

ROLE OF HYSTEROSCOPIC GUIDED ENDOMETRIAL BIOPSY IN DIAGNOSIS OF ENDOMETRIAL PATHOLOGY IN PATIENTS WITH UNEXPLAINED RECURRENT IMPLANTATION FAILURE

By

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ABSTRACT

Background: Hysteroscopy is one of the most important investigations in women with recurrent implantation failure (RIF). It allows reliable visual assessment of the cervical canal and uterine cavity and it is considered to be the gold standard to diagnose intrauterine pathology and has minimal intra-operative and post-operative morbidity.

Objective: To evaluate the role of hysteroscopic guided endometrial biopsy in diagnosis of endometrial pathology in patients with unexplained recurrent implantation failure.

Patients and methods: This prospective study was done on 100 patients attended Sayed Galal Hospital from March 2018 to September 2019, with history of recurrent implantation failure.

All patients were evaluated by full history taking include (Personal, Menstrual, Obstetric, Past), Full clinical examination (General, Abdominal, Local), transvaginal ultrasound, hysteroscopy and biopsy. Samples were collected to be examined for histopathology to detect any disease and to be tabulated for computerized analysis.

Results: Of the 100 patients of infertility with a history of recurrent implantation failure undergoing endometrial biopsy guided by hysteroscopy, 48 (48%) showed normal findings and 52 (52%) showed abnormal findings: 28 were with normal hysteroscope but endometrial biopsy showed signs of chronic endometritis (28%), 12 showed both abnormal hysteroscope and positive signs of chronic endometritis (12%), 7 showed endometrial polyp (7%), 4 showed fine intrauterine adhesions (4%), and 1 showed cervical stenosis (1%).

Conclusion: Hysteroscopy is of a great value in the evaluation and diagnosis of the endometrial pathology in patients with unexplained recurrent implantation failure.

Key words: IVF, Infertility, hysteroscope, biopsy, recurrent implantation failure, chronic endometritis.

INTRODUCTION

The endometrium is considered receptive during an individually defined period, the window of implantation (WOI), when the mother permits a blastocyst to attach and implant.

This individual receptivity status can now be objectively diagnosed using the endometrial receptivity array (ERA) (Katzorke *et al.*, 2016).

Hysteroscopy is one of the most important investigations in women with

recurrent implantation failure (RIF), it allows reliable visual assessment of the cervical canal and uterine cavity and it is considered to be the gold standard to diagnose intrauterine pathology and has Minimal intra-operative and post-operative morbidity (Coughlan *et al.*, 2014).

Endometrial scratching, also known as endometrial injury, biopsy or trauma, is currently being proposed as a technique to increase the probability of implantation in women undergoing IVF, Endometrial injury or stimulation may cause a pseudo-decidal reaction that enhances implantation, Pregnancy and live birth rates in the IVF cycle following the biopsy were doubled (Nastri *et al.*, 2013).

The most common indication for endometrial scratching was recurrent Implantation failure (RIF), the most common time frame for endometrial scratching was in the luteal phase of the cycle prior to the embryo transfer cycle (Wadhwa *et al.*, 2015).

Hysteroscopy is considered as the definitive diagnostic tool to evaluate any abnormality suspected on hysterosalpingography, transvaginal ultrasound scan or saline hysterosonography during routine investigation of infertile patients, minimally invasive hysteroscope have minimized the pain experienced by patients during the procedure and made it feasible to use hysteroscopy as a routine outpatient examination, following recurrent IVF failure; there is some evidence of benefit from hysteroscopy in increasing the chance of pregnancy in the subsequent IVF cycle, both in those with abnormal and normal hysteroscopic

findings various possible mechanisms have been proposed for this beneficial effect (El-Toukhy *et al.*, 2016).

(Cicinelli *et al.*, 2015) demonstrated that CE is a common finding in women complaining of repeated implantation failure and appropriate antibiotic treatment had improved significantly the rate of successful pregnancies, the reports suggest the presence of CE may alter endometrial receptivity and negatively affect fertility outcome.

Hysteroscopy is the only access route for direct visualization of the uterine cavity; previous publications confirmed that hysteroscopy without an endometrial biopsy has a low positive predictive value in the detection of endometritis. Endometrial biopsy has proven useful for the diagnosis of intrauterine inflammatory states. Hysteroscopy with endometrial biopsy is assumed to be the best method for the detection of intrauterine abnormalities that may interfere with implantation (Devroey *et al.* 2009).

