Arch Gynecol Obstet (2015) 291:193–199
DOI 10.1007/s00404-014-3397-z

Routine office hysteroscopy prior to ICSI vs. ICSI alone in patients with normal transvaginal ultrasound: a randomized controlled trial

Khaled Ahmed Abdel Aziz Elsetohy · Ahmed H. Askalany · Mohamed Hassan · Zamam Dawood

Received: 12 March 2014 / Accepted: 22 July 2014 / Published online: 1 August 2014

Abstract
Background Implantation failure represents a major cause of stress to both clinician and patient undergoing ICSI cycle. Even minor uterine cavity abnormalities, such as endometrial polyps, small submucous myomas, adhesions, and septa are considered to have a negative impact on the chance to conceive through ICSI.
Aim This study aimed at assessing the role of using the office hysteroscopy as a routine investigation in improving ICSI pregnancy rates.
Methodology ICSI was performed in two groups of infertile women with no abnormality detected in transvaginal ultrasonographic examination, group I: $n = 97$ and group II: $n = 96$, women in group I were subjected to hysteroscopic examination before ICSI while group II underwent ICSI without hysteroscopy. Then, ICSI was performed for all subjects of the two study groups with no statistically significant difference ($p > 0.05$) regarding 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.
Results 43.3 % of group I showed abnormal hysteroscopic findings. Group I showed a significantly higher pregnancy rate (70.1 %) than that of group II (45.8 %) ($p = 0.001$). There is statistically significant association between the use of hysteroscopy prior to ICSI and the rate of pregnancy (OR 2.77, 95 % CI [1.53–5.00]). In addition, hysteroscopy had detected abnormalities in near half of cases whose ultrasound was normal.
Conclusion Routine office hysteroscopy is an essential step for infertility workup before ICSI even in patients with normal TV/US.

Keywords Hysteroscopy · ICSI · Pregnancy rate · Intrauterine · Complications

Introduction

Implantation failure represents the major cause of stress to both clinician and patient undergoing ICSI cycle. In addition, it adds to the considerable costs associated with infertility treatment [1]. Implantation failure could be due to the embryo, uterine environment or a combination of both [2]. Even minor uterine cavity abnormalities, such as endometrial polyps, small submucous myomas, adhesions, and septa are considered to have a negative impact on the chance to conceive through ICSI [3].

The prevalence of unsuspected intrauterine abnormalities, diagnosed by hysteroscopy prior to ICSI, has been reported to be 11–45 % [4]. Therefore, it has been suggested that these abnormalities should be diagnosed and treated to optimize the condition of the uterine environment and thus, the outcome of ICSI treatment. However, this recommendation is not based on high level of evidence [5]. In addition, the benefits of hysteroscopy in patients who will undergo a first ICSI treatment have not yet been investigated [6].

The European Society for Human Reproduction and Embryology (ESHRE) and the Royal College of Obstetricians and Gynecologists (RCOG) do not recommend saline

K. A. A. A. Elsetohy · A. H. Askalany · M. Hassan · Z. Dawood
Department of Gynecology and Obstetrics, Faculty of Medicine, Cairo University, Gaiza, Egypt

K. A. A. A. Elsetohy (✉)
3rd Alsaraya Street Almanyal, Gaiza, Egypt
e-mail: kelsetohy@gmail.com

infusion sonohysterography (SIS) nor hysteroscopy as initial investigation prior to starting ICSI [7].

Previous studies indicate a trend towards a beneficial effect of screening hysteroscopy on ICSI outcome. This finding, combined with the observed high prevalence of intrauterine abnormalities, has led to the general debate on the beneficial effect of pre-IVF work-up of the uterine cavity [6].

The rationale behind this randomized controlled study is to test the hypothesis that routine hysteroscopy prior to ICSI has an additive value in term of higher rate of pregnancy.

Patients and methods

The study was conducted in the IVF centre at Kasr Al Aini teaching hospital during the period from January 2012 to June 2013.

