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Efficacy of Hysteroscopy in the Diagnosis if Chronic Endometritis in Infertile Females

Nancy Diab Mousbah[1*], Mona Khalid Omar[2], Hassan Tahsin Shoeir[3] and Ahmed Hussien Abou Freikha[2]

[1]Department of Obstetrics and Gynecology, Elmenshawy General Hospital, Tanta, Egypt.
[2]Department of Obstetrics and Gynecology, Faculty of Medicine, Tanta University, Tanta, Egypt.
[3]Department of Pathology, Faculty of Medicine, Tanta University, Tanta, Egypt.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Chronic endometritis (CE) is a chronic inflammatory condition characterized by the presence of plasma cells in endometrial stroma. CE is a subtle disease, often overlooked by clinicians due to poor symptomatology, such as uterine bleeding, pelvic discomfort, dyspareunia, and leucorrhoea.
Methods: This cohort prospective study was conducted at Tanta University hospitals aiming to evaluate the efficacy of hysteroscopy in the diagnosis of chronic endometritis in infertile females. We included a total of 80 infertile females who were subjected to complete history taking, general examination, and complete gynaecological investigations. Routine laboratory parameters were also performed. In addition, hysteroscopic examination was performed for all cases with endometrial biopsy.
Results: Our results showed that the mean age of the included cases was 26.6 years (range, 20 – 36), the mean BMI of the included cases was 30.51 kg/m2, Hysteroscopic examination revealed endometrial hyperemia (85.4%), stromal edema (52.1%), and endometrial polyps (43.75%), Hysteroscopic diagnosis of chronic endometritis was established in 48 cases (60%). Nevertheless,

**Corresponding author: E-mail: nancydiab90@gmail.com;*

pathological examination confirmed the diagnosis only in 33 cases (41.25%), Hysteroscopy had sensitivity and specificity of 81.89 and 55.3% respectively, with an accuracy of 66.25% in detecting chronic endometritis, Agreement between hysteroscopic and pathological had kappa factor of 0.325 (p = 0.004), On immunohistochemical analysis of chronic endometritis specimens, CD138 was positive in 31out of 33 cases (93.93%).

Conclusions: Office hysteroscopy is a reliable examination for investigating chronic endometritis. It could be useful for screening asymptomatic infertile patients. The chronic endometritis is a hidden condition that is difficult to detect with non-invasive examination, we suggest that hysteroscopy should be always performed in the diagnostic work-up of women with unexplained infertility, especially before starting assisted reproduction procedures. Also, endoscopic samples should be obtained during hysteroscopy to increase the diagnostic accuracy.

Keywords: Hysteroscopy; chronic endometritis; infertile females.

1. INTRODUCTION

Chronic endometritis (CE) is a subtle disease that's overlooked because of inadequate symptomatology, like dyspareunia, leucorrhea, pelvic discomfort, and uterine bleeding [1,2].

CE is difficult to diagnose; clinical and ultrasound exams are nonspecific, and histological study may be deceptive owing to the frequent presence of leukocytes in the uterine lining, particularly before menstruation [3-5]. CE is a long-term inflammatory disease marked by the presence of plasma cells in the stroma of the endometrium [6,7]. Fluid hysteroscopy may aid CE detection by enabling the identification of particular CE symptoms such as micro polyps, stromal oedema, and localised or widespread hyperaemia [3,8,9].

Endometrial receptivity may be hampered by the changes in the endometrial microenvironment seen in CE, which may lead to female infertility [1,2]. Nonetheless, prior research has shown that CE is quite common among infertile patients, particularly in those who have had several implantation failures (RIF) [10]. Interestingly, many investigations have shown that antibiotic treatment may restore normal endometrial histology and increase implantation rates in these individuals, suggesting a causal link between CE and poor endometrial receptivity [10-12].