The present work aimed to evaluate role of hysteroscopic guided endometrial biopsy in diagnosis of endometrial pathology in patients with unexplained recurrent implantation failure.

PATIENTS AND METHODS

In this prospective study, 100 patients who had undergone two or more failed IVF cycles, in which two or more good-quality embryos were transferred per procedure, participated prospectively in this study. All the participating patients had normal appearance of the uterine cavity on ultrasound and HSG, written consents were also taken from all of them before the study.

Our inclusion criteria were females in the reproductive period between 25–40 years of age with recurrent unexplained implantation failure, normal ultrasound, normal HSG findings and good quality embryo.

We excluded those with male factor for infertility, first time IVF, abnormal ultrasound or abnormal HSG.

Hysteroscopy was performed under anesthesia 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 was thinner and its visibility is better.

Exploration of the uterine cavity was done after diagnostic hysteroscopy. A vaginal speculum was placed and endometrial biopsy with a pipelle aspiration was taken and the specimen was fixed in neutral formalin before being

embedded in paraffin for histological analysis.

Statistical methods:

IBM SPSS statistics (V. 25.0, IBM Corp., USA, 2017-2018) was used for data analysis.

Data were expressed as Mean ± SD for quantitative parametric measures in addition to both number and percentage for categorized data.

The following tests were done:

1. Descriptive statistics including mean; SD and Range.
2. Chi-square test to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data.

The probability of error at 0.05 was considered significant.

RESULTS

Of the 100 patients of infertility with a history recurrent implantation failure undergoing endometrial biopsy guided by hysteroscopy, 48 (48%) showed normal findings and 52 (52%) showed abnormal findings; the abnormal findings were as follows: 28 were with normal hysteroscope but endometrial biopsy show signs of chronic endometritis (28%), 12 show both abnormal hysteroscope and positive signs of chronic endometritis (12%), 7 show endometrial polyp (7%), 4 show fine intrauterine adhesions (4%), 1 show cervical stenosis (1%).

Seventy two patients were presented with primary infertility (72%) and 28 patients were presented with secondary

infertility (28%), 18 patients were presented with endometrial hyperemia under hysteroscope (18%), 20 patients were presented with mucosal edema under hysteroscope (20%), 16 patients were presented with micropolyps under hysteroscope (16%), 40 patients were presented with chronic endometritis detected by histological biopsy (40%), 24 patients were presented with uterine abnormality under hysteroscope (24%), 12 patients were presented with uterine abnormality other than chronic endometritis (12%): (7%) endometrial polyp, (4%) fine adhesions and (1%) cervical stenosis (**Table 1**).

Table (1): Presentation of studied patients

			Total	
Infertility	Prim	Count	72	
		%	72.0%	
	Sec	Count	28	
		%	28.0%	
Endometrial hyperemia	Negative	Count	82	
		%	82.0%	
	Positive	Count	18	
		%	18.0%	
Total			Count	100
			%	100.0%
Mucosal edema	Negative	Count	80	
		%	80.0%	
	Positive	Count	20	
		%	20.0%	
Micropolyps	Negative	Count	84	
		%	84.0%	
	Positive	Count	16	
		%	16.0%	
Histological CE	Normal	Count	60	
		%	60.0%	
	Positive	Count	40	
		%	40.0%	
Hysteroscope	Abnormal	Count	24	
		%	24.0%	
	normal	Count	76	
		%	76.0%	
others	cervical stenosis	Count	1	
		%	1.0%	
	fine adhesions	Count	4	
		%	4.0%	
	Negative	Count	88	
		%	88.0%	
	polyp	Count	7	
		%	7.0%	

Fifty two patients were presented by signs of chronic endometritis under hysteroscope (Table 2).

Table (2): Incidence of chronic endometritis under hysteroscope.

			Total	
Hysteroscope + CE	Neg.	Count	48	
		%	48.0%	
	Pos.	Count	52	
		%	52.0%	
Total			Count	100
			%	100.0%

Hysteroscopic diagnosis of histological CE had 50 % sensitivity, and 63.1 % specificity (Table 3).

