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ORIGINAL ARTICLE

Routine office hysteroscopy prior to ICSI and its impact on assisted reproduction program outcome: A randomized controlled trial

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KEYWORDS

Office hysteroscopy;
ART;
Failed ICSI;
Clinical pregnancy rate

Abstract *Objective:* To assess the incidence of undiagnosed intrauterine pathology based on screening office hysteroscopy in women with normal hysterosalpingogram (HSG) and/or transvaginal ultrasonograghy (TVS), and their impact on the success rate of ICSI (intracytoplasmic sperm injection).
Design: Randomized controlled trial.
Setting: In El-Menya Infertility Research and Treatment Center (MIRTC), El-Menya, Egypt.
Patient(s): Two hundred and forty consenting patients were eligible to participate in the study, who further randomized into two equal groups, 120 patients in group I (ICSI without office hysteroscopy), and 120 patients in group II (had ICSI after office hysteroscopy). Only 110 and 105 patients completed the study in group I and group II, respectively.
Intervention(s): ICSI with or without office hysteroscopy.
Main outcome measure(s): Undiagnosed uterine abnormalities, implantation and clinical pregnancy rates.

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Result(s): Unsuspected abnormal uterine findings were diagnosed in 35/105 (33.3%) patients with normal HSG and/or TVS among patients in group II by using office hysteroscopy. Implantation rate and clinical pregnancy rate were statistically significant between group I and group II, as clinical pregnancy rate between group I, group IIa (ICSI with normal office hysteroscopy) and group IIb (ICSI with abnormal office hysteroscopy) were 27.2%, 35.7%, 42.8%, respectively ($P \leqslant 0.05$). Among group II 51 patients (48.5%) have repeated IVF or ICSI failure, 23 patients of them (45%) had abnormal hysteroscopy finding and 15 patients (65.2%) achieved pregnancy after correction of their uterine abnormalities. Hysteroscopy has high specificity (88%), high diagnostic accuracy (86.2%) but less sensitivity (80%) in predicting intrauterine abnormalities when compared to HSG and TVS (odd's ratio 1.7, CI 1.33–2.44).

Conclusion(s): The incidence of pathologic abnormalities based on hysteroscopic diagnosis was high especially with repeated IVF failure. Improvement in implantation and clinical pregnancy rates were observed after office hysteroscopy prior to ICS. So routine office hysteroscopy should be an essential step of the infertility workup before ART even in patients with normal HSG and /or TVS.

1. Introduction

Whether implantation occurs after in vitro fertilization (IVF) depends on the embryo, uterine receptivity or a combination of both (1), many couples fail to achieve pregnancy instead of repeated in vitro fertilization (IVF) or intra-cytoplasmic sperm injection (ICSI) cycles and good quality embryos for successful pregnancy rates should not be count apart over endometrial receptivity (2). Recurrent implantation failure (RIF) may be due to unrecognized uterine pathology. Hysterosalpingography, transvaginal ultrasonography, saline infusion sonography and hysteroscopy are the tools to assess the inner architecture of the uterus (3).

Hysteroscopy is considered to be the gold standard; however, the World Health Organization (WHO) recommends hysterosalpingography (HSG) alone for management of infertile women (4). The explanation for this discrepancy is that HSG provides information on tubal patency or blockage. Office hysteroscopy is only recommended by the WHO when clinical or complementary exams (ultrasound, HSG) suggest intrauterine abnormality or IVF failure (4,5). Nevertheless, many specialists feel that hysteroscopy is a more accurate tool because of the high false-positive and false negative rates of intrauterine abnormality with HSG (6–8). This explains why many specialists use hysteroscopy as a first-line routine exam for infertility patients regardless of guidelines but, the validity of hysteroscopy may be limited in the diagnosis of endometritis and endometrial hyperplasia (4).

The prevalence of minor intrauterine abnormalities identified at hysteroscopy in cases with a normal transvaginal sonography has been recorded to be as high as 20–40%. Diagnosing and treating such pathology prior to initiating IVF/ICSI, has been widely advocated without high-quality evidence of a beneficial effect (4).

