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Role of Hysteroscopy Prior to Intracytoplasmic Sperm Injection (ICSI) and its Impact on ICSI Outcome

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Original Article

Summary

Recently hysteroscopy is considered to be the gold standard for evaluation of the uterine cavity. However, its role before intracytoplasmic sperm injection (ICSI) to identify and specify the incidence of intrauterine pathologies in patients with presumed normal uterine cavity as indicated by hysterosalpingography and trans-vaginal ultrasonography needs further assessment. Therefore we conducted this prospective randomized controlled study which was conducted at Al-Najaf Fertility Center in Al-Sader Teaching Hospital and Department of obstetrics and gynecology at Al-Zahra Teaching Hospital during the period 2018-2019. The study included 32 cases (study group) and 32 controls. We found that Pre ICSI hysteroscopy enable detection and correction of some cases of missed or undetectable intrauterine pathologies even when it is unsuspected clinically in the presence of normal transvaginal ultrasonography and hysterosalpingography. Detection and treatment of such cases will have positive impact on their fertility potential and can avoid them additional costs of IVF cycles, where failures can occur due to these undetectable intrauterine pathologies or spontaneous pregnancy might be achieved after treatment. Furthermore, Pre ICSI diagnostic hysteroscopy could improve pregnancy outcome even in the presence of normal findings.

Keywords: *Infertility, Diagnosis, Hysteroscopy, ICSI , Outcome*

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1. INTRODUCTION

Infertility is one of the significant health problems worldwide, has multifaceted psychological and socio-economic burden on couples and their families in addition to its impact on health system. It is estimated that one out of six people worldwide experience some form of infertility during their reproductive lifespan. Treatments range in complexity from: Intrauterine Insemination (IUI) and in Vitro Fertilization to Preimplantation Genetics Diagnosis and Screening, to gamete and embryo donation and surrogacy. (1,2) Intracytoplasmic sperm injection(ICSI) representing one of the most advances and dramatic technological breakthroughs events that happened at the end of the past century. Actually, when it was first introduced in 1990s, it was opened a real chance and hope for a considerable number of infertile women and men of achieving pregnancy and fathering a child. Indeed, before this time, most of these cases were considered hopeless. After its introduction, the technique was widely and rapidly incorporated into the routine clinical practice of fertility centers throughout the world. Based on data from National and Regional registers worldwide, the use of ICSI increased from 39.6% of ART cycles in1997 to 58.9% in 2004.To date ,10s of 1000s of children have been born around the world as the result of ICSI. (1,2). These increasing figures of ICSI pregnancy, worldwide, might suggest extension in its indications, as it has been used increasingly in many couples without a confirmed diagnosis of sever male factor infertility, in addition to the trend of using this procedure might be used as a medical adaptation and development to the benefit of the infertile couples.(2,3). By the other hand this increasing indication and use of ICSI reflecting its efficiency which has favored a shift toward an increased use also for mild and borderline male factor infertility, for unexplained infertility and women of advanced age, although evidence supporting these indications is limited(2-4).This extensive use, even excessive, is partly due to the high level of standardization and the popularity reached by the procedure and by the tremendous increased efficacy demonstrated during recent years.(2) However, in spite of the high advances and technical development in the era of assisted reproductive treatment including the ICSI technique but still the major problem that we face in this field of treatment is the higher failure rate with its psychological impact and disappointment trauma to the infertile patients which were including in this line of treatment.(5-8). The question which always arises when dealing with infertile patient is to find out and identify any correctable cause or abnormality that might affect fertility potential and to

