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Prevalence of chronic endometritis in unexplained implantation failure

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Abstract---Background: The actual prevalence of chronic endometritis (CE) in the general population is still ill-defined. Aim of the study: was to evaluate the effects of chronic endometritis on implantation failure at ICSI through its prevalence at hysteroscopy and histology, in a population of women who experienced implantation failure at ICSI. Patients and methods: This was a prospective observational cross-sectional study that has been conducted in the International Islamic Center for Population Studies and research – Al Azhar University from 2017 till 2022. The study was conducted on 150 women who were affected by infertility and one unexplained implantation failure or more at ICSI. Results: In our study, hysteroscopy is a reliable diagnostic technique for CE in unexplained implantation failure and is highly reliable in excluding CE with sensitivity, specificity, accuracy, PPV and NPV as 96.5%, 88.17%, 91.3%, 83.3% and, 97.6% respectively. Conclusion: This study suggests that hysteroscopy is a useful diagnostic tool in women with unexplained implantation failure

as regard CE diagnosis. However, endometrial samples should be obtained during hysteroscopy to increase the diagnostic accuracy.

Keyowrds---chronic endometritis, unexplained implantation failure, in-vitro fertilization (IVF).

Introduction

The pregnancy rate following one cycle of In-vitro fertilization (IVF) and embryo transfer can be as high as 60% [1]. However, even in the very successful units, some couples fail repeatedly. Failure could be caused by many different factors such as inappropriate ovarian stimulation, suboptimal laboratory culture conditions and faults in embryo transfer techniques. Repeated implantation failure (RIF) is defined as failure to conceive following two or three embryo transfer cycles, or cumulative transfer of more than 10 good quality embryos [2]. Most commonly, RIF is associated with unexplained infertility but in fact, it also can be observed in patients with well-known causes of infertility (tubal factor, male factor, etc.) [3]. Implantation failure is related to either maternal factors or embryonic causes. Maternal factors include uterine anatomic abnormalities, thrombophilia, non-receptive endometrium and immunological factors [4].

Although uterine abnormalities are considered to have a relevant impact on the chances to conceive through IVF, conventional infertility investigations, based on ultrasound and hysterosalpingography (HSG), may miss subtle intrauterine lesions [5, 6]. At hysteroscopy prior to intracytoplasmic sperm injection (ICSI), the prevalence of unsuspected intrauterine abnormalities has been demonstrated to range between 11 and 45% [6]. One of the abnormalities, which cannot be detected with ultrasound and HSG, is chronic endometritis that is a subtle pathology often asymptomatic or only accompanied by mild disturbances. Histological identification of plasma cells in the endometrial stroma is considered the gold standard for the diagnosis [7], but due to the normal presence of leukocytes in the endometrium especially before menstruation, even histology may miss the diagnosis. Fluid hysteroscopy reliably diagnoses chronic endometritis based on the demonstration of specific signs such as micropolyps, stromal edema and focal or diffuse hyperemia [8, 9].

Chronic endometritis may hamper endometrial receptivity and may cause infertility because the endometrium is characterized by an abnormal pattern of lymphocyte subsets and, consequently, an aberrant endometrial microenvironment [10]. Chronic endometritis was identified in 30.3% of patients with repeated implantation failure at ICSI and women diagnosed with it had lower implantation rates (11.5%) after an ICSI cycle [11]. In contrast, Kasius and coworkers[7] reported that the clinical implication of chronic endometritis seems minimal since they diagnosed this condition in 2% of asymptomatic infertile patients with a normal transvaginal ultrasound examination (TVS). The same author reported that the reproductive outcome at ICSI cycles was not negatively affected by chronic endometritis and that the low prevalence and unknown clinical significance of it warrants further study [7, 12]. The aim of the study was to evaluate the effects of chronic endometritis on implantation failure at ICSI

through its prevalence at hysteroscopy and histology, in a population of women who experienced implantation failure at ICSI.

