

## Research Article

# Chromohysteroscopy after Failed Intracytoplasmic Sperm Injection (ICSI)

Emadeldin A. Khalifa <sup>¥</sup>, Mohamed A. Al Samrah, Tamer H. Mahmoud, Noha S. Abdeen

Department of Obstetric and gynecology, Faculty of medicine, Alexandria University.

## ABSTRACT

**Background:** Intra cytoplasmic sperm injection (ICSI), is a procedure adopted worldwide as the ultimate micro-assisted fertilization approach due to its clinical success.

**Objectives:** The objective of this study was to assess the value of using Chromohysteroscopy modality in infertility workup after failed ICSI procedures in evaluating uterine receptivity and detect any signs of chronic endometritis by a less invasive method.

**Methods:** prospective cohort study. A total of 50 infertile patients recruited from the infertility clinic in El-Shatby University Hospital, Faculty of Medicine, Alexandria University. Cases were allocated into two groups. The first group includes cases that had a failed trial of intracytoplasmic sperm injection. The second group includes control cases from patients seeking for fertility treatment with no previous history of intracytoplasmic sperm injection and with no history of anatomic uterine abnormalities. The selected sample size was found to be 50 women, and were randomly selected and allocated in two groups each group was 25 women after fulfilling the inclusion criteria.

**Results:** There was a statically significant increase in the incidence of endometritis among the study group 68% in comparison to 16% in the control group.

**Conclusions:** In this study. Endometrial dyeing with methylene blue at hysteroscopy improves the detection of chronic endometritis.

**Key words:** Chromohysteroscopy, Intra Cytoplasmic Sperm Injection (ICSI)

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### ¥Correspondence:

Email: [alzahraa\\_yehia@yahoo.com](mailto:alzahraa_yehia@yahoo.com)  
Tel: 01000867971-01225721586

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## INTRODUCTION

The first clinical success of intra cytoplasmic sperm injection (ICSI), in 1992, led to worldwide adoption of this procedure as the ultimate micro-assisted fertilization approach.

There are two main groups of patients that may require ICSI,<sup>(1)</sup> patients who have a severe sperm problem, which prevents them from even attempting conventional or a modified form of in-vitro fertilization (IVF)<sup>(2)</sup>, and patients who have previously attempted IVF due to any cause of infertility, but have failed to achieve fertilization (generally on more than one occasion).

Some investigators consider implantation failure to indicate a negative pregnancy test 2 weeks after embryo transfer. Others use the term to indicate either absence of a gestational sac on ultrasound 5 weeks after transfer

or of a fetal heartbeat at or beyond 3 weeks of pregnancy, and some even consider failure as absence of a live birth after IVF

Many women who have uterine problems may have no problems getting pregnant, but they may have difficulty in keeping the pregnancy as they tend to miscarry.<sup>(3)</sup> The evaluation of uterine factor of infertility can be accomplished using ultrasonography (abdominal, transvaginal, or three-dimensional modalities), hysterosalpingography (HSG), saline infusion sonography (SIS) and hysteroscopy. When there is a macroscopic abnormality, it is hardly possible to miss the diagnosis. But when there is no apparent finding, uterus is accepted as normal, although endometrial cells still can be defective.<sup>(4)</sup>

Office hysteroscopy (OH) is well-tolerated minimally-invasive procedure, which allows reliable visual assessment of the cervical canal and uterine

cavity and provides the opportunity to perform therapy in the same setting with low cost, minimal morbidity and inconvenience to the patient, and some lesions diagnosed can be operated easily using different equipment introduced through the operative channel of the hysteroscope.<sup>(5)</sup> Office hysteroscopy has been proven to have superior sensitivity and specificity in evaluating the endometrial cavity.<sup>(6)</sup>

Chromo endoscopy is a widely used technique in gastrointestinal imaging. Over the last decade; endoscopic systems have acquired great power due to high-resolution images, Chromohysteroscopy was first introduced after the study by Kucuk and Safali in 2008, where they combined Chromo endoscopy and hysteroscopy as a new avenue to improve the diagnostic value of hysteroscopy (by using methylene blue dye) in the setting of assisted reproduction.<sup>(7)</sup>

Endometritis is inflammation of the endometrial lining of the uterus. In addition to the endometrium, inflammation may involve the myometrium and, occasionally, the parametrium. The Center for Disease Control and Prevention (CDC) 2010 sexually transmitted diseases treatment guideline defines PID as any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis,<sup>(8)</sup> endometritis is a poly microbial disease involving, on average, 2-3 organisms. In most cases, it arises from an ascending infection from organisms found in the normal vaginal flora. The combination of clindamycin and gentamicin administered intravenously every 8 hours has been considered the criterion standard treatment. The combination of a second- or third-generation cephalosporin with metronidazole is another popular choice.<sup>(9)</sup>

The study was designed to assess the value of using Chromohysteroscopy modality in infertility workup after failed ICSI procedures in evaluating uterine receptivity and detect any signs of chronic endometritis by a less invasive method.

