



Effectiveness of Laparoscopy and Hysteroscopy to Optimize the Outcome of Assisted Reproductive Technology

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Identifying the cause of infertility is complex and often reveals overlapping etiologies. Because of the valuable characteristics of hysteroscopy, it has been deemed a promising surgical intervention to improve in vitro fertilization (IVF) outcomes. The present study aimed to evaluate the role and effectiveness of combined laparoscopy and hysteroscopy in the assessment of uterine pathologies in infertile women with recurrent implantation failure (RIF) after IVF, and explore whether removal of such pathologies increased the rate of pregnancy in those women.

Methods: This prospective observational cohort study included 40 infertile patients presented with either primary or secondary infertility after repeated IVF/ intracytoplasmic sperm injection (ICSI) failure. Participants were selected from Endoscopy and Assisted Reproductive units in Obstetrics and Gynecology department at Tanta University Hospital.

Results: There was a statistically significant higher rate of successful cases in the abnormal hysteroscopic findings group. There was no statistically significant difference between normal and abnormal laparoscopic findings groups as regard successful ICSI procedure.

Conclusions: Hysteroscopy is recommended to be a routine diagnostic and therapeutic tool in any case with RIF or recurrent IVF/ICSI failures before a new attempt as it increases the success rate. We can't recommend routine laparoscopy in any case with RIF or recurrent IVF/ICSI failures.

Keywords: Laparoscopy; hysteroscopy; assisted reproductive technology; fertilization; implantation.

1. INTRODUCTION

Infertility is a condition characterized by the failure to establish a clinical pregnancy after 12 months of regular and unprotected sexual intercourse. It is estimated to affect between 8 and 12% of reproductive-aged couples worldwide. Infertility is not just a medical problem, but many of those failing to conceive deal with medical, psychological, and financial stresses related to their condition [1].

Identifying the cause of infertility is complex and often reveals overlapping etiologies. Males are found to be solely responsible for 20-30% of infertility cases but contribute to 50% of cases overall. After a standard evaluation, between 20% and 30% of couples will have no identifiable cause for their infertility. However, these estimates include couples in which the female partner may not have been thoroughly evaluated with laparoscopy for pelvic pathologies such as endometriosis [2].

More than 3 decades after the introduction of in vitro fertilization (IVF) and despite the improved success rates of assisted reproductive technologies (ART), the argument for performing laparoscopy or hysteroscopy as a part of the infertility workup still stands [3].

Gynecological laparoscopic surgery has been progressively and successfully introduced into practice as, this minimally invasive surgery is associated with low morbidity, less postoperative pain, and improved cosmetics [4]. In addition to diagnostic indications, operative procedures at the time of laparoscopy proved to enhance both spontaneous and assisted conception rates [5].

Considering the side effects of being an invasive procedure with potential risks of general anesthesia, vascular and gastrointestinal injuries, laparoscopy is thereby essential only if it would be expected to change management decisions, or to provide direct laparoscopic correction of the abnormality [6,7].

Uterine cavity assessment has been suggested as a routine investigation before an IVF cycle,

considering evidence that uterine anomalies may result in recurrent implantation failure (RIF) [8,9].

Because of the valuable characteristics of hysteroscopy, it has been deemed a promising surgical intervention to improve IVF outcomes, especially in RIF patients, and was believed to function well even before the first IVF cycle to decrease both emotional and financial costs [10].

The present study aimed to evaluate the role and effectiveness of combined laparoscopy and hysteroscopy in the assessment of uterine pathologies in infertile women with RIF after IVF, and explore whether removal of such pathologies increased the rate of pregnancy in those women.

2. PATIENTS AND METHODS

This Prospective observational cohort study was carried out at Endoscopy and Assisted Reproductive units in Obstetrics and Gynecology department at Tanta University Hospital from November 2018 to December 2020. Approval from Ethical Committee and informed written consent were obtained. There were adequate provisions to maintain the privacy of participants and confidentiality of the data, the patient's name was replaced by a serial number, and her address was confidential.