The objective of the current study was to assess, by screening office hysteroscopy, the incidence of undiagnosed intrauterine pathology in asymptomatic women (normal HSG and TVS), and their impact on the success rate of intracytoplasmic sperm injection (ICSI).

2. Patients and methods

This study was conducted in the El-Menya Infertility Research and Treatment Center (MRTC), from October 2007 to October 2010; all patients (530) who were referred to the center were asked to participate in the study. Two hundred and ninety patients were excluded from the study for different causes, thus leaving a population of 240 eligible patients who were included in this randomized trial (Fig. 1). Patients were excluded from the study if they have uterine factor of infertility, abnormal HSG or abnormal transvaginal ultrasonography, previous intrauterine surgery or contraindication for hysteroscopy. All patients have HSG in the past 2–3 months before included in the study. Evaluation of the patients by TVS was done by the authors in the center and all patients should have additional reports from another specialized ultrasonography centers.

Before entering in the study, the purpose of the study was clearly explained to all women attending our center, and a printed explanatory consent form was signed and obtained by all subjects enrolled.

2.1. Ethical approval

The study protocol was approved by scientific ethical committee research of the Department of Obstetrics and Gynecology, Faculty of Medicine, El-Menya University at its monthly meeting on August 2007. Also approval was ascertained from the Institutional Review Board of the University Hospital-Quality Control Unit-of the Faculty of Medicine, El-Menya University on December 2007.

2.2. Randomization

All patients were prospectively randomized and divided into two equal groups consisting of 120 patients each. Randomization was achieved with sealed envelopes containing computer-generated random numbers in blocks of 8. At the end of the study 10 patients from group I and 15 patients from group II were excluded from the results as they did not complete the study. Patients in group I were subjected to ICSI without office hysteroscopy, whereas patients in group II underwent ICSI after performing office hysteroscopy using non-touch vaginoscopic technique.

2.3. Vaginoscopic technique

Hysteroscopy was performed using a 3.5-mm mini-hysteroscope (Versascope, Gynecare, Ethicon, Sommerville, NJ,

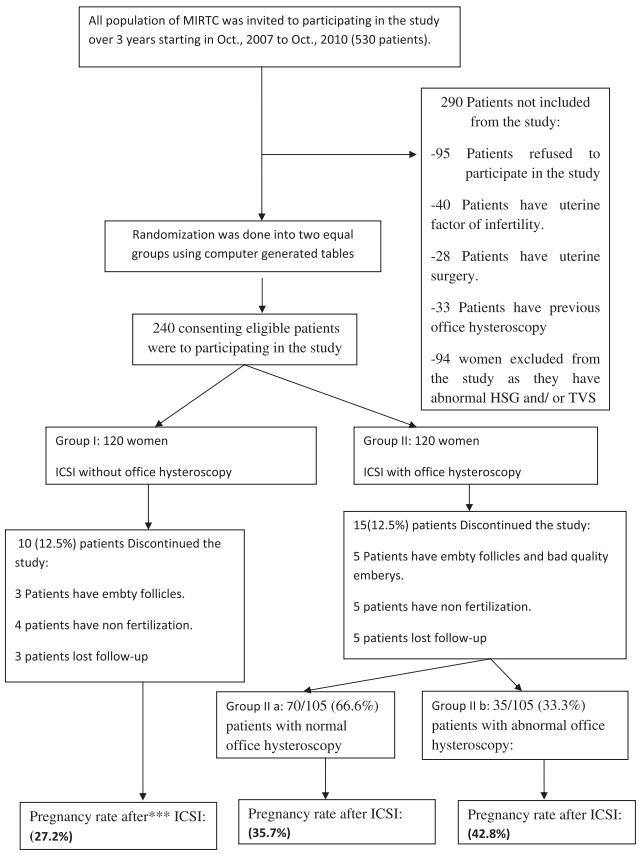

Figure 1 Consort guideline of the study. *HSG = hysterosalpingogram; **TVS = transvaginal ultrasonography; ***ICSI = intracytoplasmic sperm.

USA) with a 0° grade. Optic Illumination was provided by a 250-W Xenon light source. The images were viewed on a high-resolution color monitor using three-chip camera, and unusual lesions were recorded directly on laptop. Normal saline was used for uterine distension and was instilled from a flexible 500-ml bag wrapped in a pressure cuff connected to a manometer and pumped up to 80–120 mmHg.

No pharmacological preparations or local anesthetics were administered before the examination as the technique avoids the need to introduce a speculum and a tenaculum; the vagina, being a cavity, can be distended by introducing the distension medium through the hysteroscope placed into the lower vagina; the anatomy can then be followed by gentle movements of the instrument towards the cervix and cervical canal. The endometrial surface was inspected systematically, and the tubal ostia were identified. The hysteroscope was then pulled back towards the internal uterine orifice (IUO) to obtain a panoramic view of the whole cavity. The endocervical canal was inspected during withdrawal of the hysteroscope.

Abnormal finding was recorded and treated according to the standard protocol of each pathology specific for the center. In patients with normal hysteroscopic finding, chromohysteroscopy (infusion of 5% methylene dye into the uterine cavity) was used to identify areas suspected to be endometrial hyperplasia or endometritis, endometrial biopsy tissue was taken with the biopsy forceps under direct visualization.

2.4. The controlled ovarian stimulation (COS) protocol

Ovarian hyperstimulation was achieved using the standard long protocol of MIRTC. Pituitary down regulation (PDR) was achieved using leucrine 0.1 mm daily for 10 days or until the onset of menses. PDR was confirmed by the combined findings of endometrial thickness < 5 mm and absence of ovarian cysts $\geqslant 20$ mm, then ovarian stimulation was achieved using recombinant FSH. The dose of gonadotropin was individualized based on female age, baseline day 3 FSH level and previous response to controlled ovarian hyperstimulation (COH). HCG in a dose of 10,000 IU was given when at least three follicles reached > 18 mm in diameter. Oocytes were retrieved 36 h after HCG injection under transvaginal ultrasound guidance. Fertilization of the oocytes was performed using the standard ICSI techniques, all patients have embryo transfer by the 2nd author (only three grad I embryo were transferred) according to the MIRTC protocol under ultrasound guidance. All patients had luteal phase support with progesterone using prontogest vaginal suppositories (Prontogest, IBSA) 400 mg/day starting on the day of oocyte retrieval and continued till the day of pregnancy test. All patients with positive urine pregnancy test were scheduled to have two early pregnancy scans at 6 weeks and at 8–10 weeks to confirm the presence of clinical pregnancy.

2.5. Follow up

Clinical pregnancies (was defined as cases who had sonographic evidence of intrauterine pregnancy with positive fetal cardiac activity) were calculated and biochemical pregnancies as well as ectopic pregnancies were excluded. Implantation rate was determined by dividing the number of intrauterine gestational sacs with embryonic cardiac activity by the total number of embryos transferred.

2.6. Statistical analysis

Data entry and analysis were all done with IBM compatible computer using software SPSS version 13. Quantitative data were presented by mean and standard deviation, while qualitative data were presented by frequency distribution. Correlation, Chi-square, Student t-test and one way ANOVA test were used. The probability of less than 0.05 was used as a cut off point for all significant tests. Univariate and multivariate logistic regression analyses were performed to assess the predictive value of each variable separately and after adjusting for other variables. The relative impact of each of the predictors' tests was assessed by comparing the performance of different combination models using ROC AUC as a measure of the overall performance of each model.

3. Results

The present study included 560 patients, 95 patients of them refused to participate in the study, 195 patients were excluded from the study and 270 consenting patients were eligible to participate in the study, who were further divided into two equal groups, statistical analysis included only 110 patients in group I (ICSI without office hysteroscopy), and 105 patients

in group II (had ICSI after office hysteroscopy). Group II was sub classified into group IIa (70 patients with normal office hysteroscopy) and group IIb (35 patients with abnormal office hysteroscopy findings that were corrected before ICSI. Ten patients from group I and 15 patients from group II were excluded from the statistical analysis as they did not complete the study (Fig. 1).

