical history, complete clinical examination, and biochemical and hormonal profile, all cases (<40 years), that were previously diagnosed with primary unexplained infertility were subjected to endometrial biopsy.

2.3. Exclusion criteria

Patients with symptoms of intrauterine pathology, transvaginal ultrasound abnormalities, previous examination of hysteroscopy, or any instrumentation to the genital tract were excluded.

2.4. Methodology

After taking informed written patient consent, as approved by the local ethical committee, twenty-five patients of ages less than 40 years were selected. All cases were reported for fertility therapy at the Mataria teaching hospital in collaboration with the department of obstetrics and gynecology, Faculty of Medicine, Fayoum University, have undergone endometrial biopsies.

Patients were investigated for subclinical endometritis by visualized hysteroscopic features of CE as endometrial hyperemia, endometrial interstitial edema, micro-polyps, and by obtaining endometrial biopsies for histological examination. Patients were followed-up for an average of three months (the follow-up period ranged from one to six months). The body mass index (BMI) was used to classify underweight (<18.5%), average weight (18.5-24.9%), overweight (25-29.9%), and obese women (≥ 30%).

After excluding pregnancy by serum beta-HCG, the endometrial biopsies were scheduled during the follicular phase of the menstrual cycle (Day 3–14). All participants were subjected to office hysteroscopy to obtain a visualized endometrial sample.

All specimens were labeled with the date, name, and number of the patient, collection time, type of specimen, and then transported to the Department of Pathology.

2.5. Statistical analysis

Data were statistically defined where necessary in terms of mean ± standard deviation (±SD), median and range, or frequency (number of cases) and percentages. The comparison of numerical variables for independent samples between study groups was done using the Mann-Whitney U test. The Chi-square (χ^2) test was performed to compare categorical results. If the predicted frequency is less than 5, the exact test has been used instead. The accuracy of the clinical hypothesis of diagnosing endometritis was demonstrated using the terms sensitivity, specificity, positive and negative predictive values, and overall accuracy. The statistically relevant value of two-sided p values of less than 0.05 was considered. All statistical measurements were made using IBM SPSS (Statistical Package for the Social Science; IBM Corp,

Armonk, NY, USA) release 22 for Microsoft Windows.

3. Results

The main outcome measured the percentage of patients having endometritis among patients subjected to endometrial biopsy. The age of female patients recruited in the current study ranged from 24-39 years (the median age was 30.5 years). Regarding results of endometrial biopsies taken after being stained with CD138, there was statistically significant agreement between results obtained by direct visualization and endometrial biopsies (*P=0.002*). Immunohistochemistry of biopsy specimens showed the presence of CD138 cells in 21 cases (84%). Among cases that tested positive for CD138 cells, endometrial hyperemia was reported in six patients (28.5%), endometrial interstitial edema in four patients (19%), and one patient had micro-polyps (4.7%). Sensitivity, specificity, positive and negative predictive value, and diagnostic accuracy of the presence of one or more hysteroscopy features were 48%, 75%, 91%, 21%, and 52%, respectively.

The biopsies were considered "Negative" when no plasma cells were stained with CD138, and "Positive" when one or more plasma cells were observed on ten non-overlapping high-power fields in the endometrial tissue samples. Plasma cell topography was easy to identify in 21 samples, where 12 were epithelial (57.1%), three were epithelial and focal (14.3%), five were epithelial and stromal (23.8%), and one was at stromal phase (4.8%).

Histologic dating of endometrial phase was possible in 19 samples, where 13 were late proliferative (68.4%), three were mid proliferative (15.8%), and three were mid secretory (15.8%). In six cases, no histologic dating was possible either because the sample was inadequate (two samples) or atrophic (four samples).

BMI of women included in the study ranged from 22 kg/m^2 to 37 kg/m^2. According to categorization of endometritis cases, BMI results didn't reveal any evidence to support a statistically significant difference, as shown in **Table 1.**

Table 1: Categorization of endometritis cases according to their BMI.

Endometritis	**Underweight**		**Average weight**		**Overweight**		**Obese**		***P-value***
	N	%	N	%	N	%	N	%	
+ve cases	1	4.7%	4	19%	7	33.3%	9	43%	0.364
-ve cases	0	0%	1	25%	1	25%	2	50%	

N: number.

