Use of Hysteroscopy and Pregnancy Outcomes during Assisted Reproduction by ICSI, Add on cost or certified indication!

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Abstract

Aim: To evaluate the clinical efficacy of office hysteroscopy (OH) in infertile women with looking normal uterine cavity as detected in by TV/US, before starting primary ICSI cycles. Also to evaluate the value of hysteroscopy (HSC) and new ICSI outcomes in women with RIF, (history at least two previous failed ICSI attempts).

Study Design: A prospective clinical comparative cohort study.

Setting: Obstetrics and Gynecology Department, Menofia University and a private assisted reproduction unit in Cairo, Egypt.

Methodology: ICSI after hysteroscopy was performed in two groups of infertile women. Patients with normal uterine cavity (group I, No. 125) and patients with RIF (group II, No. 125). Then, ICSI was performed for all enrolled women in study groups with no statistically significant difference ($p > 0.05$) regarding demographic data (except age) and the number of oocytes retrieved and the number of embryo transfer. Then, all subjects were followed up for 3 weeks after embryo transfer for detection of pregnancy by ultrasound.

Result: There was no statistically significant difference in IR both groups (15.8% Vs. 10.2%). Also, the PR showed no statistically significant difference (32% vs. 22.4%). There was a statistically significant association between PR and hysteroscopy before ICSI in group II. Also, hysteroscopy had detected uterine cavity lesions in more than half of cases with normal TV/US.

Conclusions: In this study routine office hysteroscopy (OH) was not an added cost before ICSI even in cases with normal TV/US. OH can diagnose and treat uterine cavity lesions on the same setting. Robust and high-quality multicentric RCTs are advised before hysteroscopy can be included during the basic clinical infertility investigation.

Keywords: Hysteroscopy; ICSI; pregnancy rate; uterine cavity lesions.

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Introduction

Implantation is vital and complex process to start pregnancy, its failure could be due to a variety of reasons, including embryonic and/or endometrial factors, but remains unexplained in many cases. RIF is diagnosed in women having history of at least two previous failed ICSI attempts[1].

The presence of intrauterine pathologies can negatively affect the chance of implantation and pregnancy rates in women undergoing assisted reproduction, as implantation failure were present , has been reported to be as high as 50% in women with uterine pathology [2,3].

Hysteroscopy is considered as the gold standard for diagnosis of intrauterine pathologies. HSG, TV/US and saline infusion sonography are other tools to assess the inner architecture of the uterus [4,5] . World Health Organization (WHO) recommends HSG alone as one of the basic investigations for infertile couples. Office hysteroscopy is only recommended by the WHO when clinical or complementary exams (ultrasound, HSG) suggest or diagnose uterine cavity abnormality or there is IVF/ICSI failure [4].

Currently, there a debate for examination of uterine cavity by OH before starting IVF/ ICSI[5]. Basically ,the best methods for assessing uterine abnormalities typically include some combination of TV/US, HSG, and hysteroscopy (HSC) can only be used if uterine cavity pathology is suspected [6]. But, HSG has low specificity, high false-negative and false-positive rates[7]. TV/US is a non-invasive and reproducible technique, but it is not very sensitive [11]. . OH can be typically performed after RIF , if there is evidence of an abnormal uterine cavity from investigations[8,9]. HSC allows reliable visual assessment of the uterine cavity to diagnose intrauterine adhesions, endometrial polyps, submucous fibroids, endometritis, or uterine malformations that could interfere with implantation, and on the same time provides the opportunity to perform therapy in the same setting such as removing endometrial polyps, submucosal fibroids[10,11]. Therefore, hysteroscopy is considered as one of the common investigations proposed for women undergoing IVF treatment is to evaluate the uterine cavity[13].