As regarding the admission characteristics, there were no statistically significant differences between both groups (Table 1); also there was no statistically significant difference in the mean basal hormonal levels (estradiol, FSH, inhibin B and antimullerian hormone), in the mean number of oocytes retrieved, fertilization rate, and number of embryo transferred (Table 3). Unsuspected abnormal uterine findings were diagnosed in 35/105 (33.3%) patients with normal HSG and/or TVS among patients in group II by using office hysteroscopy (Table 2). Implantation rate and clinical pregnancy rate were statistically significant between group I and group II, as clinical pregnancy rate between group I, group IIa (ICSI with normal office hysteroscopy) and group IIb (ICSI with abnormal office hysteroscopy) were 27.2%, 35.7%, 42.8%, respectively ($P \leqslant 0.05$) (Table 4). Among group II 51 patients (48.5%) have ICSI failure or repeated IVF (RIF), 23 patients of them (45%) had abnormal hysteroscopy finding and 15 patients (65.2%) achieved pregnancy after correction of their uterine abnormalities.

Hysteroscopy has high specificity (88%), high diagnostic accuracy (86.2%) but less sensitivity (80%) in predicting intrauterine abnormalities when compared to HSG and TVS taking the histopathological diagnosis as the standard diagnostic test (odd's ratio 1.7, CI 1.33–2.44) (Table 5 and 6).

4. Discussion

The presences of uterine pathology was documented in 10–62% of women with infertility (9,10), in 10–60% of women undergoing pretreatment assessment for IVF–ET (11,12), and in 19–50% of women who failed to conceive following assisted reproductive technologies (13). 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 (13).

In the present study, unsuspected abnormal uterine findings were diagnosed in 35/105 (33.3%) patients with normal HSG and/or TVS among patients in group II with statistically significant high specificity (88.2%), +ve predictive value (67.2%), diagnostic accuracy (81.8%), and low −ve predictive value (65.2%) (95% CI 1.33–2.44, odd ratio 1.7) than HSG and/or TVS. These results in agreement with many other studies (3,13–19), as the abnormal hysteroscopic findings were (30–45%). Comparative studies of HSG or TVS in evaluation of uterine cavity abnormalities did not yield uniformly accurate results with unacceptable high false negative rate, low positive predictive rate and poor diagnostic accuracy values. Therefore, it appeared that in approximately one third of the patients where HSG and/or TVS is interpreted as normal there will be abnormalities, which may cause a false reassurance and will actually lead to failure of conception (13–19). On the other hand Fatemi et al. (1) and Karayalcin et al. (20) 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. (2) found very high incidence of uterine pathology in their studies (64%) with repeated IVF failure.

HSG or TVS has been proposed as 1st diagnostic tests of the uterine cavity abnormalities but the present study and most other studies (5–9) clearly demonstrated that they suffer from a low sensitivity and specificity than that of hysteroscopy. The differential diagnosis of intrauterine abnormalities necessitates secondary investigation in the form of hysteroscopy to confirm and possibly treat the pathology. HSG results may also be

Table 1 Patients admission characteristics of the study groups.

	Grope I (N = 110)	Grope II (N = 105)	P-value
Age (years): range (mean ± SD)	23–37 (31 ± 12.324)	22–39 (33 ± 11.14)	NS[a]
Height (cm): range (mean ± SD)	145–170 (163 ± 1.74)	150–165 (160 ± 2.25)	NS
Weight (kg): range (mean ± SD)	55–87 (71.20 ± 8.35)	62–90 (74.50 ± 3.40)	NS
B.M.I. (kg/m^2): range (mean ± SD)	21.60–27.55 (24.75 ± 1.37)	23.41–28.65 (23.04 ± 2.6)	NS
Duration of infertility (years)	3–12 (7.5 ± 2.4)	4–14 (9.3 ± 1.15)	NS
Type of infertility: (N-%)			
Primary infertility	67 (60.9%)	65 (61.9%)	NS
Secondary infertility	43 (39%)	40 (38%)	NS
Causes of infertility: (N-%)			
Male factor	24 (21.8%)	25 (23.8%)	NS
Ovarian factor	30 (27.2%)	28 (26.6%)	NS
Tubal factor	31 (28%)	28 (26.6%)	NS
Unexplained	23 (20.9%)	21 (20%)	NS
Others[b]	2 (1.8%)	3 (2.8%)	NS
Number of ICSI trial: (N-%)	48 (43.6%)	51 (48.5%)	NS
1st trial	20 (18%)	22 (20.9%)	NS
2nd trial[c]	15 (13%)	17 (16%)	NS
More than two[c]	8 (7.2%)	12 (11.4)	NS