Subjects with primary or secondary infertility candidate for ICSI by various indications were scheduled for a first IVF/ICSI treatment cycle with no abnormality detected, apart from intramural myomas without uterine cavity deformity, during transvaginal ultrasonographic examination performed during the follicular phase of the menstrual cycle were included in our study.

Subjects with uterine factor of infertility, a history of recurrent miscarriage, abnormal HSG, or abnormal transvaginal US, inter-menstrual blood loss, previous intrauterine surgery or contraindication for hysteroscopy were excluded from our study.

This study followed the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO), and was approved by the medical ethical review committee of Cairo University.

The purpose of this study was clearly explained in Arabic language to all subjects attending the centre before their enrolment to the study, and an informed consent form was signed and obtained by all of those enrolled.

Before inclusion in the study, all patients were evaluated prior to ICSI by recent hormonal profile (within 6 months), HSG done within the past year, and transvaginal ultrasound for the wife in addition to recent semen analysis for the husband. Evaluation of the patients by TV/US was done by the study investigator with additional reports from another specialized US centres.

All eligible subjects were randomized into the two study groups; group I: ICSI with hysteroscopy group and group II: ICSI without hysteroscopy group. Randomization was done using a computer generated table of random numbers.

Patients of both groups were subjected to ICSI procedure, and then they were followed up till the end of pregnancy.

Hysteroscopic examination was scheduled in the early–mid follicular phase of a menstrual cycle (day 3–12). A vaginoscopic approach was used without anesthesia, in an outpatient setting. Hysteroscopy was performed using a 4.3-mm outer-diameter continuous flow hysteroscope with a five French working channel and a 30 direction of view. The uterine cavity was distended by saline infusion. The endocervical canal, uterine cavity, tubal orifices and endometrium was inspected methodically and findings recorded on a standardized form. Intrauterine abnormalities were defined as endometrial polyps, polypoidal endometrium (in case of multiple polyps in different stages between sessile to pedunculated affecting the whole endometrium and not localized to a certain area of endometrium), septate uterus, adhesions and chronic or acute endometritis, and submucous myomata previously undetected by ultrasound. Also cervical stenosis was noted due to its impact on easiness and hence results of ET. Therapeutic hysteroscopy was performed in the same hysteroscopy session if any of the predefined intrauterine abnormalities were detected or scheduled for operative procedures later. It is left to the judgement of the operator physician to decide to perform a septum resection in a subsequent session with laparoscopic observation. ICSI was performed within 3 months of hysteroscopic examination.

Laparoscopy was done according to the routine practice of applying it in cases with infertility when indicated. It was used for the following conditions: an abnormal finding is HSG, surgical correction of problems in tubes (hydrosalpinx) or ovaries (ovarian cysts) or unexplained infertility. In addition, since our primary outcome was rate of pregnancy; so, any contributing factor that could alter the occurrence of pregnancy would have been taken care of in both groups.

Fertility treatment Induction of ovulation was done using the long protocol. Oocyte retrieval was carried out 36 h after HCG administration. Luteal phase supplementation consists of 800 mg natural progesterone suppository in two separate dosages (Prontpgest®/Cyclogest® 400 mg 1 × 2/day) for 2 weeks after ovum pick-up.

Follow up

Pregnancy test was done 2 weeks after ET and positive test confirmed by an US 1 week later.

Statistical analysis

All statistical tests were done using a significance level of 95 %. A value for $p < 0.05$ was considered statistically significant. SPSS software (Statistical Package for the Social Sciences, version 20.0, SSPS Inc, Chicago, IL,

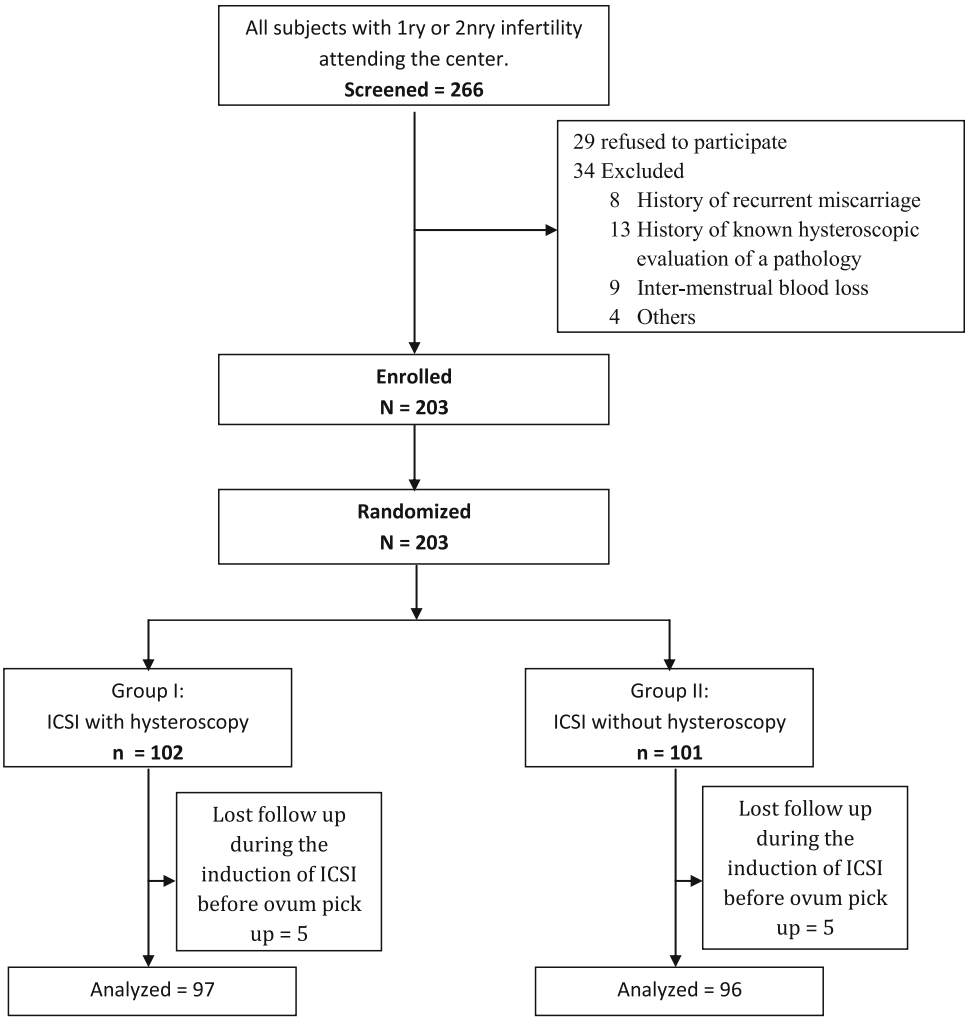

Fig. 1 Consort diagram

USA) was used for the statistical analyses. Data were presented as (mean ± SD) for continuous variables and as frequency and percent for categorical variables. Comparisons between the two groups were done using Pearson Chi-square for categorical variable and the unpaired Student's *t* test for continuous variables.

Results

All subjects (266) who were referred to the centre were asked to participate in the study. Twenty-nine subjects refused to participate and 34 subjects were excluded for different causes, thus leaving a population of 203 eligible patients who were included in this study. The dispositions of these subjects are shown in (Fig. 1).

Baseline characteristics

ICSI was performed in 193 infertile women randomized into two groups; 97 Group I: with hysteroscopy and 96 Group II: without hysteroscopy; with no statistically significant difference ($p > 0.05$) regarding age, weight, height and BMI as shown in Table 1. There were no significant difference ($p > 0.05$) between the two groups regarding types and causes of infertility, as shown in Table 1. Fifty-eight subjects (59.8 %) of group I had primary infertility compared to 65 subjects (67.7 %) of group II. The duration of infertility had shown no significant difference ($p > 0.05$) between the two groups, with an average of 5.9 ± 3.7 and 5.7 ± 3.4 years for group I and group II, respectively. In addition, 32 (33 %) and 28 (29.2 %) of subjects in group I and II, respectively, had laparoscopy whether diagnostic for assessment of tubal patency, presence of endometriosis or adhesions; or operative for ovarian cystectomy, tubal disconnection or ovarian drilling with no statistically significant difference between the two groups ($p > 0.05$), as shown in Table 2.

