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Recurrent implantation failure hysteroscopy versus endometrial biopsy

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Abstract---Background: Between all of the complications that might be faced through in-vitro fertilization (IVF), recurrent implantation failure (RIF) management still the greatest challenge due to the total success speeds of IVF in females with RIF is very low, Objective: The purpose of this research is to assess function of Hysteroscopic stimulated Endometrial Biopsy in the Diagnostic of Endometrial Pathology in cases Un-clarified RIF. Design: This was A cross-sectional research. Participants and methods: This study was done on 100 patient attended Sayed Galal hospitals from September 2019 to May 2020 with RIF history. All cases were assessed by full-history tracking including the (Personal, Menstrual, Obstetric and Past), Complete clinical test (General, Abdominal and Local), transvaginal 3D ultrasound, hysteroscopy and biopsy. Samples were gathered to be tested for histopathology to diagnose any disease and to be arranged for computer analysis. Results: Of the 100 cases of infertility with a past of recurrent implantation failure (RIF) experiencing endometrial biopsy guided by hysteroscopy, 59 (59%) exhibited ordinary results and 41 (41%) exhibited anomalous results. Conclusion: For RIF instances, diagnostic hysteroscopy must be a comprehensive examination that assesses the whole uterine cavity and detects hyperemia, mucosal edema, and micro-polyps, which.

Keywords---Chronic endometritis; Biopsy; Hysteroscope; Infertility; Recurrent implantation failure.

Introduction

Recurrent implantation failure (RIF) was described as failure to conceive subsequent 2 or 3 embryo transmission rounds, or collective transfer of 10 good quality embryos. Within the past decade, investigations to increase the success prevalence in reproductive medicine were concentrated mostly on how to understand and optimize of pregnancy quality.

The appearance of personalized medicine in ovulation induction and embryological field was moved the concentration to evaluating the personal situation of the endometrium.

The endometrium is counted as a receptive through an independently definite time interval, the window of implantation (WOI), when the mother allows a blastocyst to assign and implant.

This personal receptive status could nowadays be detected accurately by the use of the endometrial receptivity array. (1)

Hysteroscopy is a core method for the studies in females with recurrent implantation failure (RIF), it permits dependable visual examination of the uterine function and cervical canal, and also it was believed to be the gold-typical diagnosis for intrauterine pathology and has Nominal intra-operative and postoperative illness. (2)

Endometrial scratch, as well defined as endometrial injury, biopsy or trauma, is presently suggested as a method to rise the possibility of implantation in females experiencing IVF, Endometrial injury might lead to a pseudo-decidal response that improves implantation, Pregnancy and rates of live birth in the IVF round subsequent the biopsy were become double. (3)

The utmost frequent sign for endometrial scratch was RIF, the greatest frequent time framework for endometrial scratch was in the luteal phase of the sequence previous to the embryo transmission sequence, and present indication proposes a position for endometrial scratch to females experiencing IUI or aiming to get natural pregnancy. 4

Infertility is a comparatively popular gynecological disease with a growing incidence rates recently; related investigations have presented the chronic endometritis (CE) incidence in infertile cases ranging (0.2–46 %).

Infertility and natural abortion might be accompanying by CE, late investigations concluded that the prevalence of CE was 14 % for RIF cases afterward IVF and females with CE had low rate of implantation (11.5 %) in the IVF round subsequent to therapy than those with CE missing (32.7 %).

Additionally, **Cicinelli et al., (5)** confirmed that CE is a frequent result in females complain of repetitive implantation failure and suitable anti-biotic therapy had highly raised the rates for effective pregnancy in females with no marks of CE in

comparison with females with continuing CE, the studies recommend the existence of CE can modify the endometrial receptiveness and negative influence fertility consequence.

The purpose of this research is to assess function of Hysteroscopic stimulated Endometrial Biopsy in the Diagnostic of Endometrial Pathology in cases Unclarified RIF.

Patients and Methods

From September 2019 to May 2020, 100 patients with a history of recurrent implantation failure who had had two or more failed rounds of IVF in which two or more good-quality embryos were transferred each treatment were studied in cross-sectional research at Sayed Galal hospitals.

Comprehensive history taking (Personal, Menstrual, Obstetric, and Past), full clinical examination (General, Abdominal, and Local), 2-D and 3-D ultrasound, and HSG were performed on all patients.

All the contributing cases had ordinary look of the uterine cavity on 2-D, 3-D ultrasound and HSG, printed agreements were made by all participants the study initiation.

Cases were notified about the study procedures, why it is being presented, what substitutions there are and the hazards and assistances to her in short and long-term.

Our inclusion criteria include females in the reproductive period between 25–40 years of age with recurrent unexplained implantation failure, having a normal semen analysis of the husband, normal (2D and 3D) ultrasound, normal uterine cavity findings in HSG, good quality embryo, BMI less than 40, normal hormonal tests (FSH, LH, TSH, Prolactin) and normal ovarian reserve.

We excluded those females with male factor for infertility; first time IVF, suspected reproductive tract infection, abnormal ultrasound or HSG and hysteroscopic surgical operation during the past three months.

Hysteroscopy was done under anesthesia in the proliferative stage of the round (between days 6-12) to exclude the chance of spontaneous disturbance occurrence in pregnancy and for the benefit that the endometrium was thinner and its improved vision.

During hysteroscopy, (NaCl of concentration 0.9%) was utilized to swell the uterine cavity, with the usage of gravity-produced pressure (1 meter above the patient).

Examination of the uterine cavity contained of a panoramic vision of the cavity afterward examining the tubal Ostia, cornua, anterior and posterior walls and detailed valuation of the endometrial mucosa by movement of the hysteroscope

close to every uterine barrier to get a vision parallel to the endometrial surface to recognize any anomaly of the mucosa and biopsy was taken through the process. The sample was secured in neutral formalin earlier of being merged in paraffin. Samples were collected to be examined for histopathology to detect any disease and to be tabulated for computerized analysis.

In our study; we are looking for findings that could not be detected by ultrasound or HSG.

Chronic endometritis, fine uterine adhesions and endometrial polyps are the most undetectable causes of recurrent implantation failure that cannot be visualized by U/S or HSG.

Statistical Analysis: SPSS 22.0 for Windows was used to gather, tabulate, and statistically analyze all data (SPSS Inc., Chicago, IL, USA). The Shapiro Walk test was used to check for normal distribution. Frequencies and relative percentages were used to depict qualitative data. The difference between qualitative variables was calculated using the Chi square test (χ^2) and Fisher exactly as specified. For parametric data, mean $\pm$ SD (standard deviation) was used, while for non-parametric data, median and range were used. For parametric and non-parametric variables, the Independent T test and Mann Whitney test were employed to determine the variance between quantitative variables in two groups. The diagnostic value indices for hysteroscope findings, including specificity, sensitivity, positive and negative predictive values, were calculated by: When P-value $\leq$ 0.05, significance level is considered.

Results

Table 1
Demographic data of the researched groups

Demographic data	Mean $\pm$ SD	Range
Age (years)	34.71 $\pm$ 4.03	25 – 40
BMI (kg/m ²)	24.51 $\pm$ 4.58	16 – 39
Duration (years)	8.48 $\pm$ 2.84	5 – 17
Number of failed IVF cycles	3.78 $\pm$ 0.927	2 – 6
Types of infertility	Number	Percentage
Primary infertility	72	72%
Secondary infertility	28	28%

The 100 cases of infertility with a recurrent implantation failure past undergoing endometrial biopsy guided by hysteroscopy, 59 (59%) presented ordinary results and 41 (41%) presented anomalous results. 22 cases were with normal hysteroscope but endometrial biopsy show signs of chronic endometritis (22%). 12 cases show both abnormal hysteroscope and positive signs of chronic endometritis (12%) and (4) cases show endometrial polyp (4%) and 3 cases show fine intrauterine adhesions (3%). Table-2