Despite the fact that the connections between CE and RIF have been extensively studied, no research has yet looked at the effect of CE on "unexplained infertility" (UI). When routine examinations fail to reveal any abnormalities, UI is diagnosed in approximately 15% of couples seeking medical assistance [13]. Because of the meagre spontaneous pregnancy rate (between 2% and 4% per menstrual cycle) [14-16] and the absence of obvious therapy targets, these patients are submitted to ARTs with inadequate results [17].

The goal of this research was to determine the CE prevalence in UI patients. Furthermore, we looked at the incidence of spontaneous conception in women who had CE and had received proper antibiotic therapy. The goal of this study was to see whether hysteroscopy was effective in diagnosing chronic endometritis in infertile women.

2. PATIENTS AND METHODS

This prospective cohort study that was carried out on 80 patients at The Department of Obstetrics and Gynaecology Tanta University Hospitals. Patients that their age Group (20-36 years), regular ovulatory cycles (assessed with mid-luteal progesterone > 30 nmol/L), normal husband's semen analysis (according to WHO criteria), patients were included exclusively if trying to conceive naturally, without medical assistance (including ARTs), normal HSG (at least one patent fallopian tube) and normal post coital test were included.

Patients that their BMI <18 kg/m or > 30 kg/m, previous myomectomy, endometriosis, autoimmune diseases, thrombophilic conditions, serum antisperm antibodies, and previous ARTs, chronic general disease (Immunological, Hypertensive, Dm, Hepatic), Suspicion of any Gynecological Malignancy, severe Vaginal Bleeding, any failed Hysteroscopic Procedure (Difficult insertion or Patient refusal) were excluded.

2.1 All Patients in this Study were Subjected to the Following

History Taking: Including the personal, Obstetrical, Gynecological, Family, Medical and Surgical history of the female and Personal medical, surgical, and family history of the male.

Clinical Examination: All women underwent a clinical examination, including general, abdominal, and pelvic examinations, and vaginal speculum examination to exclude local causes of infertility.

Investigational Studies:

a) Routine laboratory investigation: Complete Blood Count, Prothrombin time and activity, liver function, kidney function, etc.
b) Basic investigations for female infertility include: Transvaginal or Transabdominal ultrasound for all cases, Assessment of cervix by Post coital test, Assessment of Uterine cavity and tubal patency by HSG and Ovulatory factors (hormonal profile–folliculometry).
c) Semen analysis.
d) Hysteroscopy was used for direct visualization of the uterine cavity and an endometrial biopsy was taken and sent for histopathology examination.

Timing of the Procedure: Hysteroscopy was performed during the proliferative (ie, follicular) phase for good visualization of the uterine cavity.

Procedure

1. After explanation of the procedure the patient was asked to empty her bladder, the patient was put in the lithotomy position. Normal saline was used as a distention media for uterine distension connected to the inflow channel on the sheath. A vaginal disinfection with povidone iodine 10% without placing speculum was done (vaginoscopic approach).
2. The tip of the hysteroscope was positioned in the vaginal introitus, the labia was being slightly separated with fingers. The vagina was distended with saline. The scope was driven to the posterior fornix to readily visualize the portio and slowly backwards anterior to identify the external cervical os. When this became visible, the scope was carefully moved forward to the internal os and then to the uterine cavity with least possible trauma.
3. The uterine cavity was systemically explored in a panoramic view by rotating the fore-oblique scope in order to identify any anomaly in the uterine walls and the right and left tubal ostia.
4. Suspected cases of chronic endometritis should had hysteroscopic picture which was characterized by the presence of stromal edema that causes the endometrial mucosa to appear irregularly thick and pale, and the presence of very small (less than 1 mm of size) pedunculated endometrial polyps.
5. Hysteroscopic guided biopsy was done by hysteroscopic scissors, fixed in 10% neutral buffered formalin, and sent to a pathology center.
6. Paraffin embedded blocks were prepared and sections 3-5 µm in thickness will be obtained and subjected to H&E staining for histopathological examination.
7. Confirmatory CD138 Immunohistochemistry staining for detection of plasma cells was done for cases diagnosed as CE.
8. Patients with positive chronic endometritis were treated with ceftriaxone 1gm intramuscular every 24 hours for 5 day and Metronidazole 500 mg tab. Twice daily for 10 days.