The study included 40 infertile patients who presented with either primary or secondary infertility after repeated IVF/ intracytoplasmic sperm injection (ICSI) failure. Participants were selected from Endoscopy and Assisted Reproductive units in Obstetrics and Gynecology department at Tanta University Hospital.

2.1 Inclusion Criteria

1. Age between 25-38 years.
2. BMI between 18.5 and 29.9 kg/m².
3. Patients with repeated IVF/ICSI failure (2 or more).
4. History of repeated implantation failure described as 'two or more failed IVF or ICSI cycles' or 'previously unsuccessful IVF cycles' despite the transfer of good quality embryos.

2.2 Exclusion Criteria

1. Couples with severe male factor infertility.
2. Premature ovarian failure [11].
3. Patients with a poor ovarian reserve and poor responders [12].
4. Contraindication to laparoscopy such as mechanical or large abdominal mass (> 24 weeks gestation size) [13].
5. Contraindication to hysteroscopy such as recent or active pelvic inflammatory disease and active uterine bleeding (causing poor visibility) [14].

All patients included in this study and their spouses were subjected to complete demographic including spouses demographics and medical histories such as menstrual and obstetric history and abdominal or pelvic surgeries, drug therapy or allergy, and detailed history of the previous IVF/ICSI trials. Clinical examinations were performed including vital signs, palpation of the abdomen, and vaginal examination. Routine lab investigations such as CBC, coagulation profile, liver function, kidney function taste biochemical, and hormonal tests were also performed.

Infertility workup was done on all patients (semen analysis, HSG, and hormonal profile including day 2 FSH, LH, E2, serum prolactin, TSH, and AMH) to exclude the presence of a new pathology. Autoantibodies profiles were generated like Anti Cardiolipin (aCL), lupus anticoagulant (LA) antiphospholipid, thrombophilia profile like MTHFR gene and factor V LEIDEN gene as well as testing of DNA fragmentation of the semen.

2.3 Laparoscopy and Hysteroscopy

Procedures were done from day 7 to day 11 post-menstrual as the endometrium was thin facilitating intracavity viewing, bleeding was minimal and pregnancy was ruled out.

Diagnostic laparoscopy was used for inspection of the abdominal and pelvic organs. Operative laparoscopy procedures were done according to the abnormalities revealed as cauterization of the endometriotic implants, laparoscopic ovarian cystectomy of an ovarian endometrioma, laparoscopic resection of pelvic adhesions, and salpingectomy in case of hydrosalpinx.

Hysteroscopy was utilized for a systematic evaluation of the cavity was done observing the

fundus, tubal ostia, anterior and posterior wall, and cervix canal. Any irregularity in the cavity, adhesions, polyps or myomas, and uterine septum were noted. Dealing with endometrial abnormalities was done using scissors as in the case of endometrial polyps, synechia, and septum.

2.4 IVF/ICSI – ETs Procedure

A new attempt of IVF/ICSI – ETs was done 3 months later after laparoscopy and hysteroscopy. The GnRH long agonist protocol started with the administration of 0.1 mg GnRH agonist on cycle day 21 followed by administration of gonadotropin at 150-225 IU daily starting on cycle day 2. The adjustment of gonadotropin dose was based on follicular development. Continual administration of GnRH agonist and gonadotropin lasted until the start of hCG injection, which was approximately 14 days post GnRH agonist regimen or when follicles reached from 16 to 18 mm in size.

For the GnRH antagonist protocol, administration of gonadotropin at 150-225 IU daily was initiated after monitoring of patients' follicles sizes on cycle-day 2 or 3. Gonadotropin dosage varied according to the follicular response. Approximately after the 6th day of gonadotropin injection or when follicular size reached more than or equal to 14 mm, subcutaneous administration of the GnRH antagonist began.