Table 2
Abnormal hysteroscopy findings of the researched groups

Abnormal hysteroscopy (N=19)	N	%
Endometrial hyperemia	13	13.00
Mucosal edema	18	18.00
Micro polyps	16	16.00
CE (micropolyps + edema+ hyperemia)	12	12
Fine adhesions	3	3
Polyp	4	4

* most of patients combined between more than one finding

There was statistical significance difference between combined hysteroscopy in relation to endometrial bunch biopsy. Table-3

Table 3
Distribution of the studied group regarding the relation between combined hysteroscopy and endometrial bunch biopsy

Hysteroscope	Histopathology (CE)						Chi-Square	
	Abnormal		Normal		Total			
	N	%	N	%	N	%	X2	P-value
Abnormal	19	46.3	0	0	19	19	33.76	<0.001*
Normal	22	53.7	59	100	81	81		
Total	41	100.00	59	100.00	100	100		

X2: Chi square

*: P <0.05 (significant)

The diagnostics value of Hysteroscopy was sensitivity of (46.34%) and specificity of (100%) with accuracy of (78%), which also exhibited a high negative prognostic value. Table-4

Table 4
Diagnostic value of Hysteroscope

Variables	Value
Sensitivity	46.34%
Specificity	100%
Positive Predictive Value (PPV)	100%
Negative Predictive Value (NPV)	72.84%
Accuracy	78%

There was no statistical significance difference between (Aging, BMI, infertility interval and No. of unsuccessful IVF cycles and infertility types) in relation to hysteroscopy finding. Table-5

Table 5
Distribution of the studied subjects regarding the relation between demographic and clinical characteristics to hysteroscopy findings

		Hysteroscope				T-Test	
		Abnormal		Normal		T	P-value
Age (years)	Mean $\pm$ SD	34.95	$\pm$ 4.12	34.65	$\pm$ 4.03	0.284	0.777
BMI (kg/m ²)	Mean $\pm$ SD	23.58	$\pm$ 4.29	24.73	$\pm$ 4.64	0.985	0.327
Duration (years)	Mean $\pm$ SD	8.58	$\pm$ 3.24	8.46	$\pm$ 2.76	0.168	0.867
No. of failed IVC cycles	Mean $\pm$ SD	3.63	$\pm$ 0.761	3.81	$\pm$ 0.963	0.773	0.441
Types of infertility		N	%	N	%	X ² 3.55	.059
Primary infertility		17	89.5	55	67.9		
Secondary infertility		2	10.5	26	32.1		

X²: Chi square

*: P <0.05 (significant)

In connection to the histopathological result, there was no statistical substantial variation between demographic and clinical factors. Table-6

Table 6
Distribution of the studied subjects regarding the relation between demographic and clinical characteristics (Age, BMI, infertility interval and No. of unsuccessful IVF rounds and infertility types) to histopathology findings

		Histopathology (CE)				T-Test	
		Abnormal		Normal		t	P-value
Age (years)	Mean $\pm$ SD	34.85	$\pm$ 4.16	34.61	$\pm$ 3.965	0.296	0.768
BMI (kg/m ²)	Mean $\pm$ SD	25.15	$\pm$ 4.73	24.07	$\pm$ 4.45	1,161	0.248
Duration (years)	Mean $\pm$ SD	8.90	$\pm$ 3.31	8.19	$\pm$ 2.46	1.243	0.217
No. of failed IVC cycles	Mean $\pm$ SD	3.78	$\pm$ 0.909	3.78	$\pm$ 0.948	0.004	0.997
Types of infertility		N	%	N	%	X ² .449	.503
Primary infertility		31	75.6	41	69.5		
Secondary infertility		10	24.4	18	30.5		

X²: Chi square

*: P <0.05 (significant)

Discussion

All women in this study experienced hysteroscopy for the management of any uterine lesion that was undetected earlier by hysterosalpingography (HSG). The results were 19% of cases had abnormal uterine findings.