Patients and Methods

This was a prospective observational cross-sectional study that has been conducted in the International Islamic Center for Population Studies and research – Al Azhar University from 2017 till 2022. The study was conducted on 150 women who were affected by infertility and one unexplained implantation failure or more at ICSI.

Inclusion criteria

Absence of any abnormality at transvaginal ultrasound and at HSG, age less than 40 years, and documented history of good quality embryos transferred in one or more previous ICSI cycles without signs of implantation.

Exclusion criteria

FSH on day 3 more than 10 mUI/ml. BMI (kilograms per square meter) more than 30 kg/m2. History of clinical repeated pregnancy loss. Previous surgery for myoma and/or endometriosis. Ultrasound diagnosis of ovarian endometriomas. Corticosteroid treatment or other medical treatments known to interfere with immune system. Known clinical autoimmune or other chronic general diseases such as DM. Antiphospholipid syndrome proven by (normal anticardiolipin IgG & IgM and lupusanticoaglant antibodies) previously done by the patient already. Thrombophilic condition requiring anticoagulant therapy. Severe male factor (severe oligo-atheno-terato and zoospermia). Documented chromosomal rearrangement in either parent. contraindications to hysteroscopy e.g heavy vaginal, PID, bleeding, recent uterine perforation … etc., and Unwillingness to give informed consent. After an informed written consent, all patients included in this study have been subjected to the following:

History taking

Including the personal, obstetrical, gynecological, Family, Medical and Surgical history of the female as well as personal, medical, surgical, and family history of her husband.

Clinical examination

A clinical examination, including general, abdominal, and pelvic examinations, as well as a vaginal speculum examination has been done to all patients.

Investigational studies

- Routine laboratory investigation: Complete Blood Count, Prothrombin time and activity, liver function, kidney function, blood sugar, etc.

- Basic investigations for male and female infertility include: TVS and folliculometry, HSG, hormonal profile of the lady, FSH, LH, E2, TSH, Prolactin and AMH), and semen analysis for the husband.

Diagnostic hysteroscopy and an endometrial biopsy

Patients meeting the inclusion criteria were referred to hysteroscopy. It was done under general anaesthesia in the proliferative phase of the cycle (between days 6-12), to exclude the possibility of disturbing spontaneously occurring pregnancy and for the advantage that the endometrium is thinner and its visibility is better. An endometrial biopsy was taken and sent for histopathology examination.

Diagnostic hysteroscopy

Diagnostic hysteroscopy was performed using a rigid hysteroscope (continuous flow; 30-degree forward-oblique view) assembled in a 4-mm diameter diagnostic sheath with an atraumatic tip (Karl Storz Endoscopy, Tuttlingen Germany). A high-intensity cold light source and fiberoptic cable were used to illuminate the uterine cavity. Normal saline (0.9%) was used as the distention medium, keeping the pressure between 100 and 120 mm Hg using a pressure adjustable cuff system, with the aim to use the lowest pressure required to distend the uterine cavity adequately. After the procedure, patients were observed for possible side effects and complications.

The findings at diagnostic hysteroscopy were documented on a special data collection form that included the following information: (1) the appearance and shape of the endocervical canal (2) cervical length (subjectively assessed), and cervical direction. (3) the appearance of the endometrium (4) shape of the uterine cavity (5) presence and location of structural anomalies if any. (6) Duration, possible side effects, and complications of the procedure. Suspected cases of chronic endometritis should have hysteroscopic picture. The diagnosis of chronic endometritis was based on the demonstration of micro-polyps (less than 1 mm of size), stromal edema and focal or diffuse hyperemia, as previously published [8, 9].

Histological examination of an endometrial sample

Endometrial samples were fixed in neutral formalin and later embedded in paraffin for histological examination. Five-micrometer sections were stained with hematoxilin-eosin and examined by the same senior pathologist who was unaware of previous hysteroscopic findings. Histological diagnosis of chronic endometritis has been based on the presence of superficial stromal edema, increased stromal density and, pleomorphic stromal inflammatory infiltrate dominated by lymphocytes and plasma cells [13]. Using an Olympus BX40 microscope, the degree of plasmacytic inflammation was determined as number of plasma cells per 40× high-power field (HPF).

Ethical Considerations

This study was approved by the Ethics Committee of Faculty of Medicine, AL Azhar University. All women gave their informed written consent to use, anonymously, their data for research purposes. Signed written informed consent was obtained from all patients. All participants in this study received a detailed explanation about the aim, objectives and methodology of the study before enrollment. There are adequate provisions to maintain privacy of participants and confidentiality of the data are as follows: A code number was given to every participant with the name and address kept in a special file. The patient name when we use the research, and the results of the study only in a scientific manner and not to use it in any other aims.

The benefits of the study to the patients included in the study

The appropriate diagnosis and management.

Sample Size Calculation

Sample size was calculated by SPSS windows version 28 program with α-error of 0.05, 80% power and 80% confidence interval. The prevalence of the disease was 66% dependent on previous study had the same objective and research question [14]. Also, the design effect was 1 and the population size was 100000 during calculation. So the sample size was 148 cases.

Statistical analysis

The SPSS windows version 28 program was used in this study to analyze the data. For uni-variable analysis, the data were expressed in numbers and percentages for qualitative data used, while in quantitative parametric data after testing of normality using skewedness score, keratosis score, and the normality graphs as histogram and box plot, the mean ± standard deviation (SD) were used for normal parametrical data, while the median and IQR were used for non-parametrical one. For bi- variables analysis and for hypothesis testing Chi-square test was used for non-parametric values relationships to determine the level of significance, Monte Carlo test as correction for Chi-Square test when more than 25% of cells have count less than 5 in tables with more than two groups and Fischer Exact test was used within the two groups, on the other hand T-test, ANOVA and Pearson correlation test were also used for quantitives data significance. The statistical significance correlation reached if P value less than 0.05. The study included measure of sensitivity for hysteroscopy in diagnosis of chronic endomertrtis as a negative test for exclusion depended on the result of the following statistical procedures. Sensitivity: Probability that a test result was positive when the disease is present (true positive rate, expressed as a percentage). Sensitivity = (true +ve)/ [(true +ve) + (false –ve). Specificity: Probability that a test result was negative when the disease is not present (true negative rate, expressed as percentage). Specificity = (true –ve) / [(true –ve) + (false +ve)]. PPV (positive predictive value): probability that the disease is present when the test is positive (expressed as a percentage of true positive cases to all positive). PPV = (true +ve) / [(true +ve) + (false +ve)]. NPV (negative predictive value):

probability that the disease is not present when the test is negative (expressed as a percentage of true negative subjects to all negative). NPV = (true –ve)/ [(true –ve) + (false –ve)]. P value < 0.05 was considered significant.

Results

This prospective, observational, analytical, cross-sectional study has been conducted on one hundred fifty women, who were affected by infertility and one or more unexplained implantation failures. The final results are as follow: Table (1) shows that, in our study, 59.3% of cases are at or below 30 years old while, 40.7% are above 30 years old. Mean&SD is 30.56 ± 4.33 years. Range (23-39).

Table 1
Descriptive socio economic characters for the whole sample cases according to age

Age groups	Numbers	%
≤ 30 years	89	59.3%
> 30 years	61	40.7%
Mean ± SD	30.56 ± 4.33 years	
Mini age	23 years old	
Max age	39 years old	

Table (2) shows that, most of cases have primary infertility representing 69.3 % of cases, while secondary infertility represents 30.7%.

Table 2
Distribution of cases according to type of infertility

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

Table 3
The relation between the infertility type and residence

		Residency		Total		
		Rural	Urban		X2	P-VALUE
Infertility Type By number of cases	Primary	36	68	104	14.6	0.002
	Secondary	40	6	46		
Total		76	74	150		

Table (4) shows that, n our sample population 46% of cases had implantation failure once (69/150), while 54% of cases (81/150) experienced at least two unexplained implantation failures (RIF), with the mean 3 times.

Table 4
Number of implantation failure among the whole sample cases

		Number of cases	Percent
Failed implantation	single	69	46%
	repeated	81	54%
	Total	150	100%
	number of failed previous implantation	Mean ± SD	3.02 ± 1.34

Table (5) shows that maximum number of implantation failure in the study is 6 times

Table 5
Distribution of cases according to number of failure in implantation

Implantation Failure					
		Numbers	Percent	Valid Percent	Cumulative Percent
Number of failure	1.00	69	46.0	46.0	46%
	2.00	32	21.3	21.3	67.3%
	3.00	25	16.7	16.7	84%
	4.00	18	12.0	12.0	96%
	5.00	4	2.7	2.7	98.7%
	6.00	2	1.3	1.3	100%
	Total	150	100.0	100.0	

Table (6) shows that, there is a strong, statistically highly significant relationship between the presence of chronic endometritis (CE) and unexplained implantation failure (P value 0.000). Among cases with histopathologically confirmed CE (n=57), 23 cases and 34 cases experienced single implantation failure and RIF respectively. However, out of the cases without CE (n= 93), 46 and 47 cases gave documented history of single implantation failure and RIF respectively.

Table 6
The relation between the implantation failure and chronic endometritis cases

		Failed implantation		Total	X2	P-Value
		Single n	Repeated n			
Chronic endrometritis by biopsy	Chronic endometritis	23	34	57	21.1	0.000
	No chronic endometritis	46	47	93		
Total		69	81	150		

Table (7) shows that, there is a highly significant relationship between residence and number of previous unexplained implantation failure, as 50/66 of the rural areas cases experienced RIF (P value 0.0012)

Table 7
The relation between the implantation failure and residence of the cases

Residence	Implantation		Total	X2	P – VALUE
	Repeated N	Single N			
Urban	31	53	84	18.7	0.0012
Rural	50	16	66		
Total	81	69	150		

Table (8) shows that, there is no significanct difference among cases with or without endometritis according to residence, that related to chi square test significance

Table 8
The difference between cases according to residence

		Residence		Total	X2	P VALUE
		Rural N	Urban N			
Chronic endometritis	Chronic endometritis (N)	28	29	57	.88	0.758
	No chronic endometritis(N)	48	45	93		
Total		76	74	150		

Table (9) shows that, There is no significant difference among cases with or without CE as regard type of infertility (P value 0.452).

Table 9
Relation between the chronic endometritis and type of infertility

		Primary N	Secondary N	Total N	X2	P Value
Endrometritis by biopsy	Chronic endometritis	39	18	57	10.1	0.452
	No chronic endometritis	65	28	93		
Total		104	46	150		

Table (10) shows that, 89.3% of cases were without other abnormal findings during hysteroscopy as endometrial polyp, fine adhesions, or cervical stenosis.

However, only 5.3%, 4% and 1.3% of cases detected with endometrial polyp, fine adhesions, and cervical stenosis respectively during hysteroscopy.

Table 10
Distribution of other findings among cases during hysteroscopy

		Number	Percent
Other Findings	No other finding	134	89.3%
	Endometrial polyp	8	5.3%
	Fine adhesions	6	4%
	Cervical stenosis	2	1.3%
	Total	150	100%

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

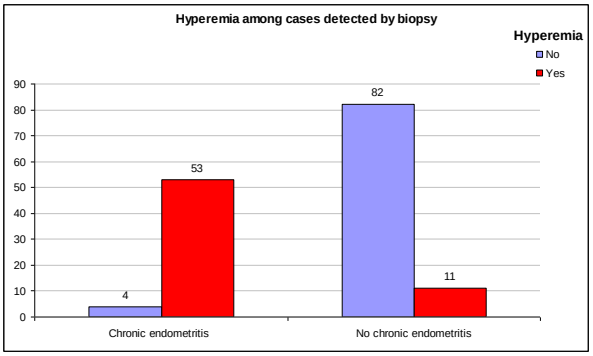

Figure 1. Distribution of hyperemia as a finding by hysteroscopy among cases, after histopathological examination

This figure shows that, 53 cases have stromal edema during hysteroscopy, which represents 80.3% of hysteroscopically diagnosed cases as having CE(53/66). Biopsies from all these cases are also positive for CE (53/57) (Figure 2).

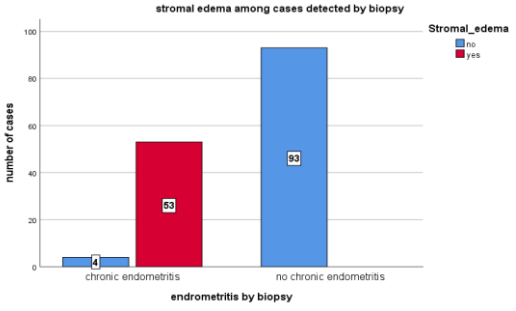

Figure 2. Distribution of stromal edema as a finding by hysteroscopy among cases, after histopathological examination

This figure shows that, 39 cases have endometrial micropolys during hysteroscopy, which represents 59% of hysteroscopically diagnosed cases as having CE (39/66). Biopsies from all these cases are also positive for CE (39/57) (Figures 3).

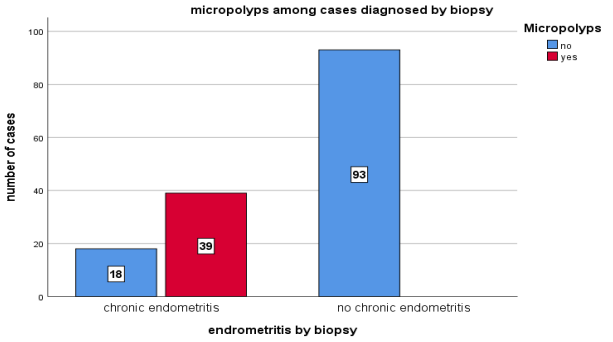

Figure 3. Distribution of micro polyps as a finding by hysteroscopy among cases, after histopathological examination

Table (11) showed; hysteroscopy is a reliable diagnostic technique for CE in unexplained implantation failure and is highly reliable in excluding CE with sensitivity, specificity, accuracy, PPV and NPV as 96.5%, 88.17%, 91.3%, 83.3% and, 97.6% respectively.

Table 11
Describe the degree of sensitivity and specificity of hysteroscopy in comparative with the biopsy histological examination which is gold standardized test applied in our study

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

PPV: Positive predictive value. NPV: Negative predictive value.
TP: True positive cases. TN: true negative cases.
FP: false positive cases. FN: false negative cases.

Discussion

In our prospective study, we aimed to investigate the prevalence of CE in Egyptian women with unexplained implantation failure for the potential association between undiagnosed CE and impaired receptivity of the endometrim to be assessed. This cross-sectional, observational, analytical study was conducted in the ART unit belonging to the International Islamic Center for Population Studies and Research, at Al-Azhar University. This is the largest governmental ART center in Cairo, with available resources to accomplish our study also, with high flow of patients coming from all over the country, that allowed to ensure recruitment of patients representing different Egyptian areas in the study. A study population of infertile Egyptian women affected with one or more unexplained implantation failure at ICSI have participated in this study after informed written consent. In order to study the association between chronic endometritis and implantation failure, we will be primarily looking for undiagnosed chronic endometritis in all participants through a hysteroscopy and endometrial biopsy which are readily available in the center.

We included a total of 150 infertile females with documented history of one or more unexplained implantation failure. In our study, 59.3 % of cases are at or below 30 years old, while 40.7% are more than 30 years old, but the whole cases under 40 years old, with average age 30.5 ± 4.33 years. Patients more than 40 years are not included as age is one of factors associated with poor outcome at ICSI [15]. In our sample, 53.3% are urban, 46.7% are rural. In the current study, the mean BMI of the included cases was 25.4± 3.53 Kg/m2, as ladies with BMI more than 30 Kg/m2 were not included in the study owing to the associated decrease in reproductive outcome. Patients with a BMI more than 30 Kg/m2 have up to 68% lower odds of having a live birth after the first ART cycle compared with women with a BMI less than 30 kg/m2 [16]. A large retrospective study of over 6,000 women, found a delayed spontaneous conception in obese women, mainly due to 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/m2 with P value (0.024) [17].

Most of cases in our sample have secondary school or university educational level, representing 39.3% and 24.7% respectively.The possible explanation for that, is that less educated couples may find more difficulty travelling to Cairo,or communicating with fertility centers, so are less encouraged than the more educated couples. In our study, the Mean &SD duration of infertlity is 7.9 ±3 years, and most of participants are infertile for around 5 years. Its reported that duration of infertility is one factors associated with poor outcome at ICSI [18]. Most of our cases have primary infertility 104/150 (69.3 %), while 46/150 have secondary infertility representing (30.7%). Interestingly, secondary infertility in our sample population is significantly higher in patients with rural residence (P-value0.002). Also, secondary infertility is significantly higher in ladies with lower educational levels. The propable explanation for that, may be the relatively insuffient health care in rural areas. Moreover, the less educated Egyptian women are unwilling to seek early medical care due to cultural reasons and insufficient health education.

In our study sample, 46% of cases had implantation failure once (69/150), while 54% of cases (81/150) experienced at least two unexplained implantation failures (RIF), with the mean 3 times. Most of primary infertility cases in our study gave documented history of one implantation failure (64/104), while most of secondary infertility cases have at least two unexplained implantation failures RIF(41/46). The propable explanation is that patients with primary infertility are more encouraged to seek evaluation and management in the International Islamic Center ART unit once they had a failed ICSI. We found that, there is a highly significant relationship between residence and number of previous unexplained implantation failure, as 50/66 of the rural areas cases experienced RIF (P value 0.0012). This also, may be related to type of infertility most frequently associated with them in our study as well as, the relatively more difficulty they are facing to come to our center in Cairo.

There is a highly significant difference between the age groups as regard number of previous unexplained implantation failure. While most of cases at or below 30 years old have single implantation failure (70/89), RIF is significantly higher in the age group more thant 30 years (44/61) with (P value 0.0000). Moreover, the increase in age have positive strong (0.68) interrelation with number of pervious unexplained implantation failures. This may be explained that younger couples are more encouraged to come to our center as well as by the negative effect of age on reproductive outcome as mentioned [18].

Prevalence of Chronic Endometritis in Unexplained Implantation Failure

Although, 44% of our sample cases are diagnosed by hysteroscopy as having chronic endomertrtis (66/150), the prevalence of CE in our study by histopathological examination is 38% (57/150). In our study, There was no significant difference among cases with or without CE according to residence (P value 0.758), level of education or as regard type of infertility (P value 0.452).The present study however, showed that there is a strong, statistically highly significant relationship between the presence of chronic endometritis (CE) and unexplained implantation failure (P value 0.000). Among cases with histopathologically confirmed CE (n=57), 23 cases and 34 cases experienced single implantation failure and RIF respectively. However, out of the cases without CE (n= 93), 46 and 47 cases gave documented history of single implantation failure and RIF respectively.

For that, we agree with Espinós et al. [19], In their SWOT (Strengths, Weaknesses, Opportunities, Threats) analysis when they advised not to include chronic endometritis in the initial baseline study before assisted reproduction. The reason for that, is not to delay other assisted reproduction treatments. However, they advised to test for CE in cases of repeated implantation failure and pregnancy loss after IVF with viable embryos and before continuing with costly reproductive processes, as results could be improved. Kitaya et al. [20] investigated the prevalence of chronic endometritis (CE) in infertile women with a history of repeated implantation failure (RIF) in their prospective study. In this study RIF was defined as serial negative pregnancy tests following transfer of at least three morphologically good cleavage-stage embryos and/or blastocysts. Endometrial biopsies from infertile women with RIF were subjected to

immunohistochemistrical/histopathologic diagnosis of CE. In this study, the prevalence of CE was 33.7%. Interestingly, they found that CE was found frequently in couples with male factor infertility, so a role of partners in CE is suggested.

Also, they found that after the first-line doxycycline treatment, the histopathologic cure rate in the following endometrial biopsy was 92.3%. And, after the second-line metronidazole/ciprofloxacin treatment, the overall cure rate was 99.1%. The live birth rate in the first ET cycle (P=.031, RR 1.48, 95% CI 1.03-2.12) and cumulative three ET cycles (P=.037, RR 1.39, 95% CI 1.02-1.90) following antibiotic treatment in the cured RIF/CE group (32.8% and 38.8%, respectively) was significantly higher than in the RIF/non-CE group (22.1% and 27.9%, respectively) [20]. This supports our finding of a statistically significant relation between CE and implantation failure, as improvement in reproductive out come is noted after successful treatment of CE in Kitaya et al. [20] study. Most recently Cheng et al. [21] concluded that, Patients with cured CE following oral antibiotic administration therapy had significantly higher CPR, IR, and OPR/LBR in comparison with patients without CE. Also, patients with persistent CE following oral therapy had significantly lower IR, CPR, and OPR/LBR in comparison with patients without CE. And, patients with cured CE had significantly higher IR, CPR, and OPR/LBR in comparison with persistent CE patients. This also supports our finding of a potential aeteological role of CE in RIF.

In their review of the published articles, Kimura et al. [22] showed that, the prevalence of CE ranges from 2.8-56.8% in infertile women, from 14-67.5% in women with RIF, and from 9.3-67.6% in women with recurrent pregnancy loss. Also, we agree with Agrawal et al. [23] who found the prevalence of chronic endometritis (CE) in infertile women undergoing ART is (33.3%). Additionally, they found antibiotic treatment may improve reproductive outcome in the frozen embryo transfer cycles.

Hysteroscopy versus Histopathology in diagnosis of CE

We found 64 cases have hyperemia during hysteroscopy, which represents 96.9 % of hysetroscopically suspected cases as having CE (64/66). Biopsies from these cases are positive for CE in only (53/57). Also, 53 cases have stromal edema during hysteroscopy, which represents 80.3% of hysteroscopically suspected cases as having CE, biopsies from all these cases are positive for CE (53/57). Finally, 39 cases have endometrial micropolys during hysteroscopy, which represents 59% of hysteroscopically suspected cases as having CE (39/66). Biopsies from all these cases are also positive for CE (39/57). In our study, histopathological examination confirmed the diagnosis of CE in 55/66 cases suspected to have CE by hysteroscopy (True Positive), while 11 cases were found to be free from CE (False Positive). On the other hand, histopathological examination confirmed absence of CE in 82/84 negative cases by hysteroscopy (True Negative), while only two cases were found to have the pathological condition (False Negative).

Based on our findings in the present study, hysteroscopy has sensitivity, specificity, accuracy, PPV and NPV as 96.5%, 88.17%, 91.3%, 83.3% and, 97.6% respectively in diagnosis of CE. So, hysteroscopy is a reliable diagnostic technique

in cases unexplained implantation failure that can reliably diagnose chronic endometritis. Also, hysteroscopy is highly reliable in excluding CE as it has been reported in previous studies as well [24]. 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 [8, 9, 25]. All of these signs were reported by our study in hysteroscopic diagnosis of CE, hyperemia, stromal edema and endometrial micropolyps, it was 96.9%, 80.3% and 59% respectively. In another experience, at hysteroscopy chronic endometritis was characterized by consistent association of stromal edema and either focal or diffuse hyperemia; in some cases, this finding is associated with endometrial micro polyps (less than 1 mm in size) [8].