The suspected cases of endometritis found during the procedure in the hysteroscopy group were 11 cases. Ten cases were confirmed to have endometritis with overall diagnostic accuracy of 52%, as shown in **Table 2.**

Table 2: Diagnostic accuracy of hysteroscopy in diagnosing endometritis.

Suspected endometritis	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
	48%	75%	91%	21%	52%

PPV: positive predictive value, NPV: negative predictive value.

4. Discussion

Despite the improvement of diagnostic tools in reproductive medicine, infertility remains unexplained in up to 25% of cases. Moreover, the precise prevalence of infertility in developed countries is uncertain because of a lack of registration and well-conducted studies [4].

At present, there is a widespread use of several elements in basic infertility testing, there is a marked variation in the work of specialists, and trends of practice are affected by both modern assisted reproductive technologies (ART) and the growing age of couples seeking infertility assistance [16]. This is why we were trying to search for valuable, simple, rapid, relatively inexpensive, and accurate methods for these patients.

Chronic endometritis has been recently linked to infertility. Most CE cases show no symptoms or just mild ones; therefore, the diagnosis is usually difficult and rarely clinically suspected [6].

The gold standard remains the histological examination of the endometrial biopsy. The presence of plasma cells in endometrial stroma is the only widely recognized histological criterion for chronic endometritis diagnosis [17].

The present study was conducted on 25 female patients <40 years attending the

infertility clinic at Mataria teaching hospital complaining of unexplained primary infertility during the period from May 2018 to April 2019. Patients underwent office hysteroscopy for obtaining a visualized endometrial biopsy.

Our primary goal was to determine the prevalence of chronic endometritis diagnosed immunohistochemically in women with unexplained primary infertility. Our secondary aim was to evaluate the importance of office hysteroscopy in the CE diagnosis. In this study, we found that 21 patients (84%) had chronic endometritis.

This result agreed with a study performed by Cicinelli *et al.* (2018) on 95 women with unexplained infertility, which stated the prevalence of chronic endometritis was 57% [18].

However, a higher prevalence of CE was found in a cross-sectional study performed by Eckert *et al.* (2002) on 152 women, stating that 109 (71.7%) women had endometritis [19]. We believe the difference in such results was because of different inclusion and exclusion criteria, as the study included patients with suspected pelvic inflammatory disease and patients, who had an intrauterine device. Furthermore, a retrospective study was performed by Cicinelli *et al.* (2005) on 106 women with unexplained infertility from January 2009 through June 2012 and showed that 70 (66.0%) women were diagnosed with CE [20]. This study had almost the same inclusion and exclusion criteria as in our study; however, we believe the difference in such results was due to potential biases associated with retrospective research and preferential referral of patients for hysteroscopy.

On the other hand, Bouet *et al.* (2016) reported a lower prevalence rate in a study performed on 46 women and reported that the prevalence of CE was 14% [16]. The low prevalence rate in this study is mainly related to different diagnostic criteria as the CE diagnosis was considered positive if five or more plasma cells were detected on ten non-overlapping high-power fields in the endometrial tissue samples, while CE was considered positive in our study when only one or more plasma cells were observed on ten non-overlapping high-power fields in the endometrial tissue samples.

In another study by Song *et al.* (2018) on larger sample size, 1551 women underwent hysteroscopy and endometrial biopsy [21]. The overall prevalence of chronic endometritis was 24.4 % in the population surveyed. Having a different sample size and a different population, in general, could be the reason behind such differences. Another important factor that could affect the prevalence of CE in this study was the stage of the cycle from which the endometrial sample was obtained as 302 samples were obtained during the secretory phase. In that study, it was found that the prevalence of chronic endometritis during the proliferative phase was higher (26 %) than the secretory phase (17 %). A possible explanation for the disparity is that plasma cells are located inside the deeper endometrial layer. Since the endometrium has a thicker superficial layer in the secretory phase, at this stage, the biopsy

specimen will probably contain a reduced portion of the deeper, more compact layer.

In our study, we found twenty-one (84%) cases were diagnosed by hysteroscopy. These results go with the conclusion made by Brown *et al.* (2000) that hysteroscopy is the gold standard for assessing endometrial pathology [22].

In this study, the hysteroscopy sensitivity was 48%, the specificity was 75%, the predictive positive was 91%, and the predictive negative was 21%. These results were similar to the study performed by Bouet *et al.* (2016) on 99 patients [16]. The study aimed to measure the prevalence of CE in RIF and RPL, as well as, the sensitivity/specificity of office hysteroscopy in the CE diagnosis. The sensitivity of hysteroscopy in the diagnosis of CE was 40%, and the specificity was 80%.

