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Assessment of Subclinical Endometritis in Unexplained Primary Infertility

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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 work: The purpose of the study was to assess subclinical chronic endometritis in cases of primary infertility and also assess the benefits of hysteroscopic procedures in the diagnosis of latent CE as a supplement to current theories. Materials and methods: The present study was conducted on 50 female patients under 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 were divided randomly into two equal groups; (Group A & Group B) each of 25 patients. In group A, patients underwent office hysteroscopy for obtaining a visualized endometrial biopsy. In group B, patients were subjected to a blind endometrial biopsy by a Pipelle de Cornier. Results: In this study, we found that 30 patients (60 %) had chronic endometritis. Twenty one (42%) cases were diagnosed by biopsies taken by the hysteroscopy while 9 (18%) patients were diagnosed by biopsies taken by the Pipelle. The diagnostic accuracy of hysteroscopy in 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%. Conclusions: Chronic endometritis should be considered in the workup of unexplained primary infertility. Hysteroscopy is a useful, simple, cost effective procedure with a high diagnostic accuracy in chronic endometritis screening in asymptomatic infertile women; however endometrial biopsy should be complemented for the CE diagnosis.
[Almandouh Hussein Bosilah, Abdelsamie Abdelmonaiem Abdelsamie, Sameh Samy Abou-Beih, Medhat Abdelrhman Abdelhalim Ibrahim, Mohammed Sobhy Bakry. **Assessment of Subclinical Endometritis in Unexplained Primary Infertility.** *Biomedicine and Nursing* 2020;6(3): 11-19]. ISSN 2379-8211 (print); ISSN 2379-8203 (online). http://www.nbmedicine.org. 2. doi:10.7537/marsbnj060320.02.

Keywords: Assessment; Subclinical; Endometritis; Unexplained Primary Infertility

1. Introduction

Infertility is defined as the inability to achieve clinical pregnancy after 12 months of frequent unprotected sexual intercourse or more. (Zegers-Hochschild *et al*., 2009). Diagnosis of unexplained infertility will be achieved without a specific medical cause following infertility work-up, including semen analysis in males and ovulation and fallopian tube assessment in females. (Van voorhis, 2006).

In fertility clinics, one of the most common conditions is unexplained infertility. (Adamson & Baker, 2003; Brandes *et al*., 2010). Despite the improvement of the diagnostic tools in reproductive medicine, infertility remains unexplained in up to 25% of cases (Brandes *et al*., 2011).

Only recently, chronic endometritis (CE) has been linked to embryonic transplantation failure and infertility (Kitaya *et al*., 2016). Chronic endometritis is a persistent inflammation of the uterine endometrial lining. It is thought to be related with irregular uterine bleeding, recurrent abortion and infertility (Polisseni *et al*., 2003; Romero *et al*., 2004).

Most CE cases show no symptoms, or only mild ones. Due to 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. (Kitaya *et al*., 2016).

Chronic endometritis was found to be present in 12–46% of endometrial biopsies in infertile patients (Johnston *et al*., 2010; Moreno *et al*., 2018).

In these cases, early diagnosis and treatment significantly improve pregnancy rates (Féghali *et al*., 2003).

However, it has been found that it is very difficult to treat chronic endometritis. Most diagnostic

tests are usually asymptomatic and difficult to identify. 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 (Matteo *et al*., 2009; Adegboyega *et al*., 2010). Though, the existence of plasma cells in the endometrial stroma is the only widely recognized histological criterion for chronic endometritis diagnosis (Kasius *et al*., 2011).

A number of conditions may interfere with the search for plasma cells, such as mononuclear inflammatory cell infiltrates, stromal cell proliferation and plasmacytoid presence of stromal cells or a marked predecidual reaction in the late endometrial secretion (Adegboyega *et al*., 2010; Resta *et al*., 2012).

As part of the infertility work-up, endometrial biopsy and histological analysis have been widely used to assess endometrial development during the luteal and/or the follicular phases The precision and intra-and inter-observer consent of the endometrial biopsy for the diagnosis of luteal phase defects has been assessed thoroughly (Myers *et al*., 2004).

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.

Aim of the work

The aim of this study is to assess and to detect subclinical endometritis in asymptomatic, primary infertile patients with unexplained cause .