HSC can identify minor intra uterine abnormalities in 30% to 45% in cases with normal TV/US. The abnormalities found by HSC were significantly higher in women with previous assisted reproductive techniques failure[13-16]. The value of HSC in women with RIF were confirmed by two prospective RCTs demonstrating significantly increased clinical pregnancy rates [17,18]. Pregnancy outcomes can be improved in patients with/ without RIF or with/without identifiable uterine pathology undergoing routine OH before IVF [14,19]. Also, a meta-analysis performed in 2008 suggested that HSC could improve the outcomes in women with RIF[12]. On the other hand, other studies have suggested there is no value for routine OH in patients undergoing ICSI assessment or in patients with RIF. In a RCT, study was designed to assess whether routine OH before the first IVF treatment cycle could increase the PR. But these results revealed that routine OH does not improve live birth rates in infertile women with a normal TV/ US of the uterine cavity [20]. A retrospective study suggested that HSC should be used as a routine infertility examination because its diagnostic rate is high in patients with repeated IVF failure. However, the clinical outcomes in patients with repeated IVF failure who had HSC with no pathology and with pathology when compared, no statistical differences were found . So, doing OH before ICSI was of no significant value in improving pregnancy outcomes [21]. On the other hand in a review the conclusion was that small number of prospective RCTs cannot clearly demonstrate that removal of uterine cavity lesions by HSC can improve IVF outcomes[22].

Nowadays hysteroscopes are available with smaller diameter and this has made the use of outpatient or office hysteroscopy feasible as a routine examination[1,6].

OH can provide accurate visual assessment, and on the same time provides a therapeutic chance to treat any detected cavitary pathology. The concept nowadays, in women with one or more failed ICSI cycles there is evidence that hysteroscopy before starting ICSI treatment could increase the chance of pregnancy rate in the subsequent ICSI cycle. On the other hand, the value of routine hysteroscopy prior to starting the first ICSI treatment cycle are lacking and not recommended [1,6,9].

Aim of study

The aim of the present study was designed to evaluate the clinical efficacy of office hysteroscopy (OH) before starting primary ICSI cycle in women with normal uterine cavity by TV/US, also to evaluate the effect of hysteroscopy (HSC) on new ICSI cycle outcomes in women RIF.

Patients and Methods

Study design: Clinical prospective observational comparative study.

Setting: at Obstetrics and Gynecology Department, Menofia University and a private Reproduction & IVF Unit, Cairo ,Egypt.

Duration: Started May 2019 and completed April 2021

Patients: 250 participants selected for ICSI divided in two groups

- ***Group 1:*** included 125 participants, for office hysteroscopy (OH) that was done before starting primary ICSI cycle.
- ***Group 2:*** included 125 participants with history of RIF after ICSI. Hysteroscopy (HSC) was done before starting new ICSI cycles.

Ethical consideration: Ethical approval No. 19519OSGN-2019 of the institutional board committee before the start was given and a written informed consent from each included patient was a must during the study.

Inclusion Criteria:

- Women indicated for IVF/ICSI using the standard long GnRH-a protocol.
- Ages eligible for the study: 20 years to 38 years.
- No evidence of uterine pathology by TV/US and HSG .
- BMI between 20 and 35.
- Normal male factor (WHO semen critrria,2010)

Exclusion Criteria:

- Unexplained poor responders during the pending ICSI cycle,(AFC 4 or less and AMH 0.8 ng /m)
- Past or current medical disorders.

All patients that included in the study the following were done:

- Proper history, examination and investigations including TV/US,

HSG and fertility hormonal profile ,FSH,LH,AMH,E2.

- Office hysteroscopy performed during the he proceeding menstrual cycle, using a rigid hysteroscope.
- Controlled ovarian hyper stimulation-embryo transfer (COH-ET) using the standard long protocol of the private ART Unite.
- **Study Outcomes documented :** by
- **Biochemical pregnancy:** a positive pregnancy test performed 2 weeks after ET. HCG >5 IU/l was considered as chemical pregnancy.
- **Clinical pregnancy:** using B-mode TV/US performed 5 weeks after E T. shows a gestational sac.

- **Implantation rate:** calculated as the viable embryo numbers divided by the transferred embryo numbers, multiplied by 100.
- **Live birth rate:** based on the number of live births out of the total number of transfer cycles.
- **Miscarriage rate:** the miscarriages before 20 weeks of pregnancy out of the total pregnancies.