Histopathologic examination was repeated after course of treatment in the next month.

Statistical Analysis: IBM's SPSS statistics (Statistical Package for the Social Sciences) for windows (version 25, 2017) was used for statistical analysis of the collected data. Shapiro-Wilk test was used to check the normality of the data distribution. All tests were conducted with 95% confidence interval. P (probability) value < 0.05 was considered statistically significant. Descriptive: Quantitative variables were expressed as mean and standard deviation, median, inter-quartile range, minimum and maximum as appropriate while categorical variables were expressed as frequency and percentage. ROC: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated using the receiver operating characteristic (ROC) curve and the crosstabs function. Agreement and Reliability: Cohen's kappa (κ) was run to measure reliability and agreement between for

chronic endometritis diagnosis by Hysteroscopy compared to Pathology

3. RESULTS

In this study the patients (total number = 80) were aged 20–36 years; mean ± SD 26.58 ± 4.491 year and BMI ranged from 21 to 30 with mean 24.51.

The distribution of the studied cases according to hysteroscopic signs of chronic endometritis, total number of cases (80), in which 48 cases (60%) showing signs of chronic endometritis, while 42 cases (40%) were free.

Total number of cases (80), In which (41) cases showed Hyperemia, (25) cases showed Stromal Edema and (21) cases showed Endometrial Polyp.

The distribution of the studied cases according to histopathologic results, The total number of cases (80) in which (33) cases were diagnosed with chronic endometritis, while (47) cases were free.

Table 1. Distribution of the studied cases according to age and BMI

All patients (n= 80)	Mean & SD	Median	Range	IQR
Age (years)	26.58 ± 4.491	27.00	20, 36	22.25, 30.00
BMI (kg/m2)	24.51 ± 2.342	24.28	21, 30	22.79, 26.13

Data is expressed as mean and standard deviation, median, range and inter-quartile range or as percentage and frequency

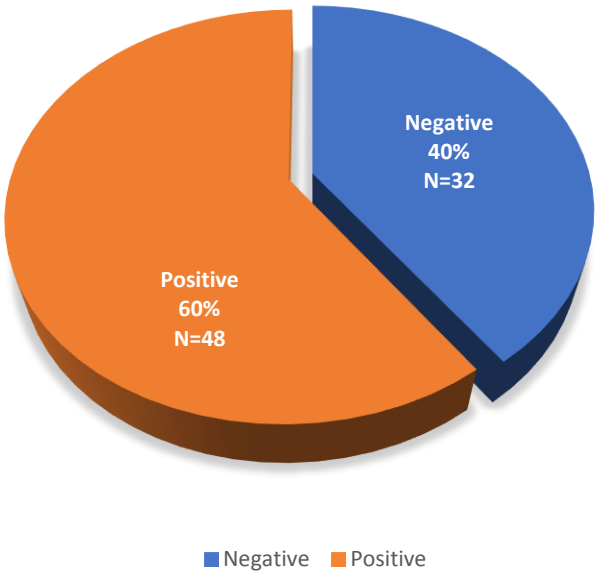

Fig. 1. Distribution of studied cases according to hysteroscopic findings

Table 2. Distribution of the studied cases according to clinical findings by Hysteroscopy

Clinical findings	Hysteroscopic findings (n=48)		P
	No.	%	0.001*
Stromal edema	25	52.1	
Hyperemia	41	85.4	
Endometrial polyp	21	43.75	