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. A recent study evaluated the prevalence of chronic endometritis in patients with RIF and recurrent pregnancy loss (RPL) in total, 85 patients with a mean age of 36.08 ± 5.76 years by hysteroscopy and immunohistochemistry for CD138. The prevalence of RIF-related CE was 23.4% (11); 21.3% (10) of the cases were diagnosed by hysteroscopy. The prevalence of RPL-related CE was 36.8% (14) and 31.6% (12) based on hysteroscopy and immunohistochemistry staining, respectively. The sensitivity, specificity, and positive and negative predictive values of hysteroscopy in diagnosing CE were 86.36%, 87.30%, 70.37%, and 94.82%, respectively. The authors concluded that, Hysteroscopy is a reliable diagnostic technique in cases with RIF after IVF and RPL that can reliably diagnose chronic endometritis [26].

Also, we agree with Cicinelli et al.[8], where, 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% [8]. Zolghadri et al. [27] reported that endometritis was detected in 67.6% of cases by hysteroscopy versus 42.9% by pathological examination in unexplained recurrent spontaneous abortion.

However, a recent retrospective cohort study done to evaluate the role of hysteroscopy in the diagnosis of chronic endometritis (CE). Endometrial biopsy specimens were taken after hysteroscopy for routine histology and immunohistochemistry for plasma cells using a CD138 epitope. Song et al. [28] found that, among cases positive for CD138 cells, the prevalence of hysteroscopic features was: endometrial hyperemia, 169 of 322 (52.5%); endometrial interstitial edema, 27 of 322 (8.4%); and micro-polyps, 11 of 322 (3.4%). The sensitivity, specificity, positive and negative predictive value, and diagnostic accuracy of the presence of one or more hysteroscopy features were 59.3%, 69.7%, 42.1%, 82.8%, and 66.9%, respectively. The overall accuracy of hysteroscopy in diagnosis of CE is only 67%, so it should not be used to replace histologic examination as the diagnostic tool of choice. They

recommended that, in women in whom is highly suspected, endometrial biopsy should be obtained to examine plasma cells by immunohistochemistry, that should remain the preferred method for diagnosis [28].

In our study, isolated hyperemia was found to be the least reliable sign as regard CE diagnosis. Its reported that, areas of red endometrium may be caused by vascular wall breaking due to the employment of CO2, hormone effects, hypertension, immunologic diseases, and other causes [29]. Finally, hysteroscopy is the gold standard for uterine factor evaluation allowing a direct visualization of uterine cavity and in most of the cases an immediate treatment of intrauterine anomalies without hospital admission or anesthesia [30]. A panoramic hysteroscopic view of the uterine cavity can detect some lesions previously unsuspected in approximately 10% of the infertile women who have no cause of infertility detected by conventional investigation [31]. However, the gold standard for the diagnosis of CE is the histological demonstration of plasma cells in the stromal area of the endometrium in endometrial specimens, although no universally accepted criteria for the diagnosis of CE have been determined [22]. In their multi-centre, retrospective, observational study, Cicinelli et al. [32] found that immunohistochemistry (IHC) for MUM-1 showed higher reliability in the paired comparison of the individual samples than CD-138 in the diagnosis of CE. Li et al. [33] established the minimum number of immunohistochemical analysis of CD138+ plasma cells to identify a clinically relevant CE to be ≥5 CD138+ cells in at least one HPF. In a recent retrospective study, antibiotic treatment was an effective way to improve the reproductive outcomes of women with CD138+/HPF ≥5, and persistent CE was associated with poorer pregnancy outcomes [34].

Conclusion

The results of this prospective cross- sectional study add further evidence to the relationship between CE and impaired receptivity of the endometrium. The study shows that CE is common in women complaining of unexplained implantation failure at ICSI, specially between those with repeated failure. Also, this study suggests that hysteroscopy is a useful diagnostic tool in women with unexplained implantation failure as regard CE diagnosis. However, endometrial samples should be obtained during hysteroscopy to increase the diagnostic accuracy.

Recommendations

Bearing in mind that chronic endometritis is a hidden condition that is difficult to detect with noninvasive examination, we suggest that hysteroscopy combined with endometrial samples should be always performed in the diagnostic work-up of women with unexplained implantation failure. National plan should be organized to increase the expertise of infertility specialists in hysteroscopy. More studies including more cases from different infertility centers should be conducted, including private centers as well.

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