plan treatment accordingly. However, in a considerable number of patients no identifiable cause can be found (9,10). Uterine abnormality has been blamed as a contributing factor for about 50% of reproductive failure in both primary and secondary infertility and these figures might be similar or higher in failure after ICSI trials. These including high percentage of benign abnormalities and it has been thought to be associated with poor receptivity of uterine endometrium. Obviously, such abnormalities necessitate precise evaluation of uterine cavity and endometrium (11,12). Endometritis, endocrine abnormalities, immunologic factors, thrombophilias, congenital and acquired anatomic factors may contribute to implantation failure, resulting in recurrent pregnancy loss or infertility. Despite the continues advances in ICSI technique, the successful rate still relatively low and the implantation remain the rate-limiting step for successful ICSI treatment. The major underlying reason for the implantation failure is usually attributed to embryo quality and/or uterine receptivity. Implantation failure is generally related to inadequate endometrial receptivity in two thirds of cases and abnormalities of the embryo in one third. Uterine abnormalities have been reported in 21 to 47% of patients undergoing in vitro fertilization (IVF) cycles (12-14). Although it is expensive, ICSI or In vitro fertilization (IVF) treatment is effective with successful outcome in about one third of patients and the main drawback of this line of treatment is the relatively low success rate due to implantation failure. It is well known that uterine factors can contribute for about 15% to 20% of the infertility cases. These uterine abnormalities or pathology may have negative impact in the implantation rate and the chance of successful pregnancy. The prevalence of uterine pathology has been found to be up to 50% in asymptomatic women with implantation failure. This high incidence and prevalence of uterine abnormality is thought to be associated with poor endometrial receptivity and therefor necessitate evaluation of the uterine cavity. (15-21). For a long time hysterosalpingography (HSG) has been regarded as the gold standard to evaluate both the uterine cavity and tubal patency. Although HSG is relatively easy to perform with low cost and can be done as outpatient procedure but recently several studies have shown unsatisfactory results of HSG in the detection of intrauterine abnormalities with variable sensitivity and specificity (21-25).

Transvaginal sonography is known as the initial imaging study of choice to evaluate female infertility. Sonography is an accurate, non-invasive, and cost-effective imaging modality for examining the infertile women. However, it has been found that (20% - 40%) of small

intrauterine abnormalities can be missed by trans vaginal sonography. The diagnosis and treatment of such pathology before including the patient in any line of assisted reproductive techniques (IUI, IVF and or ICSI) has been widely advocated (26,27)

Recently hysteroscopy is considered to be the gold standard for evaluation of the uterine cavity. However, there is large debate about its indication for infertile women with normal hysterosalpingography and or normal trans-vaginal ultrasonography. The World Health Organization (WHO) recommends hysterosalpingography (HSG) alone for evaluation of infertile female, based on its role in the diagnosis and confirmation of tubal patency or obstruction. Furthermore, WHO recommend hysteroscopy only when there is suspected uterine abnormalities, which were suggested by trans vaginal sonography or HSG or in cases of IVF failure. We believe that such recommendation cannot stand with commencing evidence of the low sensitivity and specificity of the TVS and HSG in the diagnosis of intra uterine abnormalities and the worldwide spread use of hysteroscopy as a diagnostic and therapeutic tool. This explains why many specialists use hysteroscopy as a first-line routine exam for infertility patients regardless of guidelines. In current fertility practice, the position of hysteroscopy is still under debate. although there are a collecting data from many randomized controlled studies which support hysteroscopic effectiveness in the diagnosis and treatment of intra uterine pathologies and abnormalities in addition to its tolerability by the patients, however, there is great debate around its effectiveness and indication in infertile women with normal initial investigation like normal hysterosalpingogram and or normal trans-vaginal ultra sound, as the role of hysteroscopy in improving fertility in such cases is still under debate and questionable. The Royal College of Obstetrics and Gynaecologists has categorized hysteroscopic treatment as a grade B recommendation in its evidence-based guidelines on fertility assessment and treatment and does not recommend hysteroscopy as an initial investigation unless clinically indicated, The European Society for Human Reproduction and Embryology (ESHRE) has adopted a similar viewpoint. The World Health Organization (WHO) also recommend hysteroscopy for infertile women only when other initial investigation like hysterosalpingography and or trans vaginal ultra sound suggest intrauterine abnormality or in cases of recurrent IVF failure (28-33)

Besides allowing accurate visual assessment of the uterine cavity, hysteroscopy also provides an opportunity to treat any intrauterine pathology detected during the examination. The

development of smaller and narrower hysteroscopes has made the use of outpatient or office hysteroscopy available as a routine examination. Hysteroscopic evaluation of uterine cavity for women with infertility enables direct visualization of the cervical canal and the uterine cavity, it offers assistance for the interpretation of uncertain findings from other diagnostic methods, and it permits the treatment of most benign intrauterine pathologies. (34-42).

