The European Research Journal

http://www.eurj.org

Original Article

e-ISSN: 2149-3189

DOI: 10.18621/eurj.2016.5000185919

Hysteroscopy before the first in vitro fertilization: a 7-year experience from a single center

Safak Hatirnaz[1], Mine Kanat Pektas[2], Alev Ozer[3], Ebru Saynur Hatirnaz[4]

[1]Department of Obstetrics and Gynecology, In Vitro Fertilization Center, Private Konak Hospital, Izmit, Turkey
[2]Department of Obstetrics and Gynecology, Afyon Kocatepe University School of Medicine, Afyonkarahisar, Turkey
[3]Department of Obstetrics and Gynecology, Sutcu Imam University School of Medicine, Kahramanmaras, Turkey
[4]Department of Histology and Embryology, In Vitro Fertilization Center, Private Clinart Hospital, Trabzon, Turkey

ABSTRACT

Objective. This study aims to evaluate the importance of performing hysteroscopy prior to the first attempt of in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) by specifying the incidence of intrauterine pathologies and the success of IVF/ICSI cycle. ***Methods.*** This is a retrospective review of 357 women who underwent their first cycle of IVF/ICSI treatment during a 7- year period. All women had primary infertility due to various factors: Polycystic ovary syndrome (n=101), male factor (n=84), tubal factor (n=78) and unexplained infertility (n=94). ***Results.*** The majority of the patients had normal hysteroscopic findings whereas 29.4% of them had an intrauterine pathology. Abnormal hysteroscopic findings included endometrial polyps (13.7%), submucous myomas (5.9%), uterine septa (4.5%), endometrial adhesions (3.1%), endometritis (1.4%) and cervical stenosis (0.8%). When compared to the women with normal hysteroscopy (n=252), the women with corrected hysteroscopic abnormalities (n=105) had significantly higher fertilization rate (p=0.045), implantation rate (p=0.038), clinical pregnancy rate (p=0.022) and live birth rate (p=0.022). When compared to the women with normal transvaginal ultrasonography and hysteroscopy findings (n=252), the women with normal ultrasonography and abnormal hysteroscopy (n=35) had significantly higher implantation rate (p=0.044), clinical pregnancy rate (p=0.032) and live birth rate (p=0.030). ***Conclusions.*** The utilization of hysteroscopy before the first IVF cycle would allow the detection and treatment of intrauterine pathologies and structural uterine abnormalities that might be responsible for the failure of IVF and, thus, result in improved pregnancy rates.

Eur Res J 2016;2(3):182-187

Keywords: Hysteroscopy; in vitro fertilization; intracytoplasmic sperm injection; infertility; intrauterine pathology

Address for correspondence:
Safak Hatirnaz, MD., Private Konak Hospital, In Vitro Fertilization Center, Department of Obstetrics and Gynecology, Izmit, Turkey
E-mail: safakhatirnaz@gmail.com
Received: April 18, 2016; Accepted: June 18, 2016; Published Online: August 09, 2016

Introduction

In vitro fertilization (IVF) is an effective and expensive treatment which ends up with successful outcome in only a third of treatment cycles. The major underlying reason for this relatively lower success rate is the implantation failure is usually attributed to embryo quality and/or uterine receptivity [1, 2].

It is well known that uterine factor exists in 15% to 20% of the infertile couples. The presence of uterine pathology may negatively affect the chance of implantation. It has been found that the prevalence of uterine pathology can be up to 50% in asymptomatic women with implantation failure. Therefore, the visualization of uterine cavity by means of hysteroscopy has been proposed for women undergoing IVF treatment [3-5].

Hysteroscopy is the gold standard test for the assessment of uterine cavity. It is generally performed as a diagnostic method for the evaluation of abnormal findings detected by hysterosalpingography or saline hysterosonography which are performed during the investigation of infertile women. 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 [6-10].

Current evidence indicates that performing hysteroscopy before initiating an IVF cycle can increase the chance of pregnancy in the subsequent IVF treatment in women who have undergone one or more unsuccessful IVF attempts. However, the routine use of hysteroscopy before starting the first IVF treatment cycle is still a matter of debate [11, 12].

The present study aims to evaluate the importance of performing hysteroscopy prior to the first attempt of IVF or intracytoplasmic sperm injection (ICSI) by 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.

Methods

This is a retrospective review of 357 women who underwent their first cycle of IVF/ICSI treatment at the study center during a 7-year period between January 2007 and January 2014. All women had primary infertility due to various factors: Polycystic ovary syndrome (n=101), male factor (n=84), tubal factor (n=78) and unexplained infertility (n=94). All of the hysteroscopy and the embryo transfer procedures were performed by one operator (S.H.). All patients gave written informed consents before the initiation of treatment. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Hysteroscopic procedures

Before the procedure, all patients had a transvaginal ultrasonography and all abnormal findings were recorded. Hysteroscopy was performed under general 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, Tuttlinger, Germany). After vaginal disinfection and cervical dilatation, the hysteroscope was inserted into the external cervical os, and the scope was inserted through the cervical canal into the cavity with gentle movements. Uterine cavity distention was achieved with normal saline installation.