2. Patients and Methods:

The present study was conducted on 50 patients less than 40 years of age reported for fertility therapy, after being diagnosed with unexplained primary infertility at Mataria teaching hospital in collaboration with department of obstetrics and gynecology, Faculty of Medicine, Fayom University. Our study was carried out during the period from May 2018 through April 2019. Patients have been assessed for having subclinical endometritis by obtaining endometrial biopsies and subjected for histological examination.

Patient population:

After taking informed written patient consent, as approved by local ethical committee, fifty patients less than 40 years of age reported for fertility therapy, at the Mataria teaching hospital in collaboration with department of obstetrics and gynecology, Faculty of Medicine, Fayom University, have undergone endometrial biopsies.

Inclusion criteria:

After taking a proper history, complete clinical examination, biochemical and hormonal profile, Patients under the age of 40 years diagnosed as having primary unexplained infertility have been subjected to endometrial biopsy.

Exclusion criteria:

1. Symptoms that suggest of intrauterine pathology.
2. transvaginal ultrasound abnormalities.
3. Previous examination of hysteroscopy or any instrumentation to the genital tract.

Endometrial biopsies:

After excluding pregnancy by serum beta-HCG, the endometrial biopsies have been scheduled during the follicular phase of the menstrual cycle (Day 3–14). All participants have been randomly assigned into one of the following two groups: Group (A): this group included 25 patients who underwent office hysteroscopy for obtaining a visualized endometrial sample.

Group (B): this group included 25 patients who have been subjected to a blind endometrial biopsy by A Pipelle de Cornier.

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

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 (X2) 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, +ve predictive value, -ve predictive value, 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 present research was carried out on 50 female patients attending the infertility clinic at Mataria teaching hospital complaining of unexplained primary infertility during the period from May 2018 to April 2019. Patients have been followed for an average of 3 months, (the follow up period ranged from 1 to 6 months). Patients were randomly divided into two groups which were equal; (Group A & Group

B) each consists of 25 patients. In group A, patients underwent office hysteroscopy for obtaining a visualized endometrial biopsy. In group B, patients were subjected to a blind endometrial biopsy by a Pipelle de Cornier, as shown in (Figure 1).

The main outcome measured the percentage of patients having endometritis among patients subjected to endometrial biopsy.

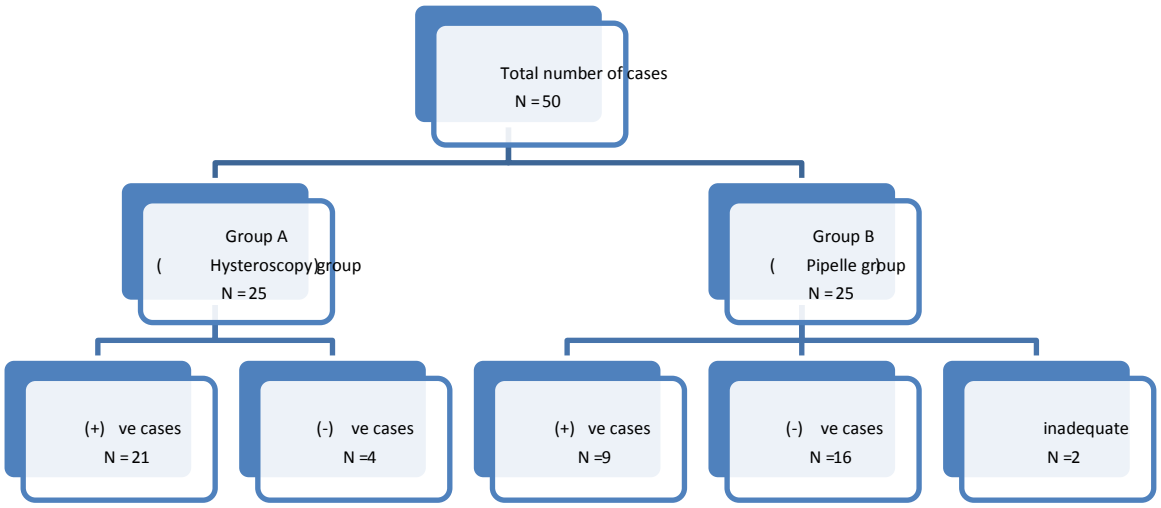

Figure (1): Diagram shows study results in the included patients

Age of women included in this study ranged from 23-39 years with median 30.5 years. In group A ages ranged from 24-39 years old, while in group B ages ranged from 23-38 years old. Number of women in relation to age is shown in (Figure 2).

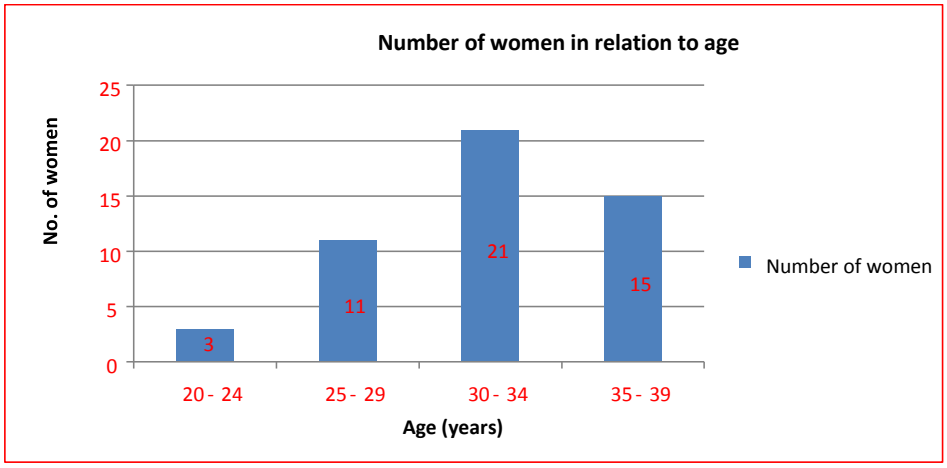

Figure (2): Bar-Chart showing age distribution in the included cases of the study

The median age in group A was 31 years, while was 30 years in group B. There was no evidence to support a statistically significant in age between the two groups of patients (P value = 0.29), as shown in (Table 1).

Table (1): The age significance between group A and group B

Group	A	B
Number of patients (N)	N1 = 25	N2 = 25
The median age	31	30
P value	0.29 (> 0.05)	

Regarding results of endometrial biopsies taken in the two groups after being stained with CD138, there was statistical significant agreement between both results (p value = 0.002), as shown in (Table 2).

Table (2): The CD138 significance between group A and group B

Group	A	B
Number of biopsies (N)	N1 = 25	N2 = 23
Positive finding	21	9
P value	0.002 (< 0.05)	

The biopsies were considered as "Negative" when no plasma cells stained with CD 138, and as "Positive" when one or more plasma cells were observed on 10 non-overlapping high power fields in the endometrial tissue samples, as shown in (Figure 3).

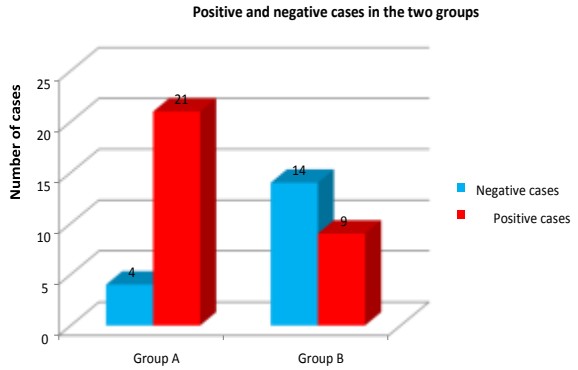

Figure (3): Biopsy grading according CD-138

Most of cases that were positive for CD138 were seen in hysteroscopy group (21 cases that represents 70% of positive cases) as opposed to only 9 cases in Pipelle group representing 30% of the positive cases, as shown in (Figure 4).

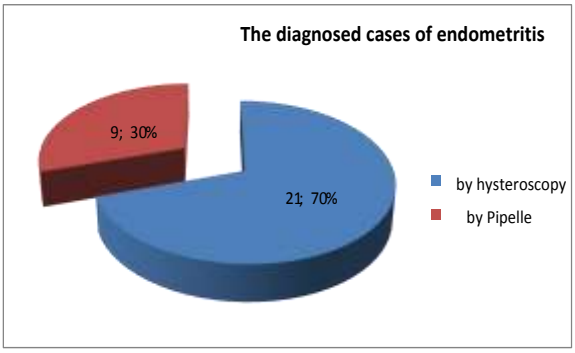

Figure (4): Number of cases diagnosed by Pipelle and hysteroscopy

In group A, Plasma cell topography was easier to identify in 21 samples out of 25 samples as follows; 12 epithelial (57.1%), 3 epithelial + focal (14.3%), 5 epithelial + stromal (23.8%) and 1 stromal phases (4.8%), as shown in (Figure 5).

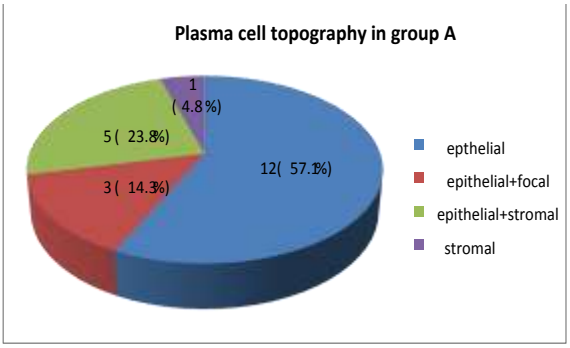

Figure (5): Plasma cell topography in the hysteroscopy group

Within the same group, istologic dating of endometrial phase was possible in 19 samples out of 25 samples as follow; 13 late proliferative (68.4%), 3 mid proliferative (15.8%), and 3 mid secretory (15.8%). In 6 cases, no histologic dating was possible either because the sample was inadequate (2 samples) or atrophic (4 samples) as shown in (Figure 6).

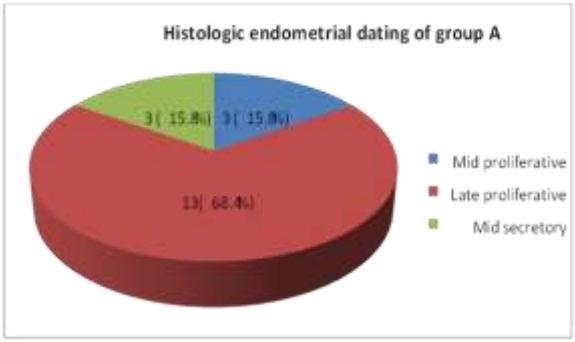

Figure (6): Endometrial phases of the hysteroscopy group

In group B, plasma cell topography was only to identify in 9 samples out of 25 samples as follow; 4 epithelial (44.44%), 2 epithelial + focal (22.22%), and 3 stromal phases (33.33%), as shown in (Figure 7).

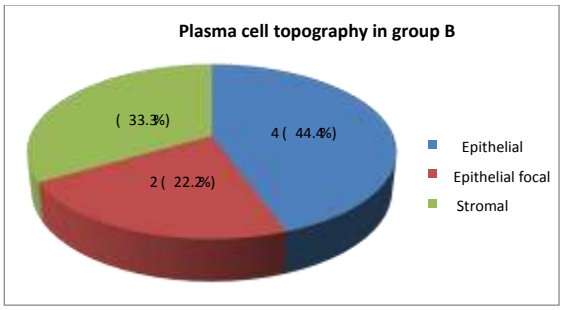

Figure (7): Plasma cell topography in the Pipelle group

Within the same group, histologic endometrial dating was possible in 20 samples out of 25 samples as follow; 6 mid proliferative (30%), 9 late proliferative (45%), 1 early secretory (5%), 3 mid secretory (15%), 1 late secretory phases (5%). In 5 cases, no histologic dating was possible either because the sample was inadequate (4 samples) or atrophic (1 sample), as shown in (Figure 8).

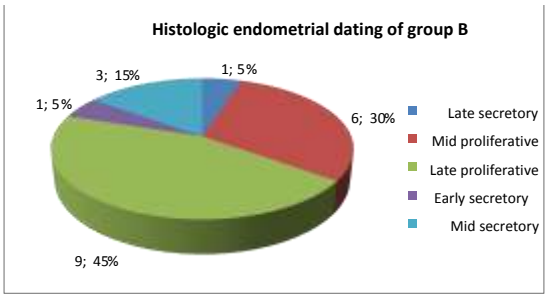

Figure (8): Endometrial phases of the Pipelle group

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) in this study. BMI of women included in the study ranged from 18 kg/m^2 to 37 kg/m^2. In group A BMI ranged from 22-37 kg/m^2, while in group B BMI ranged from 18-35 kg/m^2, as shown in as shown in (Figure 9).

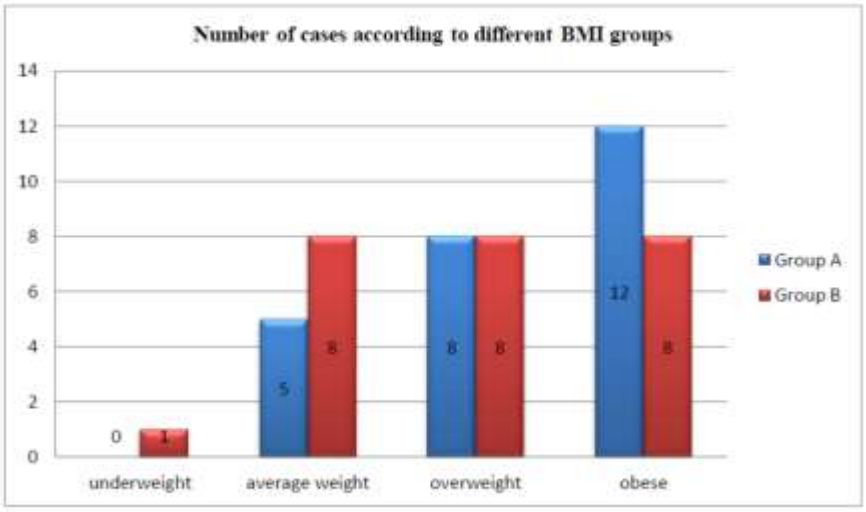

Figure (9): Categorization of endometritis cases according to their BMI

According to categorization of endometritis cases according to their BMI, there was no evidence to support a statistically significant difference between the different BMI groups, as shown in (Table 3).

Table (3): Categorization of endometritis cases according to their BMI

Endometritis	Underweight		Average weight		Overweight		Obese		P value
	NO	%	NO	%	NO	%	NO	%	
+ve cases	1	3.3%	6	20%	10	33.3%	13	43.3%	0.364 (>0.05)
-ve cases	0	0%	6	33.3%	8	44.4%	4	22.2%	

The suspected cases of endometritis found during the procedure in the hysteroscopy group were 11 cases. Of these cases, 10 cases were confirmed to have endometritis with overall diagnostic accuracy of 52%, as shown in (Table 4).

Table (4): Diagnostic accuracy of hysteroscopy in diagnosing endometritis

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

PPV: positive predictive value, NPV: negative predictive value

In this study, the histologic dating of endometrial biopsies has been correlated with the day of sampling. Histologic dating was found to be more accurate in cases free from endometritis. Of the 20 cases that were free from endometritis, 17 endometrial biopsies were accurately correlated with the day of sampling with accuracy of 85%, while the accuracy of histologic dating with endometritis cases was 76.6% (23 out of 30 patients).

Among patients with endometritis, the accuracy was found to be more in patients underwent office hysteroscopy (18 out of 21 patients) with accuracy of (85.7%) than those underwent pipelle biopsy (7 out of 9 patients) with accuracy of 77.7%.

4. Discussion

Despite the improvement of the 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 (Brandes *et al*., 2011).

At present, there is 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. (Balasch, 2000). This is why we were trying to search for valuable, simple, rapid, relatively inexpensive and accurate methods in 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 (Kitaya *et al*., 2016).

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 (Kasius *et al*., 2011).

The present study was conducted on 50 female patients under 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 were randomly divided into two equal groups; (Group A & Group B) each of 25 patients. In group A, patients underwent office hysteroscopy for obtaining a visualized endometrial biopsy. In group B, patients were subjected to a blind endometrial biopsy by a Pipelle de Cornier .

Our primary goal was to determine the prevalence of CE 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 30 patients (60 %) had chronic endometritis. Twenty one (42%) cases were diagnosed by biopsies taken by the hysteroscopy while 9 (18%) patients were diagnosed by biopsies taken by the Pipelle.