Hysteroscopy

Diagnostic hysteroscopy was successfully performed in all subjects of group I with no complications encountered, as a

Table 1 Demographic and infertility data: Patients admission characteristics of the study groups

	Group I ICSI with hysteroscopy $N = 97$ *n* (SD) (range)	Group II ICSI without hysteroscopy $N = 96$ *n* (SD) (range)	*p*
Age (years)	31.1 (5.8) (16–44)	29.9 (4.8) (20–40)	0.110
Height (cm)	159.3 (6.7) (144–177)	159.2 (5.2) (145–173)	0.888
Weight (kg)	73.5 (12.1) (52–124)	74.6 (14.4) (49–150)	0.579
BMI	29.1 (5.0) (20.3–46.7)	29.5 (5.8) (20.6–55.1)	0.596
Infertility duration (year)	5.9 (3.7) (0.5–16)	5.7 (3.4) (1–20)	0.611
	Group I ICSI with hysteroscopy $N = 97$ *n* (%)	Group II ICSI without hysteroscopy $N = 96$ *n* (%)	*p*
Infertility type			
Primary	58 (59.8)	65 (67.7)	0.253
Secondary	39 (40.2)	31 (32.3)	
Infertility causes[a]			
Male	48 (49.5)	51 (53.1)	0.613
Tubal	27 (27.8)	25 (26)	0.779
Unexplained	21 (21.6)	19 (19.8)	0.750
Ovarian[b]	15 (15.5)	17 (17.7)	0.675

[a] One subject may have more than one cause of infertility

[b] These are causes related to anovulation: PCOS, poor ovarian reserve, poor responders or ovarian cysts

Table 2 Laparoscopic findings and intervention in both groups

	Group I ICSI with hysteroscopy $N = 97$ *n* (%)	Group II ICSI without hysteroscopy $N = 96$ *n* (%)	*p*
Free	12 (12.4)	4 (4.2)	0.345
Tubal block	5 (5.2)	4 (4.2)	
Ovarian drilling	4 (4.1)	3 (3.1)	
Adhesiolysis	3 (3.1)	2 (2.1)	
Ovarian cystectomy	2 (2.1)	1 (1)	
Endometriotic patches ablation	2 (2.1)	7 (7.3)	
Tubal disconnection due to hydrosalpinx	3 (3.1)	1 (1)	
Myoma	1 (1)	2 (2.1)	
Frozen pelvis	0 (0)	1 (1)	

part of an early infertility workup before ICSI. These subjects were previously diagnosed as being normal using the transvaginal ultrasonography. No abnormality could be detected in 56.7 % of them, while 43.3 % showed abnormal hysteroscopic findings. The mean time required for hysteroscopic examination was 5.0 ± 0.8 min and the patients' tolerance to the procedure and pain perception were assessed using a pain scoring system from 1 to 5, with a mean value for pain of 2.3 ± 0.9.

Table 3 Hysteroscopic findings in group I

	n (%)
Normal hysteroscopy	55 (56.7)
Endometrial polyp	9 (9.3)
Submucous myoma	7 (7.2)
Cervical stenosis	6 (6.2)
Intrauterine adhesion	6 (6.2)
Uterine septum	6 (6.2)
Polypoid endometrium	4 (4.1)
Arcuate uterus	2 (2.1)
Unicornuate uterus	2 (2.1)

The commonest finding on hysteroscopic examination was endometrial polyp (9 out of 97 subjects 9.3 %), followed by submucous myoma (7.2 %), other findings include, cervical stenosis (6.2 %), intrauterine adhesion (6.2 %), uterine septum (6.2 %), polypoidal endometrium(4.1 %), arcuate uterus (2.1 %) and unicornuate uterus (2.1 %), as shown in Table 3.

For endometrial polyp, intrauterine adhesion and uterine septum; a five French scissors were introduced to cut them on an outpatient basis and second look was applied after once cycle. For polypoidal endometrium and submucous myoma; a bipolar continuous irrigation Storz resectoscope was used by loop resection and second look office hysteroscopy was done. For cervical stenosis; cervical dilatation up to eight hegar under anesthesia was done for the further ease of embryo transfer. Nothing was done for arcuate uterus and unicornuate uterus.

Table 4 ICSI cycles characteristics

	Group I ICSI with hysteroscopy $N = 97$ Mean (SD)	Group II ICSI without hysteroscopy $N = 96$ Mean (SD)	p
Total no. of oocytes retrieved	13.7 (5.8)	13.7 (5.9)	0.923
Fertilization rate	90 %	89 %	0.534
Total no. of embryos	2.9 (0.8)	3.0 (0.8)	0.442

Table 5 Pregnancy outcome

	Group I ICSI with hysteroscopy $N = 97$ n	Group II ICSI without hysteroscopy $N = 96$ n	Total	p
Pregnant	68	44	112	0.001
Not pregnant	29	52	81	
Total	97	96	100	
Result	Point estimate	Lower C.I.	Upper C.I.	
OR	2.77	1.53	5.00	

ICSI cycles characteristics

Then ICSI was performed for all subjects of the two study groups with no statistically significant difference ($p > 0.05$) regarding the number of oocytes retrieved, fertilization rate and the number of embryo transfer, as shown in Table 4.

Pregnancy outcome

Pregnancy rate was higher in group I (68 out of 97 subjects, 70.1 %) than in group II (44 out of 96 subjects, 45.8 %) and this difference is statistically highly significant with $p = 0.001$. The baby take-home rate was 58 in group I and 33 in group II.

There is statistically significant association between the use of hysteroscopy prior to ICSI and the rate of pregnancy (OR 2.77, 95 % CI [1.53–5.00]), as shown in Table 5.

Discussion

The value of hysteroscopy as a routine investigation in the management of infertile women is a matter of debate. The ESHRE guidelines indicate hysteroscopy to be unnecessary, unless it is for the confirmation and treatment of doubtful intrauterine pathology [7]. The two main problems that argue against the use of hysteroscopy are being invasive procedure and the debate about the real significance of the observed intrauterine pathology on fertility [7]. However, other studies reported that the procedure is minimally invasive, and unlike traditional hysteroscopy it can be performed in an office-based gynecological practice with no need for hospitalization, cervical dilatation, or anesthesia. In addition, the procedure has a very low technical failure rate [8].

In this current study there were no complications encountered in subjects who underwent hysteroscopic examination, and it was tolerable by all the tested women. Moreover, it had successfully diagnosed uterine lesions in 43.3 % of infertile women who had been previously shown no abnormality during transvaginal ultrasonographic examination.

Hysterosalpingogram (HSG) alone is recommended by the World health Organization (WHO) in the management of infertile women [9]; as it gives information on tubal patency or blockage. Brown et al. [10], in their study which evaluated the role of each of office hysteroscopy, HSG and SIS in assessment of the uterine cavity, found that office hysteroscopy should be performed only in patients with abnormal HSG.

This research study showed that infertile women who had hysteroscopic examination prior to ICSI showed significantly higher pregnancy rate than other infertile women. Many recent studies showed the positive effect of hysteroscopic examination on the outcome of in vitro fertilization. Bahadur et al. [11], showed that 21.1 % of patients had confirmed abnormalities that required to be treated before performing IVF/ICSI and concluded that routine diagnostic hysteroscopy becomes mandatory before such expensive procedures of assisted reproduction. However, Fadhlaoui et al. [12], concluded that the benefit of routine hysteroscopy is significant only in women 40 years and older.