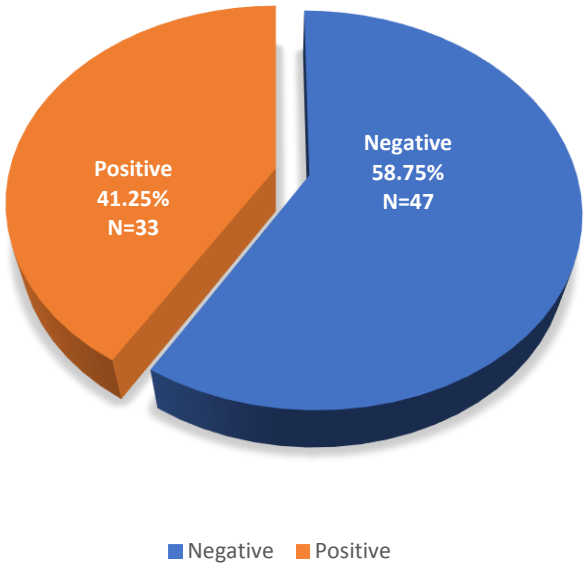

Fig. 2. Distribution of studied cases according to histopathologic findings (n=80)

Table 3. Relation between hysteroscopic and histopathologic findings

	Hysteroscopic findings				p
	Negative N=32		Positive N=48		
	No	%	No	%	
Histopathology Negative (N=47)	26	81.25	21	43.75	.025*
Positive (N=33)	6	18.75	27	56.25	

**: Statistically significant as p ≤ 0.05*

In this study (33) cases were diagnosed chronic endometritis by histopathology, This cases were stained with CD 138 marker only (31) cases were confirmed were (2) cases were free.

Cohen's kappa (κ) was run to measure reliability and agreement between chronic endometritis diagnosis by Hysteroscopy compared to Pathology. In our study number of cases diagnosed positive by hysteroscope were (48) and number of cases diagnosed negative were (32), while number of cases diagnosed positive by histopathology were (33) and negative were (47).

Table 4. CD138 Immunohistochemistry staining in the current study

Chronic endometritis patients (n=33)	
Positive CD138	93.9% (31)
Negative CD138	6.1% (2)

Table 5. Reliability analysis for chronic endometritis diagnosis by Hysteroscopy compared to pathology in the current study

	Kappa	95% CI	p
Hysteroscopy	0.325	0.318, 0.332	**0.001**

Table 6. Diagnostic profile of chronic endometritis by hysteroscopy compared to Pathology in the current study

	Hysteroscopy
AUC	0686
P	**0.002***
Sensitivity	81.8%
Specificity	55.3%
PPV	56.3%
NPV	81.3%
Accuracy	66.25%

**: Statistically significant at p ≤ 0.05, AUC: area under the curve, PPV: positive predictive value, NPV: negative predictive value*

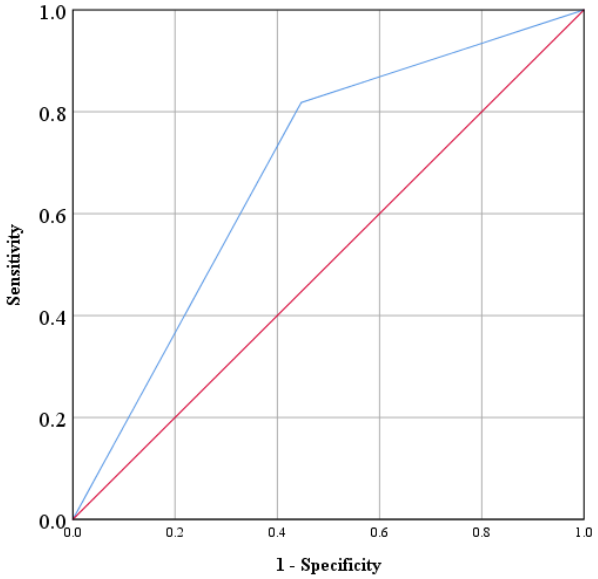

Fig. 3. ROC curve for diagnostic profile of chronic endometritis by hysteroscopy compared to pathology in the current study in which sensitivity were (81.8%), specificity (55.3%), PPV (56.3%), NPV (81, 31%) and accuracy (66.25%).