[a] Non-significant ($P \leqslant 0.05$).
[b] Others were repeated early pregnancy loss more than 8 times.
[c] Repeated IVF failure (RIF).

Table 2 Incidence of hysteroscopic findings in group II.

Type of hysteroscopic findings	Number	%
1. Normal hysteroscopy (group IIa)	70/105	66.6
2. Abnormal hysteroscopy (group IIb)[a]	35/105	33.3
(A) Endometrial polyp[b]	11	32.4
(B) Submucous fibroid[c]	4	11.4
(C) Intrauterine adhesion	4	11.4
(D) Polyploidy endometrium	7	20
(E) Uterine septa	1	2.8
(F) Endometritis[d]	2	5.7
(G) Endometrial hyperplasia[d]	3	8.5
(H) Atrophic endometrium[d]	2	5.7
(I) Others[e]	1	2.8

[a] Diagnosis was based on histopathology after hysteroscopic guided biopsy.
[b] Endometrial polyp size was 1.5–2 cm presented mainly at the posterior wall and near the corneal ends.
[c] All of them were grad 0 and less than 1.5–2.5 cc in its endometrial projection mainly present at the anterior and posterior uterine wall.
[d] Diagnosis was based on histopathology after hysteroscopic guided biopsy from suspicious areas with the help of chromohysteroscopy.
[e] These were old products of conception.

influenced if the procedures are performed at different phases of the menstrual cycle due to the variable growth changes of the endometrium. False-positive findings can be caused by air bubbles, mucus, menstrual debris that could mimic filling defects and can result from an excessive amount of contrast media in the uterus obliterating shadows caused by small endometrial lesions (7). Also, these results were greatly affected by the quality of the X-ray machine and inter observer errors in evaluation of the films. As a result, approximately 10–35% of women undergoing fertility investigations, who have a normal cavity at HSG, have been reported to have abnormal hysteroscopic findings (6,9). In comparison with hysteroscopy, TVS was reported to have 84.5% sensitivity, 98.7% specificity, 98% positive predictive value and 89.2% negative predictive value (8). TVS may not diagnose submucosal fibroids in the presence of multiple fibroids, a large polyp from hyperplasic endometrium and, or differentiate between an arcuate and a septate uterus.

Despite these drawbacks, many IVF clinics were reluctant in use of hysteroscopy for uterine cavity evaluation. As hysteroscopy has traditionally in the past required general anesthesia, careful surveillance of fluid status to minimize complications of hyponatremia and fluid overload, physician experience which need a learning curve and high cost. However, now office hysteroscopy with small diameter sheath (3–5 mm), using the non touch (vaginoscopic) technique without dilatation of the cervix (and consequently no anesthesia) with low pain score during or after the procedures. Saline was used as a distention making use of office hysteroscopy in IVF center easy, extremely safe, with no patients monitoring or laboratory studies for fluid overload (14). In addition to the previous advantages, office-based operative hysteroscopy has been shown to be easily performed with excellent surgical results (19).

Table 3 Characteristics of the ICSI cycles in the study groups.