In patients with noted uterine cavity distortion, or pathology, appropriate surgical management was administered in the same setting. Adhesiolysis was performed with the use of micro scissors. Uterine septa (the diagnosis of which was based on the extent of midline protrusion into the cavity estimated in relation to the length of micro scissors and on its structure) and/or endometrial polyps (with a maximum diameter less than 2 cm) were excised with the use of micro scissors and micro forceps, or with the bipolar resectoscope electro surgery system (Gynecare, Ethicon, Somerville, NJ). In patients with endometrial polyps with a maximum diameter of more than 2 cm or submucous myomas, removal of the lesions was achieved using monopolar diathermy through cutting loops and glycine as distending medium. During the postoperative period, all women were prescribed a four-day-long course of oral doxycycline (100 mg bid) in order to prevent any intrauterine infections.

Assisted reproduction procedures

Controlled ovarian hyper stimulation was started using a long protocol (mid-luteal gonadotropin-releasing hormone (GnRH) analog and stimulation

with recombinant follicle stimulating hormone (recFSH) after confirmation of downregulation), short protocol (GnRH analog from cycle day 2 and recFSH from cycle day 3), or a flexible antagonist protocol (recFSH from cycle day 2 and the addition of a GnRH antagonist when the leading follicles reached 14–15 mm in diameter). Transvaginal ultrasonography guided oocyte retrieval was performed about 35 hours after the administration of 10000 IU of human chorionic gonadotropin. The women were assigned to the same protocol that was used in the previous trial before hysteroscopy.

Based on the infertile couple's diagnostic workup, traditional IVF or ICSI was performed with the respective male partner's spermatozoa. Sequential culture media was used for all procedures. In the case of frozen/thaw cycles, embryo thawing and transfer were synchronized according to the serum luteinizing hormone (LH) surge on a natural cycle. Embryos are usually transferred on day 3 and sometimes on day 5 depending on the decision of the embryologist. All embryo transfers were performed with a catheter under ultrasonography guidance. The number of transferred embryos depended on multiple factors including female age, embryo availability and quality. Luteal phase support was achieved using vaginal progesterone suppositories (200 mg daily).

Statistical analysis

Collected data were analyzed by Statistical Package for Social Sciences version 18.0 (SPSS IBM, Armonk, NY, USA). Continuous variables were expressed as mean±standard deviation (range: minimum-maximum) whereas categorical variables were denoted as numbers or percentages. $p<0.05$ value was accepted as statistically significant.

Results

The demographic characteristics of the participants including age, partner age and duration of infertility are demonstrated in Table 1. The majority of the patients had normal hysteroscopic findings whereas nearly 30% of them had an intrauterine pathology (Table 2). Abnormal hysteroscopic findings included endometrial polyps (13.7%), submucous myomas (5.9%), uterine septa (4.5%), endometrial adhesions (3.1%), endometritis (1.4%) and cervical stenosis (0.8%). Complete resection was achieved in all patients with endometrial abnormalities and the endometrial cavity was assessed with hysteroscopy after the operation. The hysteroscopic appearance of the endometrial pathology was confirmed with the histopathological findings.

Table 1. Demographic characteristics of the 357 participants

Characteristics	Data
Age (years)	28.7±3.4 (23-35)
Partner age (years)	33.1±2.9 (26-40)
Duration of infertility (years)	6.8±1.5 (2-12)

Data are shown as mean±standard deviation (min-max)

Table 2. Hysteroscopic findings of the 357 participants

Findings	Data
Normal hysteroscopy	252 (70.6)
Abnormal hysteroscopy	105 (29.4)
Endometrial polyps	49 (13.7)
Submucous myomas	21 (5.9)
Uterine septa	16 (4.5)
Endometrial adhesions	11 (3.1)
Endometritis	5 (1.4)
Cervical stenosis	3 (0.8)

Data are shown as number of cases (%)

All patients underwent transvaginal ultrasonography and hysterosalpingography before hysteroscopy. No patients had saline infusion sonography. Pre-procedural transvaginal ultrasonography was able to visualize endometrial polyps in 44 patients (89.8%), submucous myomas in 17 patients (81%), uterine septa in only five patients (31.3%) and endometrial adhesions in only two patients (18.2%). Transvaginal ultrasonography failed to specify either endometritis or cervical stenosis in none of the affected patients. Pre-procedural hysterosalpingography was able to detect endometrial polyps in 25 patients (51%), submucous myomas in 10 patients (47.6%), uterine septa in 14 patients (87.5%) and endometrial adhesions in 6 patients (54.5%). Hysterosalpingography was unable to determine either endometritis or cervical stenosis in none of the affected patients.