The present study aimed to assess the importance of performing hysteroscopy prior to the first attempt of ICSI in patients with presumed normal uterine cavity as indicated by HSG and TVS and try to identify and specifying the incidence of intrauterine pathologies in a selected group of infertile women and determining the success of first IVF/ICSI cycle after the hysteroscopic procedures and compare it with control who undergo ICSI trial without hysteroscopy.

2. PATIENTS and METHODS

This was a prospective randomized controlled study which was conducted at Al-Najaf Fertility Center in Al-Sader Teaching Hospital and Department of obstetrics and gynecology at Al-Zahra Teaching Hospital during the period 2018-2019. The study was approved by the local ethics Committee of KUFA University. Informed consent was obtained from all patients. Investigations have been approved and the trial has been authorized under the decision of Ethical Committee of Kufa University, Medical College, Research Institute. We informed all cases about the technique, therapeutic effect and potential risks of hysteroscopy and informed consent has been obtained.

All patients who met the following criteria were included in the study:

1. Women with either primary or secondary infertility aged 20–39 years.
2. Normal baseline hormonal profile
3. No detectable pelvic pathology on TVS done at 2nd day cycle
4. Normal HSG done within the previous 6 months, including patent both fallopian tubes, normal uterine cavity, normal spill of dye on delayed film suggesting absent pelvic adhesions.
5. women enrolled in this study should their male partners be normal or only have mild to moderate male factor infertlity as assessed by urologist. For each patient complete history taking and physical examination were done. For male partner, evaluation was also done and classified by urologist and cases of sever male factor infertlity has been excluded.

All patients had a transvaginal ultrasonography and only patients with normal transvaginal ultrasound have been included in this study while patients with abnormal findings even if it is only suspected by TVS have been excluded from the study. Hysteroscopy was performed under spinal anesthesia using a 9-mm, 0° angle hysteroscope with an external sheath of 9-mm diameter providing inflow, outflow, and 5F working channels (Karl Storz, Germany). After vaginal disinfection and cervical dilatation, the hysteroscope was introduced into the external cervical os, and the scope was ascending gently through the cervical canal into the uterine cavity. Uterine cavity distention was achieved with normal saline installation. Patients in whom hysteroscopic evaluation revealed uterine abnormality or uterine lesion, appropriate surgical treatment was done at the same time. All patients were prospectively randomized and distributed into two main groups, group I, and group II. randomization of the patients was achieved by distributing the patients in every other group in an alternating way for each one. group I included patients without hysteroscopic evaluation and were subjected to ICSI without hysteroscopy whereas patients in group II underwent hysteroscopic evaluation and by hysteroscopy they were further subdivided into two groups ; group II (study group) which have normal hysteroscopic evaluation and they were subjected to ICSI after hysteroscopy and group IIf (follow up group) which have abnormal hysteroscopic evaluation and they were excluded from ICSI trial but not from study. Patients in follow up group (group IIf) has been followed up for at least 6 months after hysteroscopy

Statistical analysis

Data were analyzed using the statistical package for social sciences (SPSS) version 25 Data presented as frequencies (No.), percentage (%), mean, and standard deviation (SD) according to the type of variable. Appropriate statistical tests and procedures were applied accordingly at a two tailed level of significance (P. value) of 0.05.

3. RESULTS

A total of 32 cases who underwent hysteroscopy and 32 cases as control group were enrolled in this study. Demographic characteristics of both groups were almost matched and this matching reflected by the insignificant P. values across all comparisons regarding age, type of infertility, duration of infertility and body mass index (BMI), in all comparisons, P. value >

0.05, not significant (Tables 1). Regarding the comparison of hormonal levels between the study group and controls, no statistically significant differences had been found between both groups; the mean FSH level was 6.73 ± 2.28 in the study group and it was
6.35 ± 2.47 in controls (P. value = 0.520). The mean AMH was 1.93 ± 0.49 and 2.11 ± 0.62 in the study group and controls, respectively, (P. value = 0.272), In the study group the mean AFC was 14.09 ± 5.57, mean E2 was 1771.16 ± 687.0 , the corresponding mean values of these two parameters in control group were 13.84 = 5.53 and 1885.66 ± 717.74, respectively, (in both comparison P. value > 0.05, not significant), (Table 2).

