Hysteroscopic Endometrial Biopsy after Intracytoplasmic Sperm Injection Failure for women with Unexplained Infertility

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Abstract

Background: Hysteroscopy is one of the most significant examinations in females with recurrent implantation failure (RIF). It permits dependable visual evaluation of the cervical canal and uterine space and it taken into consideration as a gold standard for diagnosing intra-uterine pathology and has slight intra-operative and postoperative morbidities.

Objectives: This work aimed to clarify the roles of Hysteroscopy and endometrial biopsy in evaluation of endometrium after ICSI failure in females with un-explained Infertility.

Patients and methods: This was a prospective cohort investigation carried out at outpatient infertility clinic of the Assisted Reproductive Unit, Obstetrics and Gynecology department, Qena University Hospital. Women attend to Assisted Reproductive unit planned for intracytoplasmic sperm injection (ICSI).

Results: Based on histology as a reference standard, hysteroscopy identified the chronic endometritis pathology in 26 patients (true positives) that also found by histology. Our study revealed that Hysteroscopy had overall sensitivity, specificity, and diagnostic accuracy of 49.06%, 53.19% and 51% respectively in detecting the chronic endometritis in our patients with positive predictive value (PPV) was 54.17% while the negative predictive value (NPV) was 48.08%.

Conclusion: Hysteroscopy is of a great value in the assessment and diagnosis of the endometrial pathology in patients with unexplained RIF. There is no consensus on the everyday use of hysteroscopy before ICSI; hence, the importance of hysteroscopy as a routine in the managing of non-fertile females still remains a subject of investigation.

Keywords: IVF; Infertility; Hysteroscope; Biopsy; Recurrent implantation failure; Chronic endometritis

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Introduction

Even though uterine anomalies are considered to have a related influence on the probabilities to conceive through ICSI, conservative non-fertility studies, built on ultrasound (US) and hystero-salpingography (HSG), can overlook subtle intra-uterine lesions **(Fatemi et al., 2010)**.

One of the anomalies, that could not be identified with US and HSG, is chronic endometritis (CE) that is a subtle pathology frequently symptomless or only associated with slight disorders, CE is commonly symptomless or has indefinite symptoms, like irregular uterine blood loss, pelvic pains, and leucorrhea **(Bouet et al., 2016)**

The studies have revealed the CE rate of prevalence to be about 10-11% built on biopsies of cases who experienced hysterectomies because of benign gynecologic disorders **(Kitaya Yasuo, 2011)**. The probable connection of CE with non-fertility and/or perinatal complications has lately appeared as a topic of current studies **(Kitaya et al., 2016)**.

Histological recognition of plasma cells in the endometrial stroma is taken in to consideration as the gold standard for the chronic endometritis (CE) diagnosing **(Kasius et al., 2011)**.

However, the accurateness of histologic diagnosing may be cooperated by disorders like mono-nuclear inflammatory cell infiltrations, stromal cell proliferations, a plasmacytoid form of stromal cells, or a noticeable predecidual reactions in the late secretory endometrium (EM). Consequently, the misdiagnosis rate can be elevated than perfect. Hysteroscopy is additional effective device for CE diagnosis **(Kasius et al., 2012)**

The CE diagnosing results using hysteroscope comprise stromal edema, micro-polyps, and focal or diffuse hyperemia. The hysteroscopy assessment of endometrial inflammatory disorder revealed a much higher sensitivity for CE detection as compared to endometrial cultures **(Cicinelli et al., 2015).**

Hysteroscopy in comparison with the histological diagnosing of CE, revealed a very high diagnosing accuracy of 93.4% **(Cicinelli et al., 2010)**

There for diagnosis of specific and non-specific CE may be a subtle cause of implantation failure **(Cicinelli, et al, 2018).**

The current work aimed to clarify the role of Hysteroscopy and endometrial biopsy in evaluation of endometrium after ICSI failure in females with unexplained sterility.

Patients and methods

This was a prospective cohort investigation carried out at outpatient infertility clinic of the Assisted Reproductive Unit, Obstetrics and Gynecology department, Qena University Hospital. Women attend to Assisted Reproductive unit planned for intracytoplasmic sperm injection (ICSI).

Inclusion criteria: This study had been conducted on infertile women attend to Assisted Reproductive unit planned for intracytoplasmic sperm injection (ICSI) after failed ICSI trial with no detected abnormalities with 2D Trans vaginal U/S.

Exclusion criteria: Age more than 40 years, male factor and poor responders

Sampling: This work had been conducted on infertile couples with history of Intracytoplasmic Sperm Injection (ICSI) failure attended to outpatient clinics of Obstetrics and Gynaecology department, South Valley University hospital from March 2019 to March 2021. Endometrial sample had been taken via Hysteroscopy for all patients and had been sent for histopathological examination for detection of any histopathological abnormalities as specific or nonspecific endometritis and treatment of any other pathology could be detected.

Study Procedures: All studied cases had been exposed to the next:

Detailed history taking, involving

Individual history as Aging, marital status, special habits, present histories as history of preceding and associated symptoms, trauma, and drug or food intake, history of vaginal discharge, or bleeding, analysis of pain; site, radiation, duration, type, and associated symptoms, medical history of medical conditions or drugs taken by patients, history of previous pregnancies or abortion, number of failed ICSI trials and past history of previous operations, blood transfusion or hospital admission .

Full clinical examination

A-General examination including: Comment on patient general condition and mental state, jaundice or pallor, cyanosis, thyroid enlargement and neck vessels, vital signs: pulse, blood pressure, capillary filling time, respiratory rate and temperature, upper limb and Lower limb abnormalities.

B-Systemic examination including: *Heart examination*: For detection of any abnormal heart sounds or murmurs. *Chest examination:* For detection of any abnormal breath sound, adventitious sounds and respiratory distress. *Abdominal examination*: Including the four quadrants, loin and suprapubic areas with assessment of site of pain, tenderness, guarding or rigidity, and presence of organomegaly or ascites

C- Local examination: Including Inspection, Digital examination, Speculum, Sound and bimanual examination

Investigations

All patients had been subjected to:

Laboratory investigation: Husband Semen analysis, 3rd-day (basal) Serum follicle-stimulating hormone (FSH), prolactin, Luteinizing Hormone (LH), estradiol (E2). (basal), serum Progesterone. (basal), thyroid Stimulation Hormone (TSH), random blood sugar, CBC, C-reactive protein, C-reactive protein, renal functions testes, liver function tests, urine analysis and AMH

Imaging studies: Transvaginal US: Transvaginal US was performed for the initial assessment of intra-uterine abnormalities. Hysteroscopy: Hysteroscopy is done using a hysteroscopy, at Qena University Hospital day 2 or 3 after cessation of menstruation. The procedure was carried out under general anaesthesia. A rigid 0.4 cm nonstop flowing Bettochi hysteroscopy with 30^0 field of view was introduced into the uterus trans-cervically and the uterine space was extended via irrigations with solution of 0.9 % saline. Afterward presenting the hysteroscope via the inner uterine Os, the uterine space has been fully viewed. Afterward hysteroscopy finishing, an endometrial biopsy was accomplished using a grasper for micropolyps and suspected areas and sent for histopathological examination (**Fig.1**).

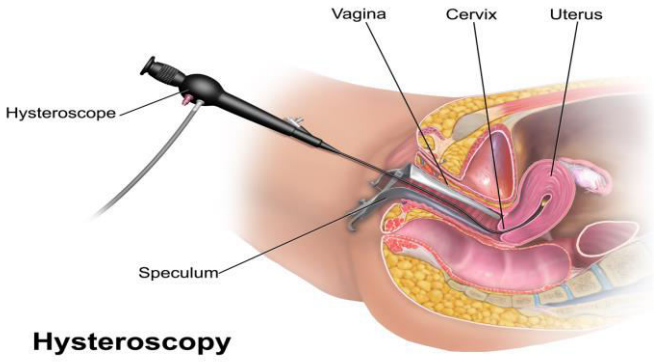

Fig.1. Anatomic depiction of a modern hysteroscopic procedure **(Ma et al., 2017).**

Ethical considerations An informed agreement has been attained from cases earlier to the enrollment in the research. An approval from Research Ethics Committee in Qena Faculty of Medicine was obtained.

Statistical analysis

Collected data analysis has been done via IBM-SPSS-16 as follow: Description of quantative data as mean and range, Description of quantative data as numbers and percentages (%), and CHi-Square testing is utilized for comparison of qualitative parameters.

Results

Sixty-seven patients were presented with primary infertility (67%) and 33 patients were presented with secondary infertility (33%). 23 (23%) patients were presented with endometrial hyperemia, 18 (18%) patients were presented with mucosal edema, 17 (17%) patients were presented with micro polyps and 48 (48%) patients were presented with CE detected by histological biopsy, (**Table .1**) This table shows that 27 (27%) patients were presented with uterine abnormality under hysteroscope. 9 (9%) patients were found to have uterine polyp, 15 (15%) patients had fine adhesions and 3 (3%) with cervical stenosis. **(Table .2)**

This table shows that 53 (53%) patients were presented by signs of CE under hysteroscope. (**Table .3).**

Based on histology as a reference standard, hysteroscopy identified the CE pathology in 26 patients (true positives) that also found by histology. (**Table .4)**

Our study revealed that Hysteroscopy had overall sensitivity, specificity, and diagnostic accuracy of 49.06%, 53.19% and 51% respectively in detecting the CE in our patients with PPV was 54.17% while the NPV was 48.08%.(**Table .5)**

Table 1. Types of infertility and pathological characteristics among the studied population

Variables		Study group (n = 100)	
		n	%
Infertility type	Primary	67	67.00%
	Secondary	33	33.00%
Endometrial hyperemia		23	0.23
Mucosal edema		18	0.18
Micropolyps		17	0.17
Histological CE		48	48.00%

Table 2. Hysteroscopic findings in the studied group:

Variables	NO	%
Normal	47	47%
Chronic Endometritis	53	53%
Cervical Stenosis	3	3%
Fine Adhesions	15	15%
Polyps	9	9%

Table 3. Incidence of chronic endometritis (CE) under hysteroscope in the studied population

Variables	(n = 100)	
	n	%
Hysteroscope with CE	53	53.00%

Table 4. Diagnosis of histological chronic endometritis under hysteroscopy and histology

Variables			Hysteroscope with Chronic Endometritis (CE)			
			Negative	Positive	Total	p- value
Histological CE	Negative	n	25 (True Negative)	27 (False Posotive)	52	0.84
		%	53.2%	50.9%	52.0%	
	Positive	n	22 (False Negative)	26 (True Positive)	48	
		%	46.8%	49.1%	48.0%	
	Total	n	47	53	100	
		%	100.0%	100.0%	100.0%	

Table 5. Predactivity (sensitivity, specificity and accuracy) for Hysteroscope

Variables	Sensitivity	Specificity	PPV	NPV	Accuracy
Hysteroscopy	49.06%	53.19%	54.17%	48.08%	51.00%

Table 6. Correlation between type of infertility, number of previous failed ICSI trials and CE

Type of infertility	Number (%)

Primary	**35 (52.2%)**
Secondary	**13 (39.9%)**
Number of previous failed ICSI trials	**Number (%)**
1	**10 (20.8%)**
2	**12 (25%)**
3 or more	**26 (54.1%)**

Discussion

The non-fertility problematic is shared in everyday medical practices. Few cases conceived with the aid of just diagnostic procedures; some never conceive despite exhaustive investigations and treatment. Basic investigations for female non fertility comprise evaluation of uterine, cervical, tubal and ovulatory parameters. Conventionally, the uterine cavity was assessed by hysterosalpingography (HSG). However, hysteroscopy is being increasingly used for direct visualizations of the uterine space and is counted better than HSG by several authors (**Makled and Farghali, 2014).**

There is some evidence of benefit from hysteroscope in growing the opportunity of gestation in the following IVF cycle, both in those with irregular and regular hysteroscopy results different potential mechanisms were suggested for this beneficial effect **(El-Toukhy et al., 2016).**

Structural irregularities of the uterine endometrial space can impact the reproductive outcomes badly, by interference with the implantations and leading to unprompted abortions. These irregularities may have an adverse influence on gestation in these women. Different hypotheses have been suggested to describe the mechanisms of sterility because of intrauterine pathologies. Most septa are relatively avascular and consequently lead to implanting failures when implanting happens over them. Other pathologies like synechiae, endometritis, cervical stenosis, and chronic cervicitis may be reasons of sub-fertility (**Vlahos et al., 2017**).

In the current study, there were sixty-seven patients were presented with primary infertility (67%) and 33 patients were presented with secondary infertility (33%),

Regarding to the pathology: 23 (23%) patients were presented with endometrial hyperemia, 18 (18%) patients were presented with mucosal edema, 17 (17%) patients were presented with micropolyps and 48 (48%) patients were presented with chronic endometritis (CE) detected by histological biopsy.

Furthermore, we found that 27 (27%) patients were presented with uterine abnormality under hysteroscope. 9 (9%) patients were found to have uterine polyp, 15 (15%) patients had fine adhesions and 3 (3%) with cervical stenosis.

In agreement with the study of **Makled and Farghali, 2014** which reported that built on hysteroscopy results, 31 cases (31%) have been lastly detected using uterine polyps; 15 cases (15%) endometrial hyperplasia; 14 cases (14%) endometritis ; 6 (6 %) submucous myomas; 7-cases (7%) intra-uterine synechiae (overall 73 patients = endometrial irregularities group); 7 cases (7%) inherited uterine irregularities (uterine irregularities group), 6 cases (6%) cervical stenosis (cervical irregularities group) and 14 cases (14%) females with no any uterine irregularities (no irregularities group).

These findings in accordance with **Gebauer et al., 2001** who reported that polyps in 51 cases in their studied groups (83patients) via hysteroscope. Polyps have been detected by curettage only in 43% of these patients.

Elsetohy et al., 2015 reported that the most common result on hysteroscopy examining was uterine polyp (9 cases out of 97 cases 9.3%), then sub-mucous myoma (7.2%), other results comprise, cervical stenosis (6.2%), uterine septum (6.2%), intra-uterine adhesions (6.2%), polypoidal endometrium (4.1%), unicornuate uterus (2.1%), and arcuate uterus (2.1%).

The relevance of routine hysteroscopy before IVF is debatable and there is no agreement on the efficacy of hysteroscope surgeries in developing pregnancy outcome. A number of reports have revealed improved gestation rate thereafter pre-IVF hysteroscopy, whereas some have showed no potential benefits (**El- Toukhy et al., 2016).**

In the current study, we found that 53 (53%) patients were presented by signs of CE under hysteroscope.

The existence of uterine pathology was 10% to 62 % of females with non-fertility and in 19% to 50 % of females who unsuccessful to attain gestation with aided reproductive technology (**Oliveria et al., 2003**). Many investigations confirmed that hysteroscopy corrections of the uterine irregularity involving uterine polyps, intra-uterine adhesion, sub-mucous fibroids, and uterine septum advances the unprompted gestation rate (**Taylor andGomel, 2008**).

Furthermore, **Elmorsy et al., 2012** revealed that of 23 cases (45 %) with irregular hysteroscope result, 15 cases (65.2 %) attained gestation thereafter corrections of their uterine irregularities.

Likewise, a recent systematic review of El-**Toukhy et al., 2008** involving 1,691-cases with 2 or more unsuccessful IVF tries established that office hysteroscope is extremely advantageous in cases with RIF history and significantly progress the gestation rates in the following IVF cycles.

A recent study of **McKnight and McKenzi, 2016** done by the Reproductive Medicine Network associated semen factors to fertility. The "new norms" via which fertility could now be described are: a sperm density higher than 15 million/ml, motility higher than 32 %, and a strict morphology higher than 4 % (51).

Based on histology as a reference standard, hysteroscopy identified the CE pathology in 26 patients (true positives) that also found by histology. Our study revealed that Hysteroscopy had overall sensitivity, specificity, and diagnostic accuracy of 49.06%, 53.19% and 51% respectively in detecting the CE in our patients with PPV was 54.17% while the NPV was 48.08%.

In the **Makled and Farghali, 2014** study, reported that hysteroscopy revealed uterine micro polyps in 31 cases (31%) of the non-fertile cases. Of these cases, only 3 cases (18%) have been suitably identified by means of analysis of specimens collected via Pipelle, The NPV was 71.1%, i.e., 28.9% of the cases who were EB negative have been shown to have uterine polyps using hysteroscope. While, the PPV was 100%, i.e., all diagnosed cases with uterine polyps by EB were confirmed to have uterine polyps using hysteroscope. The NPV was 100%, i.e., none of the cases with negative hysteroscope findings were showed to have had endometrial hyperplasia when they experienced histopathological analyzing. Furthermore, the PPV was 93.3%, (i.e., any case with a hysteroscope-built diagnosing of hyperplasia have 74.2% danger ot have an endometrial hyperplasia by EB). The NPV was 98.8%, (i.e., 1.2% of the cases who were hysteroscope-negative were revealed to have endometritis by EB. While, the PPV was 100%, (i.e., all cases who were detected to have endometritis using hysteroscope were shown to have endometritis by EB).

Abdelazim and colleagues in **2013**, reported that, despite the low sensitivities of the Pipelle device for the diagnosis of endometritis and uterine polyps (88.9% and 60%, respectively), it had an elevated NPVs (99.2% and 89.6%, respectively) and elevated accuracy (99.3% and 98.6%, respectively).

A prospective investigation of **Yang et al., 2014** performed diagnosing hysteroscope, endometrial biopsy, and cervical and endometrial Chlamydia infections testing. Hematoxylin–eosin staining showed that CE happened in 12% of these cases; hysteroscope had a sensitivity of 16.7%, and specificity of 93.2% in histologic CE diagnosis, and was counted to have a high NPV; they counted polyps of diameter <0.1cm ‘‘micro polyps’’, and were frequently accompanying with histologic CE.

Kasius et al., 2011 concluded that the reproductive outcomes thereafter beginning of IVF/ICSI wasn’t showed to be negatively impacted by histologic CE. Therefore, endometrial biopsy could not show the whole uterine space and endometrial states, as it is built on inadequate specimen collections. In contrast, embryo implantations mayn’t demand such ideal conditions, even pathologically and immune-histo-chemically approved CE mayn’t have better impact on implantations.

Hysteroscopy could scan entire uterine cavities, which simplifies the observations of endometrial width and vessel-filling state thus that endometrial receptiveness may be assessed. CE diagnosing via hysteroscope is commonly connected with chronic infections, since antibiotic therapy may clean the occult bacterial infections and rises embryo implanting rates **(Yang et al., 2014).**

The function of hysteroscope in cases with formerly unsuccessful IVF cycle has been investigated as well. A new systematic review and metanalysis of 2 randomized and 3 nonrandomized control trials on 1691 cases reported that hysteroscopic diagnosing earlier a following IVF try significantly rises the odds for conceptions in

cases with a minimum 2 unsuccessful IVF tries (**El-Toukhy et al., 2008).**

In correlation between female ages and CE we found that incidence of CE in ages from 20 to <30 years is 16.6% and from 30-35 years is 31.2% and >35 years is 52.08%.

In agree with our study **Dongmei Song, et al., 2018** found that incidence of CE in ages from 20 to <30 years is 23.6%, from 30-35 years is 24.2 % and >35 years is 28.8%

In correlation between BMI and CE we found that incidence of CE is 2% below 18, 22.9 in BMI from 18-<25 ,27.02% in BMI from 25-30 .47.9% in BMI >30

In Correlation between type of infertility and CE**,** we found that incidence of CE is 52.2% in primary infertility and 39.9 in secondary infertility and this result agree with **Dongmei Song, et al.,2018** which was 42.9 in primary infertility and 23.6 in secondary infertility.

In Correlation between number of previous failed ICSI trials and CE by hysteroscopy, we found that incidence of CE was 10% in patients with previous failed trial, 25% in previous failed 2 trials, 54% in previous failed 3 or more trials

Conclusion:

Hysteroscopy is of a great value in the assessment and diagnosis of the endometrial pathology in patients with unexplained recurrent implanting failures. There is no consensus on the routine use of hysteroscopy before ICSI; hence, the importance of hysteroscope as an everyday practice in the managements of in-fertile females still a subject of investigation.

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