## METHODS

**Study Design:** The study was conducted as a case-control study. A total of 50 infertile cases were randomly selected and allocated as two groups. The first group (Group A), included 25 infertile women that had a failed trial of intracytoplasmic sperm injection and a second group (Group B) that included 25 control cases from patients seeking for fertility treatment with no previous history of intracytoplasmic sperm injection. The inclusion criteria were women between 20-38 years of age, nullipara or multipara, failed ICSI cycle in spite of good embryos in group one, and time of hysteroscopy designated as 30 and 120 days after the IVF cycle (3 to 4 days) post menstrual. Women with a known or detected uterine anatomical abnormality, cancelled cycles or had no embryo transfer, evidence of

hormonal disturbance, or repeated curettage more than 3 times and /or evidence of Asherman, s syndrome were excluded from the study.

All patients were subjected to:

- Detailed history taking including complete obstetric and gynecologic history, history of previous ICSI cycles, number of embryos transferred, quality of embryos, and presence of any associated pelvic pathology that was present during the ICSI cycle (hydrosalpinx, endometriosis, etc...).
- Complete general and gynecological examination.
- Transvaginal ultrasonography was done for evaluation of uterus & ovaries and detects any pelvic pathology.
- All hysteroscopic operations were performed in the early follicular phase (3 to 4 days post menstrual) as conventional hysteroscopy and documentation of the findings will be done. Dorsal lithotomy position was used for all hysteroscopic procedures. 2.9 mm, 30° rigid telescope with an operative sheath of 3.5 mm will be used for examination and intraoperative antibiotics prophylaxis with 1 g ceftriaxone will be given to all patients. All procedures were done in an out-patient setting with paracervical block if needed, using xylocaine 5 ml to be injected at 3 and 9 o'clock.

**Chromohysteroscopy:**<sup>(10)</sup> in this procedure, five milliliter of 1% methylene blue dye was introduced through the hysteroscopic inlet. After 5 min of waiting distending medium flow will start again and let wash the endometrium. Uterine cavity was visualized for staining pattern. Diffuse light blue staining will be considered normal. Focal, dark blue staining above the internal cervical ostium, regardless of size and number of stained areas, will be considered positive finding.

**Ethical statement:** The study was approved by the institutional review board and the medical ethics committee at the faculty of medicine Alexandria university, Egypt. The research complied with the international ethical research guidelines of declaration of Helsinki. An informed consent was taken from all participants after explaining the aim and concerns of the study. Data sheets were coded to ensure anonymity and confidentiality of patient's data.

## RESULTS

**Ultrasound findings:** in the study group A, 21(84%) had normal ultrasound findings, 1(4%) had acute AVF and 3(12%) had RVF. In the control group, 22(88%) had normal ultrasound findings and 3(12%) \had RVF. There was no statistically significant differences between the two groups P=0.600.

**The condition of the endometrium:** In the study group 21(84%) out of the patients was normal, 2(8%) out of the patients had atrophic, 1(4%) out of the patients had thick and 1(4%) out of the patients had thick polypoidal while in the control group 23(92%) out of the patients

was normal, 1(4%) out of the patients had filmy layer of adhesion and 1(4%) out of the patients was thick. There were no statistically significant differences between the two groups, (P=0.536).

**Table 1:** Comparison between the two groups as regard to ultrasound findings

ultrasound findings	Study Group		Control Group		P Value
	No. (N=25)	%	No. (N=25)	%	
Normal	21	84	22	88	0.600
Acute AVF	1	4	0	0	
RVF	3	12	3	12	

**Table 2:** Comparison between the two groups as regard to condition of the endometrium

Condition of the endometrium	Study Group		Control Group		P Value
	No. (N=25)	%	No. (N=25)	%	
Normal	21	84	23	92	0.394
Atrophic	2	8	0	0	
Filmy adhesion	0	0	1	4	
Thick	1	4	1	4	
Thick polypoidal	1	4	0	0	

**Presence of endometritis:** In the study group 8(32%) out of the patients had no presence of endometritis (diffuse light staining) and 17(68%) had presence of endometritis (focal dark staining) while in the control group 21(84%) had no presence of endometritis and 4(16%) had presence of endometritis. There was a high statistically significant difference between the two groups, (P=0.000).

**Hysteroscopic entry through the cervical os:** In the study group 7(28%) had difficult in entry and 18(72%)

had easy entry while in the control group 5(20%) had difficult in entry and 20(80%) had easy entry. There was no statistically significant differences between the two groups, (P=0.742).

**Days of menstrual cycle at the time of hysteroscopic procedure:** In the study group A, it ranged between 5-15 with mean±S.D. 8.56±2.615, while in the control group it ranged between 5-14 with mean±S.D. 9.6±2.217. There was no statistically significant differences between the two groups, (P=0.068).

**Table 3:** Comparison between the two groups as regard to presence of endometritis

Presence of endometritis	Study Group		Control Group		P Value
	No. (N=25)	%	No. (N=25)	%	
No (diffuse light)	8	32	21	84	0.000
Yes (focal dark)	17	68	4	16	

**Table 4:** Comparison between the two groups as regard to hysteroscopic entry

Entry	Study Group		Control Group		P Value
	No. N=25	%	No. N=25	%	
Difficult	7	28	5	20	0.742
Easy	18	72	20	80	

**Table 5:** Comparison between the two groups as regard to days of menstrual cycle

Days of menstrual cycle	Study Group	Control Group	P value
Min.	5	5	0.068
Max.	15	14	
Mean	8.56	9.60	
S.D.	2.615	2.217	

## DISCUSSION

Regarding the ultrasound finding for the study group 21 of our patients showed normal with no significant finding while one patient showed Acute AVF and 3 patients showed RVF while for the control group 22 patients showed normal result with no significant finding and we had no patients having Acute AVF and 3 patients having RVF. While regarding duration of infertility the study group showed a mean age of 6.6 while control group showed 4.5.

In the present study we had in the study group 8(32%) out of the patients had no presence of endometritis (diffuse light staining) and 17(68%) out of the patients had presence of endometritis (focal dark staining) while in the control group 21(84%) out of the patients had no presence of endometritis and 4(16%) out of the patients had presence of endometritis which shows a significant increase in the incidence of endometritis among the study group which is 68% while it is only 16% in our control group.

Concerning the endometrial status we found in the study group 21 patients having a negative normal endometrial finding 2 atrophic 1 thick and another patient having thick poly poidal while in control group we had 23 negative patients.

Also, one patient having filmy adhesion and another having a thick endometrial.

In the present study we had 2 Patients in the study group having hyperplasia and also the same number was seen among the control group which is 8%

The easy of the procedure was demonstrated in our study. That in study group 18 out of 25 Patients, the entry was easy 72% while this percentage was as 80% in the control group and we had a mean time of approximately 9 minutes in both groups which prove the safety and the ease of the procedure with in a very short time interval.

The presences of uterine pathology was documented in 10–62% of women with infertility,<sup>(11)</sup> in 10–60% of women undergoing pretreatment assessment for IVF–ET,<sup>(12)</sup> and in 19–50% of women who failed to conceive following assisted reproductive technologies.<sup>(13)</sup> After exclusion of cases of abnormal uterine cavity by HSG and/or TVS, the researchers found that 45% of patients undergoing ART had abnormal endometrial findings on hysteroscopy, so hysteroscopy is highly valuable and should be applied to all such patients especially with failed ICSI but yet without sufficient evidence.<sup>(13)</sup>

Fatemi et al,<sup>(14)</sup> and Karayalcin et al,<sup>(15)</sup> demonstrated that uterine cavity abnormalities in their study population were low (11% for the 1st one and 22.9% for the 2nd one), while Gaviño-Gaviño et al,<sup>(16)</sup> found very high incidence of uterine pathology in their studies (64%) with repeated IVF failure.

Accumulating data from other studies and the present study proved that hysteroscopy is the gold standard for the investigation of uterine cavity. It is a safe test for the direct and accurate diagnosis of intrauterine abnormalities. It permits direct visualization of the uterine cavity, revealing the nature, location, shape, size and vascular pattern of any uterine cavity abnormalities. It also allows a directed biopsy and therapeutic intervention for the treatment of any pathology.

Chronic endometritis has been related to infertility and recurrent abortion.<sup>(4)</sup> Some authors reported that observation of micropolyps on micro hysteroscopy that was associated with 94% probability of chronic endometritis and considered it a reliable diagnostic sign.

Marconi et al,<sup>(7,17)</sup> and Kucuk and Safali<sup>(10)</sup> reported that the endometrium is not an absorptive epithelium in normal circumstances and that structural damage of the cells allows passage of methylene blue dye into the cells. Dark blue staining represents structural damaged areas due to endometritis.<sup>(16, 10)</sup>

The novel technique of endometrial dyeing was not intended to be the sole procedure for diagnosis, but an adjunctive method to target the biopsy to correct site for an accurate diagnosis. Hysteroscopy, with its current abilities, can never replace pathologist's eye, pathology is still the gold standard. Broader studies and/or a new vital dye can improve the diagnostic accuracy of Chromohysteroscopy,<sup>(10)</sup> endometrial dyeing with methylene blue at hysteroscopy improves the detection of chronic endometritis.

## CONCLUSION AND RECOMMENDATIONS

Chromohysteroscopy is a safe and easy procedure which can help to improve the efficacy of hysteroscopy and to increase the success rate of IVF and ICSI. It is highly recommended to be applied before cases of repeated ICSI or IVF failure. Accordingly, recurrent IVF\ICSI failure due to endometrial factor including chronic endometritis should be screened, detected and treated appropriately before referring a couple for oocyte donation. Future randomized controlled trials are warranted to determine the proper timing and technique of endometrial dyeing with methylene blue dye to improve the diagnostic value to diagnose chronic endometritis during hysteroscopy in the absence of macroscopic abnormalities.

## CONFLICT OF INTEREST

All authors declare no conflict of interest

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