This high pregnancy rate may be attributed to many aspects where the hysteroscope was used for operative correction of the uterine abnormality detected during the examination in 40 % of those who have hysteroscopic findings. All of them, except half of the cases with septum, had corrections and this may have increased the success rate of ICSI in those infertile women. Moreover, the hysteroscope causes stimulation of the cervix, touching the endometrium with stimulation of a molecular dialogue between the implanting conceptus and the endometrium described elsewhere [13]. This dialogue leads to a phenomenon called plasma membrane transformation which is changes in the plasma membrane of the luminal epithelium [13]. Also, it might induce rapid decidualization and increase the implantation competency of the endometrium [14]

In addition, irrigation of the cavity with saline may have beneficial effect on implantation and pregnancy rates in patients with tubal and uterine factors of infertility [15].

Bohlmann et al. [16] studied the prevalence of uterine anomalies in cases with recurrent abortion. He found that uterine anomalies are frequently found in those patients with two and with more than two early miscarriages (36.8–42.9 %). In our current study in infertile population, the results showed percentage of 45.4 % which is almost the same. Both studies concluded the importance of hysteroscopy as a diagnostic tool for women seeking children which affects the take-home baby rate.

Regarding the cost effectiveness of the procedure, it is an inexpensive procedure that positively affects the ICSI outcome. Thus, reducing the costs and burden that ICSI failure imposes on each couple undergoing ICSI.

The high pregnancy rates in both arms in our study in comparison to other general rates of pregnancy could be attributed to the generally young age of the patients (<35), relatively lower BMI as high BMI has negative impact on ICSI outcome [17]. This is of course in addition to the number of embryos transferred being three at least. This is to match our cultural background; as our population cannot afford many trials of ICSI. In addition, there is a general acceptance of the idea of twins, rather than in European countries.

Limitations

Limitations of this study can lie in the impact of embryo quality and technique of embryo transfer on the implantation rate. Implantation is affected by both embryological and uterine environmental factors. The quality of the embryo is affected by various factors such as age, protocol of induction, skills of the embryologist and the media used. In this study, the ovarian stimulation protocol was standardized among the participants, thus eliminating the possibility that the embryo quality could be affected by the protocol used for each patient. Other factors as patients' age, skills of the embryologist and culture media remained a confounding variables in this study. Another possible study limitation has been the timing of the hysteroscopy examinations. In this study, hysteroscopy was performed in the follicular phase of a natural cycle, since the use of oral contraceptives prior to starting IVF/ICSI treatment with GnRH antagonist co-treatment is questionable.

Conclusions

It could be concluded from this study that office hysteroscopy is the gold standard for assessment of the uterine cavity; owing to its sensitivity and specificity in the detection of uterine abnormalities. Its value in treatment of the detected uterine abnormalities adds further to its advantages. It is even safe and tolerable procedure that does not require anesthesia. Furthermore, it could play a role in improving ICSI outcome through the diagnosis of hidden or subtle uterine abnormalities that can be missed by other routine investigations; or through enhancing the implantation process and improving the endometrial receptivity in infertile patients.

Acknowledgement We would like to acknowledge Dr. Emad R. H. Issak (ClinAmygate) for his efforts in statistical analysis and preparation of this manuscript.

Conflict of interest The authors have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

References

1. Bouwmans CA, Lintsen BM, Eijkemans MJ, Habbema JD, Braat DD, Hakkaart L (2008) A detailed cost analysis of in vitro fertilization and intracytoplasmic sperm injection treatment. Fertil Steril 89(2):331–341
2. Fatemi HM, Kasius JC, Timmermans A, van Disseldorp J, Fauser BC, Devroey P, Broekmans FJ (2010) Prevalence of unsuspected uterine cavity abnormalities diagnosed by office hysteroscopy prior to in vitro fertilization. Hum Reprod 25(8):1959–1965
3. Rogers PA, Milne BJ, Trounson AO (1986) A model to show human uterine receptivity and embryo viability following ovarian stimulation for in vitro fertilization. J In Vitro Fert Embryo Transf 3(2):93–98
4. Makrakis E, Hassiakos D, Stathis D, Vaxevanoglou T, Orfanoudaki E, Pantos K (2009) Hysteroscopy in women with implantation failures after in vitro fertilization: findings and effect on subsequent pregnancy rates. J Minim Invasive Gynecol 16(2):181–187
5. Bosteels J, Weyers S, Puttemans P, Panayotidis C, Van Herendael B, Gomel V, Mol BW, Mathieu C, D'Hooghe T (2010) The effectiveness of hysteroscopy in improving pregnancy rates in subfertile women without other gynaecological symptoms: a systematic review. Hum Reprod Update 16(1):1–11
6. Smit JG, Jenneke CK, Marinus JC Eijkemans et al (2012) The inSIGHT study: costs and effects of routine hysteroscopy prior to a first IVF treatment cycle. A randomised controlled trial. BMC Women's Health 12:22 Page 2 of 6. http://www.biomedcentral.com/1472-6874/12/22
7. Crosignani PG, Rubin BL (2000) Optimal use of infertility diagnostic tests and treatments, The ESHRE Capri Workshop Group. Hum Reprod 15(3):723–732
8. El-Mazny A, Abou-Salem N, El-Sherbiny W, Saber W (2011) Outpatient hysteroscopy: a routine investigation before assisted reproductive techniques? Fertil Steril 95(1):272–276
9. Koskas M, Mergui JL, Yazbeck C et al (2010) Office hysteroscopy for infertility: a series of 557 consecutive cases. Obstet Gynecol Int, 168096–168096
10. Brown SE, Coddington CC, Schnorr J, Toner JP, Gibbons W, Oehninger S (2000) Evaluation of outpatient hysteroscopy, saline

infusion hysterosonography, and hysterosalpingography in infertile women: a prospective, randomized study. Fertil Steril 74(5):1029–1034
11. Bahadur A, Malhotra N, Singh N, Gurunath S, Mittal S (2013) Comparative study on the role of diagnostic hysteroscopy in evaluation of the uterine cavity prior to in vitro fertilization in a developing country. Arch Gynecol Obstet 288(5):1137–1143. doi:10.1007/s00404-013-2842-8 (Epub 2013 Apr 20)
12. Fadhlaoui A, Khediri Z, Khrouf M, Chaker A, Zhioua F (2013) Diagnostic hysteroscopy before the first in vitro fertilization. For whom? Tunis Med 91(5):310–316
13. Adams SM, Gayer N, Terry V, Murphy CR (2001) Manipulation of the follicular phase: uterodomes and pregnancy—is there a correlation? BioMED Central Pregnancy Childbirth
14. Li Rong, Hao Guiqin (2009) Local injury to the endometrium: its effect on implantation. Curr Opin Obstet Gynecol 21:236–239
15. Takahashi KMT, Tomiyama T, Oka C (2000) High pregnancy rate after hysteroscopy with irrigation of the uterine cavity prior to blastocyst transfer in patients who have failed to conceive after blastocyst transfer. Fertil Steril 74:S206
16. Bohlmann MK, von Wolff M, Luedders DW, Beuter-Winkler P, Diedrich K, Hornemann A, Strowitzki T (2010) Hysteroscopic findings in women with two and with more than two first-trimester miscarriages are not significantly different. Reprod Biomed Online 21(2):230–236. doi:10.1016/j.rbmo.2010.04.016 (Epub 2010 Apr 24)
17. Zhang D, Zhu Y, Gao H, Zhou B, Zhang R, Wang T, Ding G, Qu F, Huang H, Lu X (2010) Overweight and obesity negatively affect the outcomes of ovarian stimulation and in vitro fertilisation: a cohort study of 2628 Chinese women. Gynecol Endocrinol 26(5):325–332. doi:10.3109/09513591003632100