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PREVALENCE OF CHRONIC ENDOMETRITIS IN CASES OF RECURRENT IMPLANTATION FAILURE- A RETROSPECTIVE STUDY

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Abstract

Background: Chronic endometritis being chronic in nature is accidentally diagnosed during work up of infertility. Chronic endometritis is chronic inflammatory condition characterized by presence of plasma cells infiltrating endometrial stroma. It is being associated with cases of recurrent implantation after IVF - ICSI Hysteroscopy has high negative predictive value in diagnosing CE: CD – 138 immunohistochemistry presents on plasma cells is suggested for more accurate diagnosis of CE

Objective: The objective of our study is to evaluate the prevalence of chronic endometritis in women with recurrent implantation failure after ICSI.

Material & methods : Our study included 152 patients with recurrent implantation failure after 2 or more IVF – ICSI despite having good – quality embryos. Hysteroscopy followed by endometrial biopsy was performed. H & E staining and immunohistochemistry was done on biopsies sample. Association between hysteroscopic findings and immunohistochemistry and prevalence of chronic endometritis was evaluated.

Results: Out of 152 included in this study; 34.2% were detected by hysteroscopy, 29.6% were detected by CD – 138 IHC and 21% were detected by both the modalities. The sensitivity, specificity, PPV and NPV of hysteroscopy in the study was 71.7%, 81.3%, 61.5% and 87% respectively. The diagnostic accuracy of hysteroscopy in diagnosing CE was 78.2%.

Conclusion: The negative predictive value and specificity of hysteroscopy is high and combining two diagnostic methods (hysteroscopy and CD – 138 IHC) will detect most cases of chronic endometritis.

Key Words: Recurrent implantation failure, CD – 138 Immunohistochemistry, Chronic endometritis

Introduction

Successful implantation is a well-orchestrated event during the presence of a healthy embryo, receptive endometrium, embryo endometrial cross- talk, and immune protection of the embryo with foreign antigens. Recurrent implantation failure (RIF) is important cause of IVF failure. The definition of RIF has evolved with time. Coulam et al. defined RIF as the failure to achieve a clinical pregnancy after transfer of at least four good-quality embryos in a minimum of three fresh or frozen cycles in a woman under the age of 40 years. [1]The ESHRE PGD Consortium (2005) defined RIF as three failed IVF attempts with transfer of good quality embryos or failure of implantation after cumulative transfer of more than ten cleavage stage embryos of high quality or four blastocysts. [2] Simon and Laufer (2012) suggested that RIF should be defined as failure of implantation in at least three consecutive IVF attempts, in which one to two embryos of high-grade quality are transferred in each cycle. [3] RIF describes the scenario in which the transfer of embryos considered to be viable has failed to result in a positive pregnancy test sufficiently often in a specific patient to warrant consideration of further investigations and /or interventions (ESHRE 2023) [4]

Embryo implantation is governed by many factors like oocyte quality, embryo quality, embryo endometrial cross talk, immunological factors, uterine factors like anatomical, Mullerian abnormalities, inflammation like chronic endometritis [5,6,7]

Chronic endometritis may affect female infertility and is one of the great challenges in current reproductive medicine Chronic endometritis is a persistent inflammatory disorder of endometrial lining characterized by superficial endometrial edematous change, high stromal cell density, dissociated maturation between the epithelium and stroma and infiltration of endometrial stroma by plasma cells. [8] CE being chronic in nature is accidentally diagnosed during work up for AUB, chronic pelvic pain and infertility. Chronic endometritis cause inflammation and over – expression of cytokines and leukocytes which can impair the immunological tolerance of endometrium to the embryo and potentially hindering trophoblast invasion and damaging embryo viability. [9,10]

In women with C.E aberrant autophagy may compromise endometrial decidualization and endometrial cell commitment. [11] CE can be diagnosed histological examination of endometrial biopsy to detect abnormal plasma cell infiltration in endometrial stromal using H & E (hematoxylin and eosin) staining. It is difficult to distinguish plasma cells from fibroblast and monocytes of endometrial stroma. Hence it is difficult to do accurate diagnosis of CE. [12]

Recently CD – 138 immunohistochemistry which are present on plasma cells is suggested for more accurate diagnosis of chronic endometritis. Immunohistochemistry analysis of CD – 138 is identified by presence of > 5 plasma cells in at least one high power field (HPF) [13]

Hysteroscopic findings suggestive of chronic endometritis are presence of micro-polyps < 1 mm size mucosal edema focal or diffuse endometrial hyperemia. [12,13,14] Hence hysteroscopy aids in diagnosis of chronic endometritis

Material & Methods:

This is a retrospective observational study conducted on 152 infertile females with recurrent implantation failure after ICSI visiting NIMS Fertility Centre from November 2019 to September 2024.

Inclusion criteria

Infertile females of age group 21 to 40 years, with BMI < 30 kg / m^2, with recurrent ICSI failure (2 or more) despite good quality embryo.

Exclusion criteria

Patients who took antibiotic treatment for chronic endometritis, patients with endocrine, hematological and auto – immune disorders. Patient with uterine anomaly, intracavitary defects such as fibroids, synechia, hydrosalpinx

In all cases, detailed history taken, examination done, all necessary investigations along with imaging modality - 3D USG done to exclude abnormalities of uterus and evaluate endometrial cavity was done.
Hysteroscope used was a 2.9 mm 30˚degree rigid hysteroscope with normal saline as distention media hysteroscopic features such as endometrial polyps, edema, endometrial hyperemia was noted, cervical examination done to rule out any cervical pathology. Hysteroscopic guided biopsy was done on day 7 to day 11 of menstrual cycle.

Immune staining was performed using CD-138 monoclonal antibody, IHC was performed using Ventana benchmark GX auto stainer. The specimen was graded as "positive" for CE if there were > or = 5 plasma cells per high power field (HPF), prevalence rate of CE was calculated. The co-relation between hysteroscopic finding and immunohistochemical result was evaluated

STATISTICAL ANALYSIS OF DATA

Sample Size

All 152 operative cases who underwent diagnostic hysteroscopy after meeting the inclusion criteria, from November 2019 to September 2024 were considered for study.

Statistical analysis of data

All statistical analysis was performed in SPSS version 21 and Microsoft excel
Quantitative variables were presented by mean, median, standard, deviation etc.
Qualitative variables were presented by proportions or percentage
Z – test was used to compare proposed
Chi - square test was used to check the dependency of one variable to other.
Sensitivity and specificity were also used
P value < 0.05, considered statistically significant

Ethical consideration:

Ethical committee has granted exemption as ethical approval is not required.

Results

Our Study at NIMS Fertility Centre included total 152 women, out of these women 104 suffered primary infertility while 48 suffered secondary infertility. 69 women were in the age group of 21 – 29 yrs. 83 women were in the age of ≥30 years. Out of these women; 35 women had normal BMI while 117 were overweight. Most of the cases were asymptomatic except for 50 cases. 109 women underwent two failed ICSI while 43 women had 3 or more failed ICSI. which are shown in below table 1.

Women in with primary infertility (total cases 104) Positive hysteroscopic findings were seen in 35 cases out of 104 women (35/104 = 33.6%) CD – 138 was positive in 33 cases (33 cases out of 104 = 31.7%) Women with secondary infertility (total cases 48) Positive hysteroscopic finding were seen in 17 cases out of 48 (17/48 = 35.4%) CD – 138 was positive in 12 cases (12 cases out of 48 = 25%) as shown in Table 2.

Positive hysteroscopic findings were found in 30.2% (29 cases/109 women) in women with 2 failed IVF ICSI while 44.2% (19/43) were found positive in female with three or more failed ICSI. Positive CD – 138 was seen in 24.8% (27 case out of 109) in two failed ICSI and 41.8% (18 cases out of 43) in cases with 3 or more failed ICSI as shown in Table 3.
The Prevalence of hysteroscopic features: 14/152 = 9.2% had focal hyperemia, 16/152 = 10.5% had diffuse hyperemia, 3/152 = 1.9% had micro polyp, 7/152 = 4.6% had mucosal edema, 12/152 = 7.8% had combined features as shown in Table 4.

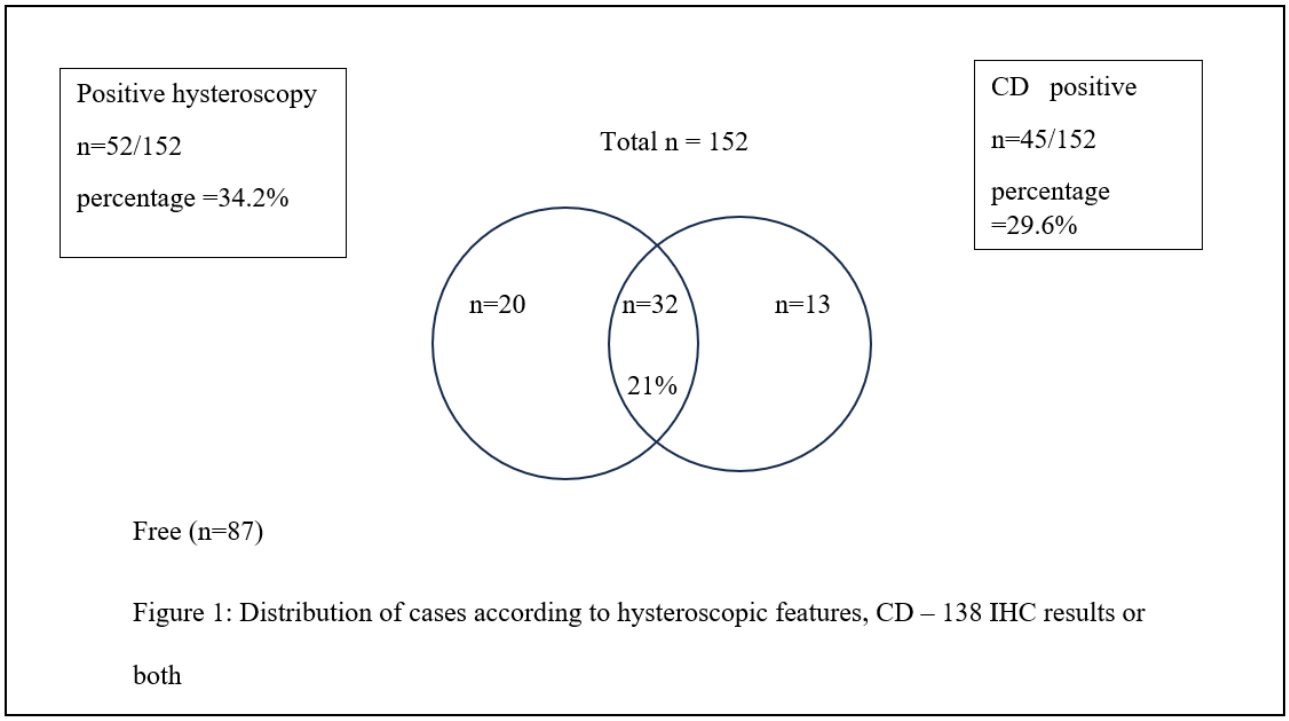

Figure 1: Distribution of cases according to hysteroscopic features, CD – 138 IHC results or both

In our study, 152 women with RIF 52 cases (34.2%) were diagnosed with CE by hysteroscopy, 45 cases (29.6%) were diagnosed positive by CD – 138 immunohistochemistry (IHC), 32 cases (21%) positive for both, hysteroscopy and immunochemistry. As shown in Figure 1.
Our study revealed that the sensitivity 71.7%, specificity 81.3%, positive predictive value 61.5% and negative predictive vale 87% of hysteroscopy were respectively. The diagnostic accuracy of hysteroscopy in diagnosing CE was 78.2% as shown in Table 5.

TABLE 1: Patient Clinical Characteristics & Background (N = 152)

Patients' history	**Number**	**Percentage**
Age in years		
< 30	69	**45.4%**
≥30	83	**54.6%**
Range	21 – 40 years	
Mean ± SD	31.10 ± 5.32	
Median (IQR)	30.0	
Infertility		
Primary	104	**68.4%**
Secondary	48	**31.6%**
BMI (kg/m^2)		
Normal (18.5-24.96)	35	**23.0%**
Overweight (25-30)	117	**77.0%**
Range	19-30	
Mean ± SD	25.9 ± 3.02	
Median (IQR)	26.0	
Failed ICSI		

2	109	**71.7%**
≥3	43	**28.3%**
Symptoms		
Free	102	**67.1%**
Chronic pelvic pain	36	**23.7%**
AUB	14	**9.2%**

SD = Standard deviation. AUB= Abnormal uterine bleeding. IQR= Interquartile range.

TABLE 2: Relation between type of infertility (primary and secondary) with hysteroscopy findings and CD 138 results (N = 152)

Variable	**Infertility**				**P value**
	Primary (N=104)		**Secondary (N=48)**		
	Number	**%**	**Number**	**%**	
Hysteroscopic findings					
Focal hyperemia	9	8.6%	5	10.4%	0.3673[a]
Diffuse hyperemia	12	11.5%	4	8.3%	0.2637[a]
Micro-polyp	2	1.9%	1	2.0%	0.4741[a]
Mucosal oedema	5	4.8%	2	4.1%	0.4287[a]
Combined	7	6.7%	5	10.4%	0.2326[a]
Hysteroscopic finding					
Positive	35	33.6%	17	35.4%	0.8314[b]
Negative	69	66.3%	31	64.5%	
CD 138 results					
Positive	33	31.7%	12	25.0%	0.3982[b]
Negative	71	68.2%	36	75.0%	

a - z = test used b = chi square test used

TABLE 3: Relation between number of failed ICSI with hysteroscopy findings and CD 138 results (N = 152)

Variable	**Number of failed ICSI**				**P value**
	2 (N=109)		**≥ (N=43)**		
	Number	**%**	**Number**	**%**	
Hysteroscopic findings					
Focal hyperemia	10	9.7%	4	9.3%	0.4003[a]
Diffuse hyperemia	9	8.2%	7	16.2%	0.1623[a]
Micro-polyp	3	2.7%	0	0%	0.036[a]
Mucosal oedema	5	4.5%	2	4.6%	0.4307[a]
Combined	6	5.5%	6	13.9%	0.1112[a]
Hysteroscopic finding					
Positive	33	30.2%	19	44.2%	0.1035[b]
Negative	76	69.7%	24	55.8%	
CD 138 results					
Positive	27	24.8%	18	41.8%	0.03764[b]
Negative	82	75.2%	25	58.2%	

TABLE 4: Distribution of the studies cases according to hysteroscopy findings (N = 152)

Hysteroscopic finding	Number	Percentage %
Free	**100**	**65.8%**
Focal hyperemia	**14**	**9.2%**
Diffuse hyperemia	**16**	**10.5%**
Micro polyp	**3**	**1.9%**
Mucosal oedema	**7**	**4.6%**
Combined	**12**	**7.8%**
Focal hyperemia + micro-polyp	**3**	**1.9%**
Focal hyperemia + oedema	**6**	**3.9%**
Diffuse hyperemia + oedema	**3**	**1.9%**

TABLE 5: Agreement (sensitivity, specificity and accuracy), (N = 152)

Variables	CD 138 RESULTS				Sensitivity	Specificity	PPV	NPV	Accuracy
	Positive (N= 45)		Negative (N= 71)						
	N	%	N	%					
Hysteroscopy findings									
Positive	**32 (a)**	**71.2 %**	**20 (b)**	**28.8%**	**71.1%**	**81.3%**	**61.5 %**	**87%**	**78.2%**
Negative	**13 (c)**	**28.8 %**	**51 (d)**	**71.2%**					
X^2(P)	**X^2: 20.54 (P<0.0001)**								

X^2 Chi-square test, P-P value for association between different categories, statically significant in p ≥ 0.05 PPV: Positive predictive value, NPV: Negative predictive value

TABLE 6: Agreement (sensitivity, specificity and accuracy) of cases with combined hysteroscopic findings (N = 152)

Variables	CD – 138				Sensitivity	Specificity	PPV	NPV	Accuracy
	Positive (N=45)		Negative (N=107)						
	N	%	N	%					
Combined Hysteroscopic findings									
Positive	**10(a)**	**22.2%**	**2 (b)**	**1.8 %**	**22.2%**	**98.1%**	**83.33%**	**75%**	**82.2%**
Negative	**35(c)**	**77.7%**	**105(d)**	**98. 1%**					
X^2(P)	**X^2: 18.04 (P<0.0001)**								

X^2 Chi-square test: FE – fisher exact test P:P value for association between different categories * statistically significant at P ≤ 0.05 PPV: positive predictive value, NPV: negative predictive value

Discussion

Chronic endometriosis being chronic in nature had silent course and is diagnosed in the workup of infertility patient. Thus, it is imperative to diagnose endometriosis and its impact on infertility. Its prevalence is often underestimated as it is difficult to diagnose. Hysteroscopy being minimally invasive allows for direct visualization of endometrial cavity for any sign of inflammation. Hysteroscopy features consistent with CE are focal / diffuse endometrial hyperemia, micro polyps (< 1mm) and stromal edema. Histopathology is characterized by superficial endometrial liming edema, asynchronous maturation between stroma and endometrium, abnormally increased stromal cell density and endometrium infiltrated with plasma cells. Accurate diagnosis of chronic endometritis is of utmost importance because of potential association between chronic endometritis and recurrent implantation failure. Two methods utilized for diagnosing CE are hysteroscopy and histopathology for plasma cell in infiltration with CD – 138 immunohistochemistry

In our study 68.4% had primary infertility, 31.6% had secondary infertility with no statistically difference between the two groups according to prevalence of CE. This agrees with Saha et al – who found no difference in rate of uterine pathology between female with primary & secondary infertility. [15]

In our study 152 women with recurrent ICSI failure were included, 34.2% were diagnosed with CE by hysteroscopy, 29.6% by IHC CD 138 and 21% were positive for both CD 138 with hysteroscopic features of CE. These results were consistent with those of EL – Sheik et al. [16]

In our study, contrast to two ICSI failure, patient with three or more ICSI failure had greater prevalence of CE. 32.9% cases reported symptoms like chronic pelvic pain, abnormal uterine bleeding and the majority of cases were asymptomatic. There was no significant difference in these symptoms between patients with or without CE.

Our study revealed that the sensitivity 71%, specificity 81.3%, positive predictive value 61.5% and negative predictive vale 87% of hysteroscopy respectively. The diagnostic accuracy of hysteroscopy in diagnosing CE was 78.2%

The Prevalence of hysteroscopic features in our study: 14/152 = 9.2% had focal hyperemia, 16/152 = 10.5% had diffuse hyperemia, 3/152 = 1.9% had micro polyp, 7/152 = 4.6% had mucosal edema, 12/152 = 7.8% had combined features.

The sensitivity and PPV vary greatly in most of the studies but majority of the studies still showed high specificity and NPV.

Our finding was contrasted with majority of earlier features that have published which showed a significant range in terms of sensitivity (16.7 – 98.4%) specificity (56.2 – 99.9%), the sensitivity and PPV vary greatly but specificity and NPV of most of the studies are still high. Our research supports the finding of Song et al where Sensitivity 59.3%, specificity 69.7%, PPV 42.1%, NPV 82.8% and Diagnostic accuracy of hysteroscopy for diagnosing CE 66.9% [17].

Tsonis et al conducted a study on a sizable number of patients (n = 2675) which showed hysteroscopic detection of CE with sensitivity 49.3%, specificity 91.7%, PPV 60.3% and NPV 87.7%.[18]

Yang et al conducted study on 202 infertile females with recurrent implantation failure. In their study, histological CE rate was 43.7% whereas CE diagnosis by hysteroscopy was 66% sensitivity, specificity of hysteroscopy to diagnose CE was 35.2% and 67.5% respectively. [19]

Cincinelli et al conducted study on infertile women where hysteroscopy's sensitivity, specificity, PPV, NPV and diagnostic accuracy to diagnose CE in their study was 55.4%, 99%, 98.4% 94.5% and 43.4% respectively. [20]

Zargar et al conducted study on total 85 female with recurrent implantation failure. The patient underwent diagnostic hysteroscopy and CD – 138 IHC of endometrial samples. The sensitivity, specificity, PDV and NDV of hysteroscopy in diagnosing CE were 86.4%, 87.3%, 94.8% and 70.4% respectively. [21]

Polisseni et al conducted a prospective study where 50 infertile patients underwent diagnostic hysteroscopy, endometrial biopsy using H & E staining and cervical and endometrial chlamydia infection test H&E staining demonstrated the CE occurred in 12% of these patients, hysteroscopy had a sensitivity of 16.7%, specificity of 93.2%. [22]

Zolghadri et al commonly used criteria in diagnosis of CE as the presence of ≥ 5 plasma cells from endometrial stromal fibroblast and monocytes using H & E staining. That is why it can give high false positive rate hence some pathologists found it normal to find some plasma cells in normal endometrial cavity Zolghadri et al considered only one plasma cell /HPF as positive for C.E hence found very high sensitivity (98.4%) and low specificity (56.23%) of hysteroscopy. [23]

EL Sayed SM et al in their study revealed the sensitivity 66.7%, specificity 83.1%, PPV 56.3% and NPV 88.5% respectively. The diagnostic accuracy of hysteroscopy in diagnosing CE was 79.1% [24]

Our result revealed high specificity and NPV. In other words, CE is unlikely to be diagnosed when abnormal hysteroscopic findings are absent. It has been observed that specificity and NPV in most studies are adequate for diagnosis, such as Tsonis et al, Cicinelli et al, Zargar et al, Polisseni et al and El-Sayed SM et al.[17,19,20,21,22]

Limitation

Our study performed only histopathology on the endometrial sample obtained. It neither performed any traditional culture technique nor any sequence analysis for uterine endometrium microbiota on the endometrial samples. There is promising evidence of relation of chronic endometritis and uterine microbiota in patients of recurrent implantation failure. New realms of research based on sequence analysis will definitely help in better understand

Due to strong association between chronic endometritis and poor fertility potential it is of utmost importance to diagnose chronic endometritis in our study hysteroscopy display high specificity and high negative predictive value in diagnosis of chronic endometritis. High negative predictive value implies the ability of hysteroscopy to exclude the diagnosis of CE if the hysteroscopic features are negative. But the overall efficacy of hysteroscopy to detect endometritis is modest. Thus, in infertile females with RIF, hysteroscopy should combine histological examination of endometrium using IHC with CD 138. Hence hysteroscopy combined with endometrial biopsy has better diagnostic value.

Ethical approval: The study was approved by the Institutional Ethic Committee

Conflict of interest: None

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List of Abbreviations:

Abbreviation	**Definition**
IVF	In vitro fertilization
ICSI	Intracytoplasmic sperm insemination
AUB	Abnormal uterine bleeding

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