Cycle characteristics	Group I (N = 110)	Group II (N = 105)	P-value
1. FSH day 3 (mIU/ml) (mean ± SD)[a]	7.2 ± 1.5	6.8 ± 1.4	NS[b]
2. Estradiol (E2) level (pg/ml) (mean ± SD)[a]	171.8 ± 2.1	175.4 ± 1.3	NS
3. Inhibin B (ng/l) (mean ± SD)[a]	95.8 ± 1.6	93 ± 2.3	NS
4. Antimullerian hormone (ng/ml) (mean ± SD)[a]	3.3 ± 0.4	3.5 ± 0.5	NS
5. Duration of stimulation (days) (mean ± SD)	18.3 ± 1.9	20.4 ± 1.5	NS
6. No. of HMG ampoules (75 IU) (mean ± SD)[c]	45.7 ± 12.4	48.7 ± 13.5	NS
7. Serum E2 (pg/ml) level at time of hCG injection	1831 ± 874	1874 ± 653	NS
8. Total No. of oocytes retrieved (mean ± SD)[c]	8.6 ± 4.3	9.8 ± 3.2	NS
9. Total No. of embryos (mean ± SD)[c]	4.5 ± 1.7	5.7 ± 1.2	NS
11. Endometrial thickness (mm) (mean ± SD)	11.3 ± 1.33	13.7 ± 1.22	NS

[a] Before stimulation.
[b] Non-significant ($P \leqslant 0.05$).
[c] Total number for each patient.

Table 4 Implantation rates and clinical pregnancy rates in both study groups.

	Group I (N = 110)	Group II			P-value
		Group II (N = 105)	Group IIa (N = 70)	Group IIb (N = 35)	
Implantation rate: N-%					
0%	80 (72.7%)	65 (61.9%)	45 (64.2%)	20 (57%)	S*
33.3%	20 (18%)	27 (25.7%)	18 (25.7%)	9 (25.7%)	S*
66.66%	7 (6.3%)	9 (8.5%)	5 (7%)	4 (11.4%)	S*
99.9%	3 (2.7%)	4 (3.8%)	2 (2.8%)	2 (5.7%)	S*
Clinical pregnancy rate					
Negative: *N*-%	80 (72.7%)	65 (61.9%)	45 (64.2%)	20 (57%)	S*
Positive: *N*-%	30 (27.2%)	40 (38%)	25 (35.7%)	15 (42.8%)	S*

* Significant ($P \leqslant 0.05$).

Table 5 Sensitivity, specificity, PPV[a], NPV[b] and diagnostic accuracy of hysteroscopy, HSG and TVS in the diagnosis of uterine abnormalities.

Test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)
Hysteroscopy	80	88.2	60	67.2	81.8
HSG and TVS	74.3	63.3	44.5	87.5	63.6

[a] Positive predictive value.
[b] Negative predictive value.

Table 6 Multiple regression analysis using clinical pregnancy as a dependant variable.

	Regression coefficient	Odd's ratio	95% CI	*P*-value
Hysteroscopy	0.57	1.7	1.33–2.44	0.7
HSG and TVS	0.81	0.44	1.20–4.32	0.2