Table (3): The sensitivity and specificity for diagnosis of histological CE under hysteroscopy

			Hysteroscope		Total
			Abnormal	normal	
Histologi-cal CE	Normal	Count	12	48	60
		%	50.0%	63.2%	60.0%
	Positive	Count	12	28	40
		%	50.0%	36.8%	40.0%
Total		Count	24	76	100
		%	100.0%	100.0%	100.0%

DISCUSSION

The diagnosis of unexplained infertility was done when the following criteria were met: Normal ovulatory function was established by means of basal body temperature measurement, cervical mucus changes, serum luteinizing hormone (LH) surge or mid-luteal progesterone levels, or evidence of follicular rupture during ultrasound. Semen analysis was normal, tubal patency was established by hysterosalpingography, normal uterine cavity was established by transvaginal sonography and good quality embryo.

In our study, 100 cases with recurrent implantation failure were included; 72% had primary infertility and 28% had secondary infertility with no statistically significant difference between the two types of infertility. This agrees with *Sahu et al. (2012)* who found that there was no significant difference in the rate of uterine pathology between women with primary and secondary infertility.

In our study, diagnostic office hysteroscopy showed that 24% of cases with recurrent implantation failure had abnormal uterine findings and 76% of cases had normal uterine cavity; the most common CE hysteroscopic finding was signs of chronic endometritis 16-20 % followed by endometrial polyp 7 %, fine

intrauterine adhesions 4%, and cervical stenosis 1%.

Our results agreed with *Elbareg et al. (2014)* who studied infertile women in whom standard infertility investigations revealed no abnormalities; the results were 33% of cases had abnormal uterine findings; most of these abnormalities were mild adhesions, small submucous myomas and polyps; the difference between results may be attributed to the larger number of their cases with unexplained infertility.

In a prospective cohort interventional study conducted by *Makled et al. (2014)* on cases with unexplained infertility evaluated with transvaginal sonography and diagnostic hysteroscopy; based on hysteroscopic findings, 31% were diagnosed with endometrial polyps, 14% endometritis, 15% endometrial hyperplasia, 6% submucous myomas, 7% intrauterine synechiae, 7% congenital uterine anomalies, 6% cervical stenosis and 14% women without any uterine abnormalities. The rate of abnormal hysteroscopic finding in this study is higher than that in our study. This is because it included intrauterine abnormalities which have not been excluded previously by hysterosalpingography or transvaginal sonography.

Bakas et al. (2014) assessed infertile women by transvaginal sonography (TVS) and hysterosalpingography (HSG) for initial evaluation. If there were no abnormal intrauterine findings, diagnostic hysteroscopy was additionally performed. In 68.2% findings at hysteroscopy were normal, whereas in 31.8% hysteroscopy revealed intrauterine lesions (polyps, septa, submucosal leiomyomas, or synechiaes).

Immune-histo-chemical staining is recommended on endometrial specimen to test plasma cell-specific surface antigens CD38 and CD138, in order to confirm the presence of plasma cells, although sometimes the above factors are still inevitable (*Song et al., 2017*).

A prospective study by *Yang et al. (2014)* did diagnostic hysteroscopy, endometrial biopsy, and cervical and endometrial Chlamydia infection test. Hematoxylin–eosin staining proved that CE occurred in 12 % of these patients; hysteroscopy had a sensitivity of 16.7 %, and specificity of 93.2 % in diagnosing histological CE, and was considered to have a high predictive value of negative result; they considered polyps smaller than 1 mm in diameter to be “micro polyps”, and were often associated with histological CE.

In our data for RIF patients, both hysteroscopy and histology CE abnormality rate were high; under hysteroscopy, mucous hyperemia, edema, and micropolyps were found in 20 % cases, while histological CE was found in 40 % cases. Hysteroscopy diagnosis for histological CE had a 50 % of sensitivity, and 63.1 % of specificity, which also showed a higher negative predictive value.

Erika et al. (2010) reported cases with CE which, after antibiotic treatment, still had lower implantation rate in the subsequent transfer cycle than the control group, but with similar clinical and ongoing pregnancy rates. Despite these reports that antibiotics can cure pathological CE (absence of plasma cell in endometrium under microscopy), all the studies showed antibiotics cannot improve the ultimate clinical IVF outcomes; some other studies reported that pathological CE, even untreated, does not affect clinical IVF outcomes.