For IVF purposes, 50,000 to 100,000 capacitated sperm were placed in culture with a single oocyte; 16 to 20 hours later, fertilization was documented by the presence of two pronuclei within the developing embryo. For ICSI purposes, micromanipulation of egg and sperm was done under magnification. A holding pipette was used to stabilize the egg while an injection pipette was used to insert a viable sperm into the ooplasm of the egg. Embryo transfer of the highest quality embryo(s) took place on day 3 or day 5 post retrieval.

The outcome was assessed through the clinical pregnancy rate; patients were asked to perform a serum pregnancy test two weeks after the embryo transfer.

2.5 Statistical Analysis

Statistical presentation and analysis of the present study were conducted using SPSS. Quantitative variables were expressed as mean

and standard deviation (SD) and were compared using the F test. Categorical variables were expressed as frequency and percentage and were statistically analyzed by the Chi-square test. P-value ≤ 0.05 was considered statistically significant.

3. RESULTS

All 40 patients enrolled in this study were below the age of 40. Six patients only presented with overweight, while the remaining 34 patients were of normal weight Table 1.

We found that -in general- an endoscopy is more accurate in the diagnosis of intracavitary uterine lesions or extrauterine lesions than ultrasound. Only 1 case was diagnosed by endometritis with ultrasound and hysteroscopy detected the presence of extra 3 missed cases. Also, 1 case was diagnosed by ultrasound to have a uterine septum, while hysteroscopy proved the presence of extra 2 missed cases. Ultrasound failed to diagnose any case with narrow uterine cavity, short cervix, or intrauterine synechia, while all these cases were diagnosed by hysteroscopy. There were 3 cases found to have hydrosalpinx by ultrasound, while laparoscopy proved the presence of extra 4 missed cases. Also, ultrasound failed to diagnose any case with

pelvic adhesions or endometriosis, while laparoscopy diagnosed all of them Table 2.

The majority of cases (92.5%) in our study underwent ICSI procedure using long agonist protocol for ovarian stimulation, while antagonist protocol was used for ovarian stimulation in only 3 patients. All cases had a fair to good response to the protocol of induction during the ICSI procedure with the number of oocytes retrieved ranging between 5 and 18 oocytes. All cases had successful oocyte fertilization and no more than 3 embryos were transferred intrauterine. The majority of cases (47.5%) had 2 embryos to be transferred Table 3.

We found that all patients with endometrial polyps (4 patients) and uterine septum (3 patients) tested positive for pregnancy. Only one patient with submucous myoma, one patient with intrauterine synechia, and 2 patients with endometritis also tested positive for pregnancy. Nevertheless, 6 patients with normal hysteroscopic findings tested positive for pregnancy while the remaining 15 tested negative. According to patients with narrow uterine cavity, 2 patients tested negative and only one patient tested positive for pregnancy. While the only one patient with a short cervix tested negative for pregnancy Table 4.

Table 1. Distribution of the studied cases according to demographic data

	Minimum – Maximum	Mean \pm S. D
Age (years)	21 – 38	31.63 \pm 3.85
BMI (kg/m ²)	19.4 – 26.1	23.36 \pm 1.67
Duration of infertility (years)	4 – 8	5.60 \pm 1.06

Table 2. Comparison between normal and abnormal sonographic, hysteroscopic and laparoscopic findings

	Ultrasound		Hysteroscopy		Laparoscopy	
	N	%	N	%	N	%
Normal findings	25	62.5	21	52.5	20	50
Endometritis	1	2.5	4	10		
Submucous myoma	2	5	2	5		
Narrow cavity	-	-	3	7.5		
Polyp	4	10	4	10		
Septum	1	2.5	3	7.5		
Synechia	-	-	2	5		
Short cervix	-	-	1	2.5		
Endometrioma	2	5			2	5
Subserous myoma	1	2.5			1	2.5
Hydrosalpinx	3	7.5			7	17.5
PCO	2	5			2	5
Pelvic adhesions	-	-			4	10
Pelvic endometriosis	-	-			4	10