The Comparison of Endometrial Thickness and Oocyte Pick up of the study group and controls revealed no statistically significant differences between both groups in these two parameters, (P>0.05), (Table 3).

As it shown in (Table 4) , 15/32 (46.9%) of cases in the study groups had positive PT and the remaining 17 were negative while among controls 10/32 (31.3%) were positive and 22 were negative, which indicated higher positive PT rate among study group , (46.9%) compared to that of controls, (31.3%), however, on chi-squared test, the difference in the positive PT. frequencies did not reach the statistical significance (attributed to small sample size), but when Z test for two propotions used to compare the rates, the difference appeared to be statistically significant, (P. value = 0.017), (Figure 1) .

Further analyses were performed to assess the possible inter-correlation between the positive PT rate and other characteristics and parameters of the cases in each of the study group and controls, results of Bivariate Spearman's test for these correlations are shown in (Table 5) where none of the variables showed an effect of the positive PT rate neither in the study group nor the controls, in all correlations, P. value > 0.05.

Table 1. Baseline characteristics of the study group and controls

Variable		Study group (n = 32)		Control (n = 32)		P. value
		No.	%	No.	%	
Age (year)	≤ 20	3	9.4	5	15.6	0.558
	21 - 30	18	56.3	14	43.8	
	> 30	11	34.4	13	40.6	
	Mean (SD)	27.8 (5.9)		28.2 (7.8)		0.439
Type of infertility	Primary	27	84.4	28	87.5	0.719
	Secondary	5	15.6	4	12.5	
Duration of infertility (year)	< 5	9	28.1	7	21.9	0.401
	5 - 6	5	15.6	6	18.8	
	7 - 8	9	28.1	7	21.9	
	9 - 10	6	18.8	8	25	
	> 10	3	9.4	4	12.5	
	Mean (SD)	6.8 (3.1)		7.1 (2.8)		0.688
BMI *Mean (SD)*kg/m²		24.9 (2.4)		24.5 (2.1)		0.569
SD: Standard deviation						

Table 2. Comparison of Hormonal levels of the studied groups

Parameter	Study group (n = 32)		Control (n = 32)		P. value
	Mean	*SD*	*Mean*	*SD*	
FSH	6.73	2.28	6.35	2.47	0.52
AMH	1.93	0.49	2.11	0.62	0.272
AFC	14.09	5.57	13.84	5.53	0.858
E2	1771.16	687	1885.66	717.74	0.517

Table 3. Comparison of Endometrial Thickness and Oocyte Pick up of the study group and controls

Parameter	Study group (n = 32)		Control (n = 32)		P. value
	Mean	*SD*	*Mean*	*SD*	
Endometrial Thickness (mm)	10.19	2.26	10.16	1.94	0.953
Oocyte Pick up	9.72	5.49	8.94	5.33	0.158

Table 4. Comparison Positive Pregnancy rates of the study group and controls

Pregnancy	Study group		Control	
	No.	%	No.	%
Positive	15	46.9	10	31.3
Negative	17	53.1	22	68.8
Total	32	100	32	100
P. value = 0.200 not significant				