Kasius et al. (2011) concluded that the reproductive outcome after initiation of IVF/ICSI was not found to be negatively affected by histological CE. Therefore endometrial biopsy cannot indicate the overall uterine cavity and endometrial states, since it is based on limited sample collection. On the other hand, embryo implantation may not demand such perfect condition, even pathologically and immune-histo-chemically confirmed CE may not have great effect on implantation.

Hysteroscopy can cover all uterine cavities, which facilitates the observation of endometrial thickness and vessel-filling state so that endometrial receptivity can be evaluated. CE diagnosed through hysteroscopy is likely to be correlated with chronic infection, since antibiotic treatment can clean the occult bacterial infection and increases embryo implantation rate (*Yang et al., 2014*).

The present study showed that previous IVF failure is the only independent predictor for an intrauterine pathology in women undergoing IVF, and therefore, these women seem to be appropriate candidates for screening by hysteroscopy

before an IVF attempt. This suggested that each additional IVF failure increased the risk for an intrauterine abnormality, and suggestion for an optimum number of IVF failures after which hysteroscopy should be performed seems inappropriate.

CONCLUSION

There was a high incidence of intrauterine abnormalities in women with RIF, and hysteroscope was able to efficiently detect and repair occult lesions that were not previously detected by HSG or TVS, significantly improving the pregnancy rate in women with RIF. Even in patients without intrauterine abnormalities, hysteroscope can also promote subsequent pregnancy outcome. Therefore, hysteroscope is of a great value in the evaluation and diagnosis of the endometrial pathology in patients with unexplained recurrent implantation failure, and it should be promoted as a routine examination for RIF women prior to repeat ET.

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دور فحص بطانة الرحم الموجهة عن طريق المنظار الرحمي في تشخيص أمراض بطانة الرحم في حالات الفشل المتكرر الغير مبرر للحقن المجهري أحمد الشيخ، هشام أبو سنة، محمد حسين

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خلفية البحث: منظار الرحم واحد من اهم التحقيقات في النساء المصابات بفشل الزرع المتكرر (الحقن المجهري)، فهو يتيح إجراء تقييم مرئي موثوق لقناة عنق الرحم وتجويف الرحم، ويعتبر المعيار الذهبي لتشخيص الأمراض داخل الرحم، ولديه الحد الأدنى من الاعتلال الجراحي أثناء وما بعد العملية الجراحية.

الهدف من البحث: تقييم دور فحص بطانة الرحم الموجهة بالمنظار في تشخيص أمراض بطانة الرحم عند المريضات اللتي تعانين من فشل الزرع المتكرر الغير مفسر (فشل الحقن المجهري).

المريضات و طرق البحث: أجريت هذه الدراسة على ١٠٠ مريضة حضرن الي مستشفى سيد جلال من مارس ٢٠١٨ إلى سبتمبر ٢٠١٩ بتاريخ من فشل الزرع المتكرر و تم تقييم جميع المرضى عن طريق أخذ بيانات كاملة، والفحص الطبي الكامل، والموجات فوق الصوتية عبر المهبل، ومنظار الرحم لفحص بطانة الرحم.

و تم جمع عينات لفحصها من أجل التشريح المرضي للكشف عن أي مرض وتحليله.

نتائج البحث: من بين ١٠٠ مريضة تعانين من العقم ولديهن تاريخ من فشل الزرع المتكرر اللاتي تم اخضاعهن لفحص بطانة الرحم الموجهة عن طريق منظار الرحم، أظهرت (٤٨٪) نتائج طبيعية و أظهرت (٥٢٪) نتائج غير طبيعية. وكانت النتائج الغير طبيعية على النحو التالي: ٢٨ ظهر لديهم منظار طبيعي لكن فحص بطانة الرحم اظهر وجود علامات التهاب بطانة الرحم المزمنة (٢٨٪) و ١٢ كان لديهم كل من: منظار غير طبيعي وعلامات إيجابية من

التهاب بطانة الرحم المزمنة (١٢٪) و٧ ظهر لديهم ورم بطانة الرحم (٧٪) و٤ ظهر لديهم التصاقات دقيقة داخل الرحم (٤٪) وواحدة ظهر لديها ضيق في عنق الرحم (١٪).

الاستنتاج: منظار الرحم ذو قيمة كبيرة في تقييم وتشخيص أمراض بطانة الرحم لدى المريضات اللاتي تعانين من فشل الزرع المتكرر الغير مفسر.