4. DISCUSSION

Despite the fact that chronic endometritis has been linked to infertility and recurrent abortion, it's often asymptomatic, and the diagnosis is seldom recognised clinically [18].

Chronic endometritis is difficult to diagnose since there are no consistent clinical or ultrasound signs. Histology, which is based on the detection of plasma cells in the endometrial stroma, is a traditional approach for diagnosing chronic endometritis, although it is vague and reliant on the day of the menstrual cycle when the sample is taken [19].

Because of these constraints, hysteroscopy and microbiological culture are often employed to diagnose chronic endometritis [20]. Subjective features detected by the reproductive endoscopist, such as stromal edoema, localised or widespread epithelial hyperemia, and/or the presence of micro polyps, are used to make a hysteroscopic diagnosis of chronic endometritis [21,22].

A previous Egyptian study was conducted by Mikhael VS et al. reported that the mean age of cases with unexplained infertility was 27 years [23]. This comes in line with the age reported by our study. In another study conducted by Polisseni F et al. handling the same perspective, the patients' age was between 19 and 41 years old, while the mean age has been 33.7 years old [24].

For the present research, the mean BMI of participants has been 24.51 kg/m2.

Moragianni VA et al. reported that participants having BMI over 30 have up to 68% lower odds of having a live birth following their first ART cycle in comparison to women with a BMI lower than 30 kg/m2 [25].

A larger retrospective study of over 6,000 women, found a delayed spontaneous conception has been reported in obese women, mainly caused by ovulatory infertility, and also in women with regular ovarian cycles in whom the probability of pregnancy is reduced by 5% for every unit of BMI that exceeds 29 kg/m^2 with P value (0.024) [26]. In the current study, hysteroscopic examination revealed endometrial hyperemia (85.4%), stromal edema (52.1%), and endometrial polyps (43.75%). In around 10% of infertile women who have no reason of infertility identified by traditional examination, a panoramic hysteroscopic image of the uterine cavity may reveal certain previously undetected abnormalities [27].

Hysteroscopy is the gold standard for uterine factor assessment because it allows for direct view of the uterine cavity and, in most instances, prompt correction of intrauterine abnormalities without the need for a hospital stay or anaesthesia [28].

Previous studies have reported that hysteroscopy may help in CE detection, by allowing the recognition of specific signs of CE, such as micro polyps, stromal edema, and focal or diffuse hyperemia [3,8,9]. All of these signs were reported by our study.

Chronic endometritis was shown to be linked with stromal edoema and either localised or diffuse hyperemia during hysteroscopy in another instance; in other cases, this result was connected with endometrial micro polyps (less than 1 mm in size) [20].

The prevalence of each finding could differ between our studies and others present in the literature. This heterogenicity could be explained by the difference in patient demographics, cause of infertility, and operator experience.

In our study, pathological examination confirmed the diagnosis only in 33 cases (41.25%). The actual prevalence of this condition in the general population is still ill-defined, although it has been estimated to be between 0.8-19%. This comes in accordance with our results [21,29].

A study performed by Zolghadri and his colleagues who reported that chronic endometritis was detected in 42.9% of infertile cases [30]. In another study that included a total number of 95 patients, authors found high prevalence of histological chronic endometritis (55.7%) [31]. Such result was comparable to prevalence observed by other authors in patients affected by repeated IVF failures (55.7%, 46.67%, and 43.56%, respectively, in three studies) [10,32,33] and recurrent miscarriage (52.78%, 56.07%, and 43.66% in three studies) [7,30,34], suggesting a strong correlation between CE and defects in implantation and embryo development.

Furthermore, the prevalence of this condition was reported to be extremely high (≈72%) in women with suspected pelvic inflammatory disease [27,35]. On the contrary, another study reported much lower prevalence of chronic endometritis, that was confirmed in 6 out of 50 cases (12%) [24].