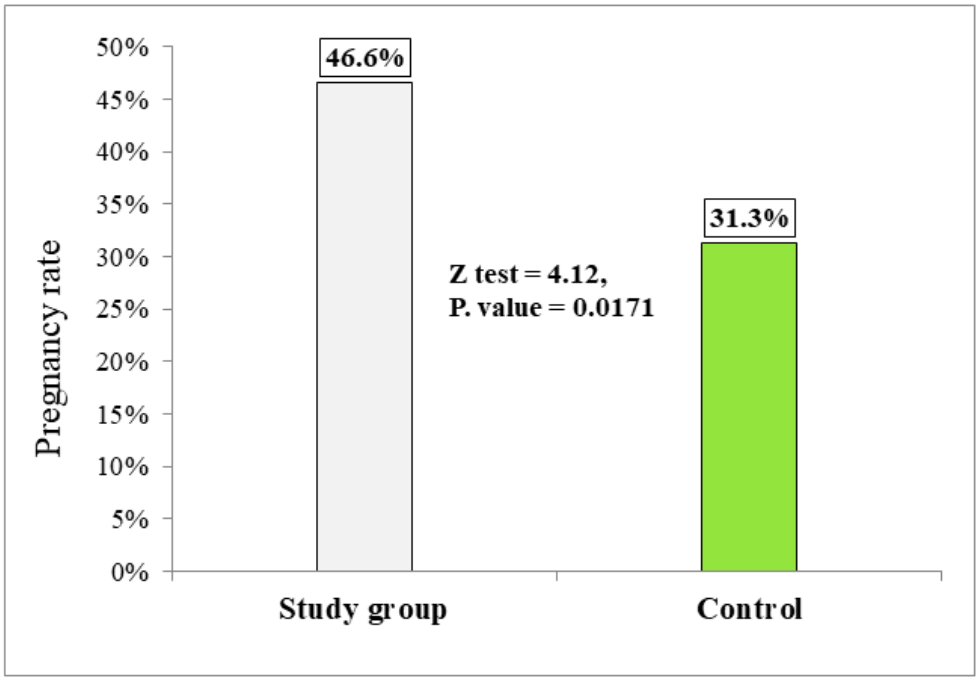

Figure 1. Bar-chart showing the positive PT rate of the study group and controls

Table 5. Results of bivariate correlation analysis between positive PT rate and other variables among the studied groups

Variable	Study group (n = 32)		Controls (n = 32)	
	*R**	*P. value*	*R*	*P. value*
Age (year)	0.016	0.822	-0.004	0.984
Duration	-0.097	0.597	0.205	0.262
BMI	-0.114	0.533	-0.05	0.786
FSH	0.142	0.442	-0.007	0.969
AMH	-0.198	0.278	-0.261	0.15
AFC	-0.246	0.175	-0.254	0.16
E2	-0.014	0.94	-0.021	0.907
Endometrial Thickness	-0.043	0.816	0.15	0.414

R: correlation coefficient

4. DISCUSSION

There is a large debate on the indication and use of diagnostic hysteroscopy in the evaluation and management of infertile women with normal imaging study by transvaginal ultrasonography and or hysterosalpingography. Currently, the European Society of Human Reproduction and Embryology (ESHRE) guidelines indicate hysteroscopy to be unnecessary, unless it is for the confirmation and treatment of doubtful intrauterine pathology. Regarding the use of hysteroscopy prior to ICSI the current recommendation supports the use of hysteroscopy before initiating an IVF/ICSI cycle in patients with history of one or more previous unsuccessful IVF attempts, because it can increase the chance of pregnancy in the subsequent IVF treatment in such patients. However, the use of hysteroscopy in patients with infertlity before their first ICSI trial and its impact on the implantation rate and clinical pregnancy rate is still under controversy and our current study try to add more information and evidence for the already collecting data in this field. Our study reveals that three patients out 35 which have had normal transvaginal ultrasonography and hysterosalpingography have been found to have uterine abnormality during their initial hysteroscopy. The uterine abnormalities which were declared by initial diagnostic hysteroscopy including uterine polyps in two patients and

uterine septa in one, which have been corrected surgically by hysteroscopy at the same session. Although those three patients have been excluded from the study group i.e. don't undergo ICSI trial but they don't exclude from the study as they were followed up during the study for at least six months. Interestingly, spontaneous pregnancy has been reported and confirmed during follow up in two of them. Although these findings can be criticized by the small number of patients but obviously it supports the already existing data and studies which argue the sensitivity and specificity of both hysterosalpingography and trans vaginal ultrasonography in the detection of intra uterine abnormalities. Most of these studies shown that both HSG and trans vaginal ultrasonography associated with significant false negative results, and with variable sensitivity and specificity (21-27)

According to these results encountered, our current study supports the use of hysteroscopy as part of evaluation of female infertlity even in the presence of normal hysterosalpingography and or normal trans vaginal ultrasonography especially for female patients with normal SFA of their male partners and when simple conventional treatment of infertlity has been failed. Regarding the pregnancy rate, the results presented in this study demonstrate a beneficial effect of pre ICSI hysteroscopy in ICSI outcome which has been found to be statistically significant in the clinical pregnancy rate between patients in control group, who did ICSI without hysteroscopy and the study group with pre ICSI hysteroscopy (31.3%) and (46.9%), $P < 0.05$ respectively.

Similar results have been in encountered by Hossam Eldin Shawki et al who found a significant difference in the clinical pregnancy rates between patients in group I (ICSI without office hysteroscopy) and group II (ICSI with office hysteroscopy (29.5% and 38.3%, $P < 0.05$ respectively).(43) However, unlike our study, Shawki et al. study although it included a large number of cases as compared to our study but it included female patients with history of failed ICSI trials while our study including only patients during their first ICSI trials These results were comparable with many other similar studies (44-50).

Hatirnaz et al study evaluated the importance of performing hysteroscopy prior to the first attempt of in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) by estimating the incidence and types of intrauterine pathologies and the success of IVF/ICSI cycle (51). During their study, Hatirnaz et al reported 29.4% incidence of intrauterine

pathology in pre ICSI hysteroscopy with high pregnancy rate in the group of patients with abnormal hysteroscopic findings who undergo ICSI after hysteroscopic surgical correction than patient with normal hysteroscopy who undergo ICSI trial after normal diagnostic hysteroscopy.

The positive impact of pre ICSI hysteroscopy on ICSI outcome as it was encountered during our study may be attributed to the reliable ability of hysteroscopy to detect and treat a significant number of cases with pre ICSI missed or undetectable intra uterine pathologies that might interfere with successful implantation as it has been shown in our study. By detecting and excluding such patients with underlying intrauterine pathologies and preventing them to procced with ICSI trial until surgical correction have been done will obviously increasing the pregnancy rate of first ICSI trial by excluding a significant number of cases with low predictable implantation rate.

Furthermore, the statistical analysis of the results encountered in our study when it is correlated to other factors and patients' characteristics shows that this positive impact of pre ICSI hysteroscopy on successful implantation and pregnancy rate is independent of these factors which further support its true beneficial effect on the pregnancy rate.

The fertility beneficial effect of pre ICSI hysteroscopy cannot be attributed only to its statistical effect by excluding patients with suspected low implantation rate who have obvious intrauterine pathology and might be related to other factors. It is well known that implantation rate can be affected by several technical factors during the process of embryo transfer procedure like the easy by which the procedure done, degree of cervical stenosis and if the embryo transfer procedure was associated with some bleeding or not. Obviously, all these technical factors become more favorable in patients with pre ICSI hysteroscopy as it was observed during this study and the impact of these factors should also be considered when explain these results. Hysteroscopy has been speculated to induce some degree of endometrial trauma and stimulate post-traumatic reaction that involve release of local growth factors and cytokines in addition to the effect of irrigation saline used during the procedure of hysteroscopy. All these factors have been hypothesized to induce immunological reaction which further enhancing the uterine receptivity and the likelihood of successful implantation by mechanism similar to well-documented increased chance of natural conception after hysterosalpingography (51-56,)

5. CONCLUSIONS

Pre ICSI hysteroscopy enable detection and correction of some cases of missed or undetectable intrauterine pathologies even when it is unsuspected clinically in the presence of normal transvaginal ultrasonography and hysterosalpingography. Detection and treatment of such cases will have positive impact on their fertility potential and can avoid them additional costs of IVF cycles, where failures can occur due to these undetectable intrauterine pathologies or spontaneous pregnancy might be achieved after treatment. Furthermore, Pre ICSI diagnostic hysteroscopy could improve pregnancy outcome even in the presence of normal findings. Based on our conclusions, we recommend the utilization of hysteroscopy as integral part of evaluation of female patients presents with infertlity and demands for reviewing the guidelines for more extension in its indication and not to be limited for patients with history of failed ICSI or clinically suspected uterine pathology.

Ethical Clearance: Ethical clearance and approval of the study are ascertained by the authors. All ethical issues and data collection were in accordance with the World Medical Association Declaration of Helsinki 2013 of ethical principles for medical research involving human subjects. Data and privacy of patients were kept confidentially.

Conflict of interest: Authors declared none

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