Table 3. Distribution of the studied cases according to the ICSI procedure

		N = 40	%
Protocol	Long	37	92.5
	Antagonist	3	7.5
Number of oocytes retrieved		5 - 18	10.18 ± 3.50
Number of embryos transferred	1	6	15.0
	2	19	47.5
	3	15	37.5

Table 4. Distribution of the studied cases with different hysteroscopic and laparoscopic findings regarding successful ICSI procedure (positive pregnancy test)

		Pregnancy		Total
		+ve	-ve	
Hysteroscopy				
Normal	N	6	15	21
	%	33.3%	68.2%	52.5%
Endometritis	N	2	2	4
	%	11.1%	9.1%	10.0%
Myoma	N	1	1	2
	%	5.6%	4.5%	5.0%
Narrow cavity	N	1	2	3
	%	5.6%	9.1%	7.5%
Polyp	N	4	0	4
	%	22.2%	.0%	10.0%
Septum	N	3	0	3
	%	16.7%	.0%	7.5%
Synechia	N	1	1	2
	%	5.6%	4.5%	5.0%
Short cervix	N	0	1	1
	%	.0%	4.5%	2.5%
Laparoscopy				
Normal	N	8	12	20
	%	44.4%	54.5%	50.0%
Endometrioma	N	1	1	2
	%	5.6%	4.5%	5.0%
Subserous myoma	N	0	1	1
	%	.0%	4.5%	2.5%
Hydrosalpinx	N	5	2	7
	%	27.8%	9.1%	17.5%
PCO	N	2	0	2
	%	11.1%	.0%	5.0%
Pelvic adhesions	N	1	3	4
	%	5.6%	13.6%	10.0%
Pelvic endometriosis	N	1	3	4
	%	5.6%	13.6%	10.0%

Table 5. Comparison of the studied cases with normal and abnormal hysteroscopy and laparoscopic findings regarding successful ICSI procedure (positive pregnancy test)

Pregnancy		Normal	Abnormal	Total
Hysteroscopy findings				
+ve	N	6	12	18
	%	28.6%	63.2%	45.0%
-ve	N	15	7	22
	%	71.4%	36.8%	55.0%
Total	N	21	19	40
	%	100.0%	100.0%	100.0%
Chi-square	X2	4.821		
	P-value	0.028*		
Laparoscopic findings				
+ve	N	8	10	18
	%	40.0%	50.0%	45.0%
-ve	N	12	10	22
	%	60.0%	50.0%	55.0%
Total	N	20	20	40
	%	100.0%	100.0%	100.0%
Chi-square	X2	0.404		
	P-value	0.525		

Interestingly, the number of successful cases in the abnormal hysteroscopic findings group was double the number of successful cases in the normal hysteroscopic findings group with the presence of statistically significant differences between both groups. There was no statistically significant difference between normal and abnormal laparoscopic findings groups as regard successful ICSI procedure Table 5.

4. DISCUSSION

Recurrent implantation failure is defined as a failure to achieve a clinical pregnancy after the transfer of 4 or more good-quality embryos in a minimum of 2 IVF cycles in a woman under the age of 40 [15]. The failure of implantation may be a result of embryo factors, uterine factors, or maybe multifactorial.

The current results were comparable to the results of the Dijkhuizen et al which was conducted on 50 female patients and found that 27 patients had normal ultrasound findings which represented 54%, while 20 patients had polyps and the remaining 3 had myoma which represented 40% and 6% respectively [16].

The study of Cepni et al aimed to test the efficacy of transvaginal sonography (TVS) in the evaluation of uterine cavity abnormalities in patients with failed IVF. Their 3D US examinations revealed that 30% of patients had normal findings, 27% had polyps, 6% had fibroid

and 56% had asymmetrical thickening [17]. These findings of both studies were higher than our results, and this may be attributed to the use of 3D ultrasound, while 2D ultrasound was used in our study.