Most of these anomalies were slightly polyps, fine adhesions and finding suggestive chronic endometritis.

In a prospective cohort interventional study conducted by **Makled et al., (6)** at Ain Shams University Maternity Hospital on 100 participants with unsolved infertility assessed with transvaginal sonography (TVS) and diagnostic hysteroscopy, Founded on hysteroscopic conclusions, 31-cases were detected with endometrial polyps, 14 endometritis, 15 endometrial hyperplasia, 6 submucous myomas, 7 intrauterine adhesions, 7 congenital uterine anomalies, 6 cervical stenosis and 14 women without any uterine anomalies.

The rate of anomalous hysteroscopic detection in this work is higher than it in our investigation this is for the reason that it involved intrauterine anomalies which wasn't accepted before by HSG or TVS as our work.

Bakas et al., (7) assessed 217 infertile women by TVS and HSG for primary assessment.

If there were no irregular intrauterine results, diagnostic hysteroscopy was done as well.

In 148 females (68.2%), results at hysteroscopy were ordinary, but in 69 (31.8%), hysteroscopy exposed intrauterine lesions (septa, polyps, submucosal leiomyomas, or adhesions) that cause operational hysteroscopy. Undoubtedly the hysteroscopy must be done when there is doubt of intrauterine pathology on TVS or HSG.

Our results agree with **Marzieh Agha Hosseini et al., (8)** who concluded that hysteroscopy before IVF in females suffering from RIF with speciously ordinary uterine cavity rises the pregnancy rate significantly.

This explains the helpful role of hysteroscopy, like endometrial injury, provocation of immunological response, following releases of cytokines and growing factors, and amplified implantation rates; furthermore, instrumentation through the cervical canal and uterine cavity simplifies upcoming embryo transmission. CE is often asymptomatic or has only minor symptoms, such as pelvic discomfort, dyspareunia, dysfunctional uterine hemorrhage, and leucorrhea.

The true incidence of this illness in the general population is unclear due to its mild character.

Cicinelli et al., (5) concluded that polyps less than 1 mm diameter to be "micro polyps", and were frequently accompanying with histological CE, with an association greater than 90 % among hysteroscopy and pathological results.

Results show that hysteroscopy have a specificity (93.2 %) and sensitivity (16.7 %) in diagnosis histological CE was counted to have a great prognostic value of negative outcome.

Svirsky et al., (9) concluded that in 639-patients, hysteroscopy related with endometrial biopsy had abundant higher diagnosis-rate in detection anomalous uterine cavity than biopsy only.

Consequences show that endometrial biopsy has a incorrect-negative rates (88.7 %) in diagnosis of endometrial polyps, and hysteroscopy might not perform a specific hyperplasia diagnostics.

Cicinelli et al., (5) performed an investigation in 2008 including 2,190 participants, and they all exposed to endometrial and hysteroscopy biopsy. For verified histological CE cases, the usage of complete dosage anti-biotics is the presently recommended therapeutic technique.

We treat CE cases for 2 weeks with levofloxacin (0.5 gm) and metronidazole (1 gm).

Lamonica et al., (10) considered 26 patients having at minimum two IVF-ET fails and detected CE over cell-specific antigen CD138 stain.

The consequences presented that even when endometrium biopsy results become ordinary afterward anti-biotics therapy, the implantation rates and clinical-pregnancy rates were small in the following transmission round.

Our consequences displayed the divergence among pathology and hysteroscopy. From clinical practice, hysteroscopy diagnosing must be a steady examination for RIF cases, discovering the entire uterine cavity and noticing the existence of hyperemia, mucosal edema, and micropolyps, manifestations that may simply be overlooked.

Conclusion

Diagnostic hysteroscopy must be a steady examination for cases of RIF, discovering the entire uterine cavity and identifying the existence of hyperemia, mucosal edema, and micropolyps, manifestations that may simply be overlooked.

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