Data from both studies suggest that hysteroscopy is a useful diagnostic tool in the screening for chronic endometritis in asymptomatic infertile women, however, it should be complemented by an endometrial biopsy for the diagnosis of CE. Another study by yang *et al.* (2014) assessed the importance of hysteroscopy in primary infertility studies on 202 primary infertility cases, hysteroscopy's sensitivity and specificity in CE diagnosis are 35.2% and 67.5%. We partially agreed with these results [23].

However, diagnostic hysteroscopy and endometrial biopsy were submitted to a study by Polisseni *et al.* (2003) on 50 patients seeking infertility treatment in a tertiary academic hospital. When chronic endometritis was detected, the hysteroscopy sensitivity was 16.7% with 95 % confidence intervals, the specificity was 93.2%, the positive predictive value was 25%, and the negative predictive value was 89.1%. These data indicated that in asymptomatic, infertile women, hysteroscopy is not helpful in screening for chronic endometritis [7].

The diagnostic accuracy of hysteroscopy in the diagnosis of CE in our study was 52%. This result agreed partially with a study done by Moreno et al. on 65 patients assessed for chronic endometritis with an accuracy of 58% [10].

The age of women included in this study ranged from 23-39 years with a mean ± SD (31.8±4.15 years). There was no statistically significant variation in an age with CE. This result agreed with a study done by Cicinelli *et al.* (2014) on 256 patients. The patients were 23–40 years of age; the mean ± SD was 31.9± 4.1 years. There was no statistically significant variation in the age with CE [24]. Our results disagreed with the study done by Ajayi *et al.* (2015), who showed that CE occurred in low frequencies when the age of the woman is <30 years, but the incidence steadily increased as age increased till 40-44 years [25]. We believe that having a wide age range could be the reason behind such differences.

In our study, we evaluated the effect of BMI on the incidence of CE. The BMI of the current cases ranged from 22 to 37 kg/m^2. There was no evidence to support a statistically significant difference between the different BMI and the incidence of CE. In a study done by Pitsos *et al.* (2009) on a

total of 123 patients with CE and 177 without CE who were used as controls, there was also no association between the difference in BMI and incidence of CE [26]. We agreed with this study even though we had a smaller sample size.

This is in agreement with Cicinelli *et al.* (2014) study on 256 patients, who reported no statistically significant difference in the incidence of CE with different BMI despite having different BMI ranges (23±1.9) [24].

5. Conclusion

CE has been recently linked to infertility and poor reproductive outcomes in the context of ART. The purpose of the study was to evaluate the role of hysteroscopy in the diagnosis of CE in cases of unexplained primary infertility. Histological examination of an endometrial biopsy remains the gold standard in CE diagnosis. The presence of plasma cells in the endometrial stroma is accepted for diagnosis as the only histological criterion. There is a solid agreement on the usage of Syndecan-1 (CD138) for the histologic diagnosis of CE, as IHC has higher sensitivity and prevalence of plasma cells detection on microscopy Compared to using only HE staining and morphology. Hysteroscopy is a useful procedure with high diagnostic accuracy in asymptomatic infertile women screening for chronic endometritis however, endometrial biopsy for the CE diagnosis should be complemented. There is no statistically significant difference in the prevalence of CE with different age groups and different BMI. In unexplained primary infertility, the finding of endometrial hyperemia, micro-polyps, or endometrial interstitial edema during the hysteroscopic examination should alert for the diagnosis of chronic endometritis. Hysteroscopy is a recommended useful diagnostic tool in chronic endometritis screening in asymptomatic infertile women however, it shouldn't replace histologic examination as a tool of CE diagnosis. To determine the etiology of endometritis in infertile patients, further studies are required. Further highly oriented, multicenter studies with homogeneous populations and standardized CE criteria for histological diagnosis are needed to clarify the problem.

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Ethical Approval Statement: the protocol was approved by the Ethical committee of Fayoum Faculty of Medicine, Fayoum, Egypt. The researcher informed the participants about the objectives of the study, the examination, investigations that were done, the confidentiality of their information, and the right not to participate in the study.

Informed consent statement: written informed consents were obtained from all patients.

Conflicts of interest: All authors declare no conflict of interest.

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