Our results were in agreement with the results of the recent study of Al-Temamy et al which was conducted in 2019 aiming to evaluate the role and benefit of routine hysteroscopy before ICSI in women with previous failed ICSI. They found that the majority of the studied patients had normal findings (21 patients = 70%), while the number of patients that had polyps, adhesions, myoma, and septum was 5, 1, 2, and 1 respectively which represented 16.7%, 3.3%, 6.1%, and 3.3% respectively [18].

Alturki conducted a study in 2018 aiming to evaluate the use of hysteroscopy in the assessment of uterine pathologies in infertile women with RIF after IVF and determine whether removal of such pathologies increased pregnancy rates in women with RIF. Their hysteroscopy examination results matched the current results as they found out of 266 studied patients, 162 patients (60.9%), a hysteroscopy did not find any abnormality of the uterine cavity and in 104 patients (39.1%) there were one or more abnormal hysteroscopic findings. The percentage of patients with adhesions, hyperplasia, polyps, and fibroid was 22.1%, 11.5%, 44%, and 15% respectively, while patients with arcuate uterus and infections

represented only 5.6% and 0.9% of the studied group respectively [19].

The study of Demiroglu and Gurgan aimed to evaluate if the diagnosis and treatment of intrauterine lesions with office hysteroscopy is of value in improving the pregnancy outcome in patients with recurrent in-vitro fertilization and embryo transfer failure and found that they found that majority of patients with polyps and narrow uterine cavity tested negative for pregnancy (90% and 95% respectively) while all of the patients with myoma and uterine septum tested positive for pregnancy. In addition to that, all patients with normal findings tested positive for pregnancy [20].

The study of Raju and his colleagues aimed to evaluate if the diagnosis and treatment of uterine cavity abnormalities by hysteroscopy in patients undergoing IVF programs are of any value in improving clinical pregnancy outcomes. This study found a significant difference in the clinical pregnancy rates after IVF or ICSI between patients who underwent hysteroscopy and those without office hysteroscopic evaluation before ovarian stimulation for IVF treatment [21].

However, Eltokhy et al found significantly lower pregnancy rates than the present results. Only 29% of patients with normal findings had tested positive for pregnancy. Only 19% of patients with myoma and 8% of patients with uterine septum tested positive for pregnancy, while all patients with polyps tested negative for pregnancy [22].

Another case-control study aimed to evaluate the effect of hysteroscopy in 353 women with RIF with apparently normal uterine cavity before ART the results of hysteroscopy were normal in 103 women (72.5%), and they revealed inflammation in 22 (15.5%), polyp in 16 (11.3%) and Asherman syndrome in one patient (0.7%). Chemical pregnancy occurred in 58.5% of women in the hysteroscopy group versus 34.1% in the control group. Clinical pregnancy rates were 50.7% and 30.3% in the hysteroscopy and control groups respectively.¹⁸⁴

In a recent study conducted by Yu and his colleagues to investigate the fertility outcome of laparoscopic treatment in infertile women with repeated IVF failures. Patients recruited in this study were classified into 2 groups. The study group (n=45) was offered laparoscopy for

evaluation of infertility, control group (n=45) elected to proceed to IVF without laparoscopy. Pelvic abnormalities were detected in 97.8% of cases; only 1 patient had no pathologic findings. Endometriosis (26/45) was the most common abnormality detected in laparoscopy. Tubal lesions were diagnosed in 14 women. Pelvic adhesions were found in 15 patients; in 4 cases no other pathology was observed but 11 of them had coexisting tubal lesions or endometriosis. In the study group, 19 patients desired spontaneous pregnancy and among them, 16 conceived postoperatively. While the rest 26 patients in the study received IVF treatment following surgery and 14 conceived with IVF. In the control group, 12 were conceived from repeat IVF cycles. A significant difference was found in the per cycle ongoing pregnancy rates between patients in the study group and control group (41.9% vs 19.6%, $P < .05$) [23].