In our study, hysteroscopic diagnosis of chronic endometritis was established in 48cases (60%). Nevertheless, pathological examination confirmed the diagnosis only in 33 cases (44.25%). Hysteroscopy had sensitivity and specificity of 81.89 and 55.3% respectively, with an accuracy of 66.25% in detecting chronic endometritis. In addition, agreement between hysteroscopic and pathological had kappa factor of 0.325 (p = 0.004).

We also discovered that hysteroscopy has a poor positive predictive value for endometritis identification. This implies that if the hysteroscopy reveals a positive result for endometritis, it's best to assume that the result is erroneous and that the patient's endometrium is normal. When we use a test in a population with a low prevalence of the illness, we may anticipate a poor positive predictive value.
Our findings, on the other hand, revealed that hysteroscopy had a significant negative value (81.3 percent). This implies that a negative hysteroscopy in a suspected case will rule out endometritis. [36].

Zolghadri et al. reported that endometritis was detected in 67.6% of cases by hysteroscopy versus 42.9% by pathological examination [30]. This confirms the findings reported by our study.

Cicinelli and his associates reported that histological and hysteroscopic gradings agreed in

173 cases (86.5%). By considering only the women who were diagnosed with endometritis at both hysteroscopy and histology the Kappa value was 0.62 [37].

In an older study by the same previous authors, histology confirmed the diagnosis in 101 cases (63.9% of positive cases at hysteroscopy) and was positive in 9 additional cases not detected by hysteroscopy. The sensitivity, specificity, and positive and negative predictive values of hysteroscopy based on detection of only hyperemia and edema were 91.8%, 92.9%, 63.9% and 98.8%, respectively; the diagnostic accuracy was 92.7%. When considering the presence of hyperemia, edema, and micro polyps, the sensitivity, specificity, and positive and negative predictive values were 55.4%, 99.9%, 98.4%, 94.5%, respectively, with a diagnostic accuracy of 93.4% [20].

Polisseni et al. have reported that the hysteroscopy sensitivity was 16.7% (range 0.9–63.5%), the specificity was 93.2% (range 80.3–98.2%), the positive predictive value was 25% (range 1.3–78.1%), the negative predictive value was 89.1% (range 75.6–95.9%), and the accuracy was 84% (range 70.3–92.4%) [24].

On immunohistochemical analysis of chronic endometritis specimens in the current study, CD138 was positive in 31 out of 33 cases (93.93%). The transmembrane heparin sulfate proteoglycan syndecan-1 (CD138) is a syndecan, which is a specific marker of plasma cells. Therefore, in current clinical practice, CD138 immunohistochemistry is used for the detection of chronic endometritis to improve its diagnosis rate [38].

This is consistent with the results from Bayer-Garner et al. In chronic endometritis, the plasma cell membrane shows strong positive CD138 immunohistochemical staining, while the cytoplasm shows weak positive staining, making the cells easy to discriminate in 200x and 400x magnification fields. Thus, in suspected chronic endometritis specimens, when plasma cells cannot be identified using HE staining, CD138 immunohistochemical staining can effectively display plasma cells, making plasma cells easy to identify, thereby improving the diagnosis rate of chronic endometritis. Therefore, CD138 immunohistochemical staining can improve the diagnosis rate and diagnostic accuracy of chronic endometritis [39].

In another study, among the 1,189 specimens examined, plasma cells were positively identified by CD138 immunohistochemistry in 322 specimens (27.1%); a diagnosis of CE was considered to be confirmed in these cases [40].

In our study we gave treatment to cases confirmed chronic endometritis by CD138 1 gm ceftriaxone every 24 hour and metronidazole 500 mg tab twice daily for 10days.

After a month we repeated hysteroscopy with biopsy and revealed 27 cases responding to treatment and became free while 4 cases still positive for culture and sensitivity.

Generally, the drug of choice is doxycycline, administered in doses of 100 mg every 12 hours for 14 days, or alternatively, the administration of cephalosporins, macrolides, or quinolones is possible. It is preferable for the partner to also undergo the same antibiotic treatment [41,42].