Results

This study was conducted at Obstetrics and Gynecology Department, Menofia University and ART private center, Cairo, Egypt . The included women were 250 who were selected and prepared for hysteroscopy and ICSI.

The enrolled women were divided into 2 main groups:

- **Group 1:** 125 women without any uterine cavity abnormalities detected by TV/US.
- **Group 2:** 125 women with RIF (at least 2 previous failed ICSI attempts)

The analyzed data were collected and tabulated.

The following results were obtained.

Table (1): Personal and demographic data of women in the study groups

	Group 1 (n= 125)		Group 2 (n= 125)		P-value[3]
Age: (years)					
Mean ± SD	29.57 ± 5.31		31.45 ± 5.13		0.005*
Duration of marriage: (years)					
Mean ± SD	7.57 ± 4.83		8.63 ± 5.02		0.092
Median (Range)	7 (3-15)		8 (2-20)		
Weight (kg):					
Mean ± SD	72.59 ± 12.81		71.85 ± 10.45		0.621
Height (cm):					
Mean ± SD	156.25 ± 6.35		157.39 ± 6.19		0.157
BMI:					
Mean ± SD	29.75 ± 5.01		29.02 ± 3.99		0.209
Duration of infertility: (years)					
Mean ± SD	7.15 ± 4.69		7.72 ± 4.82		0.311
Median (Range)	5.5 (1.0-20.0)		7.0 (1.0-22.0)		
Type of infertility:					
Primary	90	72%	92	73.6%	0.882
Secondary	35	28%	33	26.4%	

*p <0.05 is significant

No statistically significant differences between the demographic data of women in the two groups. Age only was statistically significant higher group 2 .

Mean infertility duration in the two groups was more than 7 years with no statistical differences. Most of the women had primary infertility (more than 72% in the study groups) with no statistically significant differences.

	Group 1 (No 125)		Group 2 (No 125)		p-value
	No.	%	No.	%	
C P R	40	32%	28	22.4%	0.089
Chemical pregnancy	3.3	7.6%	0	0.0	0.251
Pregnancy:					
Single	30	75%	22	78.6%	
Twins	10	25%	6	21.4%	0.406
Miscarriage	10	25%	8	28.6	0.245
Implantation rate:	15.80% (49/310)		10.2% (37/363)		0.03*
Mean ± SD no. of embryo transferred	2.22 ± 0.84		2.46 ± 0.95		0.419
Maturity:					
Pre-term	10*	33.3%	10#	50%	0.485
Full-term	20	66.7%	10	50%	
Take home baby rate	30	24%	20	16%	0.334

* <0.05 is significant

The results of ICSI cycles in both groups were presented in table (2) CPR was 32% in group 1 Vs. 22.4% in group 2 with no statistically significant difference.

Also were no statistically significant differences in miscarriage rate and take-home-baby in both groups . There was no statistically significant difference between the mode of delivery between the two groups as 26 women of group 1 patients delivered by CS, only 4 underwent normal vaginal delivery, and 18 women of group 2 patients delivered by CS, only 2 underwent normal vaginal delivery.

This highlighted the high rate of CS nearly in 88% of patients.

In each group one preterm newborn died in the incubator within hours.

Table (3): Cases with positive pregnancy test for each specific detected subtle lesions

	No.(82)	% of cases with +ve pregnancy test in each lesion	+ve pregnancy test	CP	CPR
Mucosal elevation	6	33.3%	2	2	33.3%
Uni cornuate uterus	2	50.0%	1	1	50.0%
Pale endometrium	14	50%	7	6	85.71%
Endometrial defect	2	0.0%	0	0	0.0%
Arcuate uterus	30	40%	12	12	40%
Hypervascularization	8	37.5%	3	3	37.5%
Single adhesion band	6	16.7%	1	1	16,7%
Micro polypi	14	7.1%	1	1	7.1%
Total	**82**	**36.6%**	**30**	**29**	**35.4%**

This table shows the numbers and type of subtle lesions and the clinical pregnancy rate for each specific lesion.

Table (4) Clinical pregnancy rate in each specific corrected lesion by hysteroscopy in group 2.