Strandell and his colleagues carried out a randomized controlled trial of salpingectomy before IVF in patients with hydrosalpinges and analyzed the results from the first transfer cycle after the laparoscopy procedure to evaluate the pregnancy outcome. Salpingectomy was performed in 103 patients who subsequently underwent a mean of 2.3 embryo transfers (range 1–6), while, 56 patients in the treatment control group without surgical intervention underwent 2.2 (range 1–6) embryo transfers. The chance of birth was doubled after salpingectomy ($P = 0.014$) [24].

A retrospective study was carried out by Littman et al to investigate the fertility outcome of laparoscopic treatment of endometriosis in infertile women with repeated IVF failures. A sum of 29 patients with multiple IVF failures underwent laparoscopic treatment with a control group of 35 women who didn't undergo laparoscopy. 22 conceived after laparoscopic treatment of endometriosis, including 15 non-IVF pregnancies and 7 IVF pregnancies. In this non-laparoscopy group, 13 of 35 conceived; two of the pregnancies were spontaneous and the rest were from repeat IVF cycles. The study demonstrated a significantly higher pregnancy rate in the laparoscopy group versus the non-laparoscopy group [25].

The following Table 6 summarizes the data and findings obtained by the forementioned studies. Table 6.

Table 6. Summary of similar studies' findings

Study	n	Normal samples	Findings
Dijkhuizen (2000)	50	27 (54%)	20 (40%) polyps & 3 (6%) myoma
Cepni (2005)	-	30%	27% polyps, 6% fibroid & 56% asymmetrical thickening
Al-Temamy (2019)	30	21 (70%)	5 (16.7%) polyps, 1 (3.3%) adhesion, 2 (6.1%) myoma, and 1 (3.3%) septum
Alturki (2018)	266	162 (60.9%)	104 (39.1%) abnormal hysteroscopy; adhesions (22.1%), hyperplasia (11.5%), polyps (44%), fibroid (15%), arcuate uterus (5.6%) & infections (0.9%)
Demiroglu (2004)	421	Tested positive for pregnancy	- Polyps and narrow uterine cavity tested negative for pregnancy (90% & 95%). - Myoma & uterine septum tested positive for pregnancy
Raju (2006)	520	Statistically significant difference in clinical pregnancy rates between - Group I & Group IIa (26.2 & 44.44%, P<0.05). - Group I and Group IIb (26.2 & 39.55%, P<0.05).	
Eltokhy (2016)	702	29% of normal tested positive for pregnancy	- 19% myoma patients & 8% uterine septum patients tested positive for pregnancy. - Polyp patients tested negative for pregnancy
Hosseini (2014)	353	103 (72.5%)	22 (15.5%) inflammation, 16 (11.3%) polyp & 1 (0.7%) Asherman syndrome.
Yu (2019)	90	1	97.8% pelvic abnormalities, endometriosis (26/45), 14 tubal lesions, 15 pelvic adhesions.
Strandell (2001)	103	56	Birth doubled after salpingectomy (P = 0.014)
Littman (2005)	64	-	- 22 conceived after laparoscopic treatment of endometriosis, including 15 non-IVF pregnancies & 7 IVF pregnancies. - Non-laparoscopy group: 13 of 35 conceived; 2 pregnancies were spontaneous & others were repeat IVF cycles.

5. CONCLUSIONS

Hysteroscopy is recommended to be a routine diagnostic and therapeutic tool in any case with RIF or recurrent IVF/ICSI failures before a new attempt as it increases the success rate. We can't recommend routine laparoscopy in any case with RIF or recurrent IVF/ICSI failures before the approved presence of any abnormality that requires laparoscopic intervention before the next ICSI trial.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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