In the present study, there was a statistically significant difference observed in terms of clinical pregnancy rate between group I and group II (29.5% and 38.3%, $P < 0.05$), between group I and group Ia (27.2% and 38%, $P < 0.05$) and between group I and group IIb (27.2% and 42.8%, $P < 0.05$), respectively. These results were in concordance with many other similar studies (2,13,16–18) and this proved that instead previous diagnosis of an apparently normal uterine cavity, pathologic abnormalities were found in a significant number of patients and an improvement in clinical pregnancy rates in patients who have office hysteroscopy prior IVF or ICSI, particularly on those were endometrial pathology was found and corrected was obtained. While in the other hand Gaviño-Gaviño et al. (2) and Lorusso et al. (15) stated that hysteroscopy also seems to be the best way to repair the uterine cavity when pathological conditions are present. However, performing office hysteroscopy before IVF–embryo transfer is of no significant value in improving pregnancy outcomes. Demirol and Gurgan (21) in their randomized controlled trial although they found a significant difference in the clinical pregnancy rates between patients in group I (who did have office hysteroscopic evaluation) and group IIa (who have normal hysteroscopic findings) (21.6% and 32.5%, $P = 0.044$, respectively) and between group I and group IIb (who have abnormal hysteroscopic findings) (21.6% and 30.4%, $P = 0.044$, respectively) while there was no significant difference in the clinical pregnancy rate of patients in group IIa and group IIb (32.5% and 30.4%). They concluded that patients with normal HSG but recurrent IVF–embryo transfer failure should be evaluated prior to commencing IVF–embryo transfer cycle to improve the clinical pregnancy rate. In the same way Bozdag et al. (3) in their review found that there is paucity of data on the role of hysteroscopy in failed IVF cycles and in the available two randomized controlled trials, pregnancy rates appear to be increased when hysteroscopy is performed. However within the hysteroscopy group, pregnancy rates are comparable among the normal or surgically corrected subgroups and so further studies are warranted. El-Toukhy et al. (22) in their meta analysis, they founded an evidence of benefit from outpatient hysteroscopy in improving the pregnancy rate in the subsequent IVF cycle (pooled relative risk = 1.75, 95% CI 1.51–2.03). The evidence from randomized trials was consistent with that from non-randomized controlled studies and future robust randomized trials comparing outpatient hysteroscopy or mini-hysteroscopy with no intervention before IVF treatment would be a useful addition to further guide clinical practice (22). The previous data and the results of the present study in the context of IVF, lower pregnancy rates have been reported in the presence of uterine cavity abnormalities, and their correction has been associated with improved pregnancy rates (10). Practitioners should be more inclined to recommend hysteroscopy as part of a basic IVF workup.

In the present study, implantation rate was significantly higher between in group I and group II, and between group I and group IIb and these results go hand in hand with the law of diminishing return as long as uterine pathology will be found and corrected it certainly will rise the clinical pregnancy rate, but in a paradoxical phenomena the implantation rate and the clinical pregnancy rate were significantly higher between group I and group II in which office hysteroscopy reveal no pathology and this in need for an explanation? In the authors opinion it might be a different reason as stimulation of the cervix, touching of the endometrium will stimulate the molecular dialogue that occur between the implanting conceptus and the endometrium involves cell–cell and cell–extracellular matrix interaction that mediated by a variety of adhesive molecules, growth factors, cytokines, chemokines, certain modulatory proteins, matrix enzymes, hormones, and prostaglandin by creation of changes in the plasma membrane of the luminal epithelium in a phenomena called plasma membrane transformation (i) (23), and this was similar to the same effect obtained by doing dummy or mock catheter introduction through the cervix at the time of ovum retrieval prior to embryo transfer. Irrigation of the cavity with saline may have a beneficial effect on implantation and pregnancy rates in patients with tubal or uterine causes of infertility (ii) (24), also saline will mechanically remove harmful anti-adhesive glycoprotein molecules on the surface endometrium involved in endometrial receptivity as (i.e., COX-2, MUC-1 and integrin-$\alpha V\beta 3$) (iii). Local injury to the endometrium might provoke wound healing involving a massive secretion of different cytokines and growth factors, including leukemia inhibitory factor, interleukin-11 and heparin-binding EGF-like growth factor, which might induce rapid growth of the endometrial cells (decidualization) and increase its implantation competency (iv) (25).

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.

5. Conclusion

Instead previous diagnosis of apparently normal uterine cavity, the incidence of pathologic abnormalities based on hysteroscopic diagnosis was high especially with repeated IVF failure. Improvement in implantation and clinical pregnancy rates were observed after office hysteroscopy prior to ICSI, particularly on those where abnormalities were founded and corrected. So routine office hysteroscopy should be an essential step of the infertility workup before ART even in patients with normal HSG and/or TVS.

Conflict of interests

None.

Contribution to authorship

1st author: Design the study, recruitment of patients, did randomization, did office hysteroscopy, follow up of the cases, write the paper and did analysis of the results.

2nd author: Collect and revise academic data, help in writing the paper and analysis of the results.

3rd author: Recruitment of patients, did ovum retrieval, did embryo transfer, follow up of the patients and reviewing of the manuscript.

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