	No. (125)	%	CP	CPR
Polyp	44	33.6%	14	31,8%
Septum	16	128%	6	37.5%
Adhesions	10	8%	3	30%
Hysteroscopic myomectomy, grade 0	6	4.8%	2	33.3%
Myoma and polyp	2	1.6%	0	0%
(CS Niche)	2	1.6%	0	0%

Table 4 shows the type of detected and corrected lesions in group 2 with RIF and the clinical pregnancy rate for each specific lesion. All lesions were treated by hysteroscopy. The CPR after correction and ICSI occurred in 64% ,(80/125).. The CPR was 22.4% in group 2 in comparison with 32% in group 1.

Discussion

In clinical practice, evaluation of the uterine cavity is usually done TV/US prior to IVF/ICSI. Due to the perceived advantages of hysteroscopy ,it is considered the gold standard for the diagnosis of uterine cavity pathology [23, 24]. Also it has the potential for simultaneous detection and treatment of diagnosed intrauterine lesions, so pre-IVF/ICSI screening OH has gained widespread acceptance[25].

Hysteroscopy prior to IVF/ICSI is an issue with debate. Pre-IVF hysteroscopy in women with unexplained infertility for detecting effect of unsuspected intrauterine lesions on pregnancy outcome was evaluated. High prevalence rate of unsuspected intrauterine lesions was found in women with unexplained infertility and clinical pregnancy rates were not significantly higher in patients who underwent pre-IVF hysteroscopy[26].

All women included in our study were selected and prepared for ICSI and hysteroscopy, in group 1 women had normal uterine cavity as revealed by TV/US. In group 2 ,all included women had history of RIF after previous ICSI. Unification of study parameters and exclusions of fertility barriers were done in both groups to avoid their effect on the results. Women in groups 1 and 2 were comparable with their demographic data , duration, and type of infertility. Age and AMH were statistically significant higher in group 2. This difference can be zexplained by time needed for diagnosis and correction of lesions.

In this work the mean duration of infertility at the time of ICSI was relatively long, more than 7 years in study groups. Which to some extent may be reflected in the decrease in the take home baby rate.

There was no statistically significant difference in the basal endometrial thickness in the group of women with corrected uterine lesions and those with normal uterine cavity.

The AMH level as a test for ovarian reserve was lower in group 2 women with uterine lesions than those with normal uterine cavity in group 1. This can be explained by the statistically significant increased age of women in both groups (31.45 years in group 2 versus 29.57 years in group 1; respectively). Throughout the induction period there were no statistically significant response differences in both groups. Also IR, CPR and take-home baby rate were insignificant in both groups.

In 12% of women undergoing first IVF [20] and in 27% of women with RIF [27], screening hysteroscopy prior to IVF revealed intrauterine pathology that may not be detected by routine TV/US. Hysteroscopy allows detection and treatment of many of uterine cavity lesions which may improve IVF outcomes[13]. In our study uterine cavity lesions were detected during HSC before new ICSI in 64%,(80/125) of women with RIF . Endometrial polypi were found and treated in 33.6% (44/125).

Implantation and subsequent ICSI outcomes can be affected by different intracavitary lesions. Endometrial polyps are the most frequently observed pathological finding, reported 82% of the women implicated in about 50% of cases of abnormal uterine bleeding and in 35% of infertility cases [29], and are usually benign lesions.[28]. Polyp removal by hysteroscopy prior to IUI can increase the chance of CPR compared with simple diagnostic hysteroscopy [24]. This clearly explains the comparable CPR and take-home baby rate in both groups in our present study . CPR after polyp removal in our study was 31.8% in women underwent ICSI after polypectomy .

Cochrane review about hysteroscopic resection of endometrial polyps prior to infertility treatments, did not identify any analyzable randomized trials which allow them to reach any sound scientific evidence on the safety and efficacy of endometrial polypectomy in sub fertile women, and concluded that well designed, methodologically sound, randomized controlled trials are urgently needed. On the other hand, removal of endometrial polyps in sub fertile women is commonly practiced in many clinics to improve the reproductive outcome because the procedure is minimally invasive and hysteroscopic polypectomy provides an opportunity for a histological diagnosis to exclude malignancy[24].

Based on that if an endometrial polyp is detected during an ART cycle and less than 20 mm in size, it can be managed expectantly without compromising clinical pregnancy or live birth rates. Also, when polyp 10 mm in size are found in symptom-free patients prior to ART, expectant management may be considered, given that spontaneous regression following the menstrual cycle has been observed in 27% of cases [30].

Hysteroscopic polypectomy prior to infertility treatment was cost-effective for both IUI and IVF/ICSI treated women when comparing sensitivity analysis between pregnancy rates and polypectomy costs. The procedure doubles the pregnancy rate, shortens time to pregnancy, and is cost-effective across a range of polyp sizes.

It was found in Cochrane review that there is a large benefit with the hysteroscopic removal of submucous fibroids for improving the chance of clinical pregnancy in women, but unexplained subfertility cannot be excluded. Removal of endometrial polyps suspected on ultrasound in women by HSC prior to IUI may increase the clinical pregnancy rate. The review advised randomized studies to substantiate the effectiveness of the hysteroscopic removal of suspected endometrial lesions in women with unexplained subfertility or prior to IUI, IVF or ICSI[24].

Results in our study were in favor of hysteroscopic adhesolysis in 8%, (10/125) of cases with mild to moderate intrauterine synechia with improved CPR of 30% ,(3/10) comparable to the 32% in group 1.

The most common subtle abnormality observed in the current study were arcuate uterus, pale endometrium and micro polypi with 35.9% and 16.7% and 11.5% of cases and their pregnancy rate were 39.3%, 53.8% and 11.1% respectively. These results matched with the finding of the In-SIGHT study performed in 2016 that found women who were known to have small submucous myoma or polyp in the endometrium or other subtle uterine cavity lesion had not decrease pregnancy outcomes[32].

Reproductive performance in women with subtle lesions in comparison to women with normal uterine cavity, there was no statistically significant difference. CPR and take-home baby rate were comparable in both groups. So the presence of these subtle uterine lesions did not affect the take-home baby rate and hence it does not need any specific treatment.

This confirms the data of TROPHY study published in the Lancet in 2016 concluded that OH before IVF in women with a normal TV/US of the uterine cavity and a history of failed IVF treatment cycles does not improve the live birth rate. Further research was recommended to evaluate the value of surgical correction or therapy of specific uterine cavity abnormalities before IVF.

The results of this didn't match also with meta-analysis that was done in 2014 and found women who had OH before doing IVF, got high live birth rate[33]. Also, didn't match with several studies that found performing hysteroscopy preceding IVF improve rate of pregnancy [20, 34, 35].

Finally, although "statistically significant" generally means that the result obtained is real and cannot be chancified, yet not everything that can be counted counts , and not everything that counts can be counted. This is because, the statistical significance is based on three factors; the magnitude of difference observed, the range of variations in the values obtained, and the sample size taken.

Therefore, p value is not an absolute indication of the importance of the result as it depends on the result itself and its implications.

Having said that, statistically significant or even highly significant differences may be of little or no importance in itself. In another words, difference is a difference if it makes difference. And attaching a fancy p value to trivial observations does little to enhance their importance.

In contrast, difference may not be statistically significant - but still important - may be because the number of subjects is not large enough to show the difference, i.e. the study may not have the power to show an effect of that size.

Conclusions

In this study routine office hysteroscopy (OH) was not an add cost before ICSI even in cases with normal TV/US. OH can diagnose and treat uterine cavity lesions on the same setting.

Recommendations

- The study supports the importance of the correction of any significant uterine cavity lesion to have a successful IVF/ ICSI cycle with outcomes comparative to patients with normal uterine cavity.
- Intervention to correct any subtle uterine abnormalities is not needed as this does not add to the success rate of IVF/ICSI cycle.
- Robust and high-quality multicentric RCTs are advised before hysteroscopy can be included during the basic clinical infertility investigation.

Conflict

There were no conflicts of interest.

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