Where antibiotic therapy fails and/or where the presence of endometritis persists, an endometrial culture with a relative antibiogram should be considered and an appropriate antibiotic treatment must be prescribed.

Sardo ADS et al. reported that persistence of signs of chronic endometritis at subsequent hysteroscopy, the protocol can be repeated up to three times. In the presence of confirmed tuberculous endometritis, the patient should be given a specific antibiotic therapy for tuberculosis (isoniazid, ethambutol, rifampicin, and pyrazinamide for 2 months, followed by isoniazid and rifampicin for another 4 months) [41].

Kitaya K. et al. reported that oral antibiotic treatment potentially improves the pregnancy outcome in infertile women with CE [22].

In their retrospective analysis, Cicinelli et al. investigated pregnancy outcomes after antibiotic treatment in CE patients with a history of RIF. In the subsequent fresh day 3 ET cycle, the live birth rate (60.9%, 28/46 vs. 13.3%, 2/15) was higher in the cured CE group than in the persistent CE group. No difference was found in the live birth rate between the patients undergoing single course antibiotic treatment and those undergoing multiple course antibiotic treatment [10].

Cicinelli et al. recently reported similar results in 95 infertile CE women with unexplained etiology. The cumulative live birth rate per patient after

spontaneous conception in the course of a12-month follow-up was higher in the cured CE group (65.8%, 25/38) than in the persistent CE group (6.6%, 1/15) and non-CE group (4.8%, 2/42) [31].

Itaya K. et al, followed up the pregnancy outcome in 118 CE women with a history of RIF undergoing antibiotic treatment. All of the patients had the subsequent fresh or cryopreserved-thawed cleavage-stage embryo/ blastocyst transfer cycle after the second endometrial biopsy to confirm the clearance of ESPCs. The live birth rate per patient in the cured CE group after antibiotic treatment was 32.8% (38/116) in the first ET cycle and 38.8% (45/116) in three cumulative ET cycles, whereas one patient with persistent CE failed to conceive. The effect of the antibiotic treatment was notable in the cryopreserved-thawed blastocyst transfer cycles [12]. The live birth rate in the cured CE group was higher than that in the RIF/non-CE group (22.1%, 50/226 in the first ET cycle and 27.9%, 63/226 in the cumulative three ET cycles), suggesting that the effectiveness of the antibiotic treatment for CE is independent of endometrial scratching effect [43].

In infertile women with tuberculosis-associated CE, antitubercular chemotherapy based on a positive endometrial biopsy–polymerase chain reaction test improved their reproductive outcomes. After 6-month administration of the antitubercular agents, the clinical pregnancy rate within 12 months was about 90% [44].

Andrews WW et al. supported the idea that antibiotic treatment is a promising therapeutic option to improve the pregnancy outcome in infertile women with CE. Prospective randomized controlled trials are required to verify these results [45].

Our study has some limitations, first of all, it is a single center study that was conducted over a relatively small sample size. Also, the bacteriological examination of the collected specimens should have been done to precisely detect the implicated organisms. It is possible that in the future microbiome study of endometritis fluid or biopsy may replace histologic examination of plasma cells as the gold standard in the diagnosis of CE [21].

5. CONCLUSION

Office hysteroscopy is a reliable and useful examination for investigating chronic endometritis. It could be useful for screening asymptomatic infertile patients. Bearing in mind that chronic endometritis is a hidden condition that is difficult to detect with noninvasive examination, we suggest that hysteroscopy should be always performed in the diagnostic work-up of women with unexplained infertility, especially before starting assisted reproduction procedures. Also, endoscopic samples should be obtained during hysteroscopy to increase the diagnostic accuracy.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

Written informed consent was obtained from all participants.

ETHICAL APPROVAL

The study was approved by the Ethics Committee of Faculty of Medicine, Tanta University, Egypt.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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