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

However, a higher prevalence of CE was found in a cross sectional study performed by Eckert *et al*., (2002) on 152 women, stated that 109 (71.7%) women had endometritis. We believe the difference in such results was due to the fact that the authors were having different inclusion and exclusion criteria, as study included patients with suspected pelvic inflammatory disease and patients who had intrauterine device. Furthermore, a retrospective study was performed by Cicinelli *et al*., (2005) 106 women with unexplained infertility from January 2009 through June 2012 and showed that 70 (66.0%) women were diagnosed with CE. 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 by a study performed on 46 women, reported that the prevalence of CE was 14%. 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 10 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 10 non-overlapping high power fields in the endometrial tissue samples.

In another study performed by Song *et al*., (2018) on a larger sample size, 1551 women underwent hysteroscopy and endometrial biopsy. 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 obtained; as, 302 samples were obtained during the secretory phase. In this study, authors found that the prevalence of chronic endometritis in samples obtained during the proliferative phase was higher (26 %) compared to the secretory phase (17 %). A possible explanation for the disparity is that plasma cells appear to live 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, only 9 (18%) patients were diagnosed of CE by Pipelle. These results agreed with a study done by Makled *et al*., (2014) on 100 women, stated that analysis of samples obtained using the Pipelle endometrial suction curette detected CE in 15(15%) cases.

Moreover, Fakhar *et al*., (2008) reported 7 (7%) cases of endometritis in a study conducted on 100 patients 35 years of age and older using Pipelle biopsy. Such data suggest that in asymptomatic, infertile women, Pipelle is not effective in screening for chronic endometritis.

In our study, we found twenty one (42%) 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.

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. The aim of the study was 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 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 as they also go in line with our conclusion.

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 indicate that in asymptomatic, infertile women, hysteroscopy is not helpful in screening for chronic endometritis.

The diagnostic accuracy of hysteroscopy in diagnosis of CE in our study was 52%. This result agreed partially with study done by Moreno *et al*., (2018) on 65 patients assessed for chronic endometritis with an accuracy of 58%.

Age of women included in this study ranged from 23-39 years with mean ± SD (31.8 ± 4.15 years). There was no statistically significant variation in age with relation to CE.

This result goes hand to hand with study done by Cicinelli *et al*., (2014) on 256 patients. The patients were 23–40 years of age; mean ± SD 31.9± 4.1 years. There was no statistically significant variation in age in relation to CE.

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.

We believe that having a wider age range could be the reason behind such differences.

In our study, we evaluated the effect of body mass index (BMI) on the incidence of CE. Body mass index (BMI) of women included in the study ranged from 18 kg/m^2 to 37 kg/m2. 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 in the study, there was also no association between difference in BMI and incidence of CE. We agreed with this study even though we had a smaller sample size.

This also comes in line with a study done by Cicinelli *et al*., (2014) on 256 patients, reported no statistically significant difference in incidence of CE with different BMI despite having different BMI range (23 ± 1.9).

Conclusion

- CE has been recently linked to infertility and poor reproductive outcomes in the context of ART.
- Our review article attempted to assess subclinical chronic endometritis in cases of primary infertility and the benefits of hysteroscopic procedures in the diagnosis of latent CE should also be evaluated as an addition to existing theories.
- Histological examination of an endometrial biopsy remains the gold standard in CE diagnosis. The

presence of plasma cells in the endometrial stroma is generally accepted for diagnosis as the only histological criterion.

- There is a solid agreement on the use 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.
- The prevalence of CE in unexplained primary infertility women in our study was 60%.
- Hysteroscopy is a useful, simple, cost effective procedure with a 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 prevalence of CE with different age groups and different BMI.

Recommendation

- Chronic endometritis should be considered in the workup of unexplained primary infertility.
- Hysteroscopy is a recommended useful diagnostic tool in chronic endometritis screening in asymptomatic infertile women; however endometrial biopsy for CE diagnosis should be complemented.
- Syndecan-1 (CD138) is highly recommended for the histological diagnosis of CE due to its higher sensitivity and detection rate of plasma cells compared to the use of H & E staining and morphology alone.
- In order 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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8/2/2020