Table 3 compares the characteristics of the first IVF/ICSI cycles of the participants with respect to the hysteroscopy findings. When compared to the women with normal hysteroscopy, the women with corrected hysteroscopic abnormalities had significantly higher fertilization rate ($p=0.045$), implantation rate ($p=0.038$), clinical pregnancy rate ($p=0.022$) and live birth rate ($p=0.022$).

Table 3. IVF/ICSI characteristics of the participants with respect to hysteroscopy findings

	Normal hysteroscopy (n=252)	Abnormal hysteroscopy (n=105)	*p* value
Age (years)	28.5±3.1	29.1±3.4	0.077
Partner age (years)	32.9±3.1	33.6±2.4	0.124
Duration of infertility (years)	6.6±1.7	7.1±1.9	0.188
Cause of infertility			0.110
Polycystic ovary syndrome	70 (27.8%)	35 (29.5%)	
Male factor	60 (23.8%)	24 (22.9%)	
Tubal factor	57 (22.6%)	21 (20.0%)	
Unexplained infertility	65 (25.8%)	29 (27.6%)	
Collected oocytes per cycle	12.7±5.8	12.1±4.7	0.212
Metaphase II oocytes per cycle	6.6±2.3	6.5±3.1	0.186
Fertilized oocytes per cycle	4.2±1.7	3.4±2.2	0.106
Transferred embryos per cycle	1.5±0.9	1.2±0.4	0.128
Fertilization rate	1058/1663 (63.6%)	357/682 (52.3%)	0.045*
Implantation rate	94/378 (32.9%)	52/126 (41.3%)	0.038*
Clinical pregnancy rate	91/378 (24.1%)	50/126 (39.7%)	0.022*
Live birth rate	89/378 (23.5%)	49/126 (38.9%)	0.022*

*$p<0.05$ was accepted to be statistically significant, IVF/ICSI=in vitro fertilization/intracytoplasmic sperm injection

Table 4 summarizes the characteristics of the first IVF/ICSI cycles of the participants with respect to the combination of transvaginal ultrasonography and hysteroscopy findings. When compared to the women with normal transvaginal ultrasonography and hysteroscopy findings, the women with normal ultrasonography and abnormal hysteroscopy had significantly higher implantation rate (p=0.044), clinical pregnancy rate (p=0.032) and live birth rate (p=0.030).

Discussion

Despite the significant improvement in the area of assisted reproductive techniques, implantation rates per embryo transfer still remain relatively low. The two key factors in question for this problem are the quality of the embryo and the receptivity of the endometrium. Although it is possible to assess the embryo quality by microscopy, there are no definitive methods for the evaluation of endometrial receptivity.

Table 4. IVF/ICSI characteristics of the participants with respect totTransvaginal ultrasonography and hysteroscopy findings

	Normal ultrasonography & Normal hysteroscopy (n=252)	Normal ultrasonography & Abnormal hysteroscopy (n=35)	*p* value
Age (years)	28.5±3.1	29.0±3.2	0.117
Partner age (years)	32.9±3.1	33.3±2.9	0.118
Duration of infertility (years)	6.6±1.7	6.8±1.9	0.184
Cause of infertility			0.108
Polycystic ovary syndrome	70 (27.8%)	10 (28.6%)	
Male factor	60 (23.8%)	8 (22.9%)	
Tubal factor	57 (22.6%)	8 (22.9%)	
Unexplained infertility	65 (25.8%)	9 (25.7%)	
Collected oocytes per cycle	12.7±5.8	12.0±4.7	0.112
Metaphase II oocytes per cycle	6.6±2.3	5.5±3.1	0.186
Fertilized oocytes per cycle	4.2±1.7	3.2±1.2	0.099
Transferred embryos per cycle	1.5±0.9	1.1±0.1	0.125
Fertilization rate	1058/1663 (63.6%)	112/192 (58.3%)	0.055
Implantation rate	94/378 (32.9%)	16/39 (41.0%)	0.044*
Clinical pregnancy rate	91/378 (24.1%)	15/39 (38.5%)	0.032*
Live birth rate	89/378 (23.5%)	14/39 (35.9%)	0.030*

*$p<0.05$ was accepted to be statistically significant, IVF/ICSI=in vitro fertilization/intracytoplasmic sperm injection

It has been hypothesized that structural abnormalities of the uterine cavity such as polyps, myomas, adhesions and septa may impair endometrial receptivity by interfering with implantation. Therefore, it would be prudent to assume that the diagnosis and treatment of those abnormalities can restore uterine cavity, optimize uterine environment and thus improve IVF success rates [13-16].

There is an ongoing debate on the utilization of routine hysteroscopy in the management of infertile women who have no diagnosis or suspicion of intrauterine pathologies. 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. This recommendation is based on the facts that hysteroscopy is an invasive procedure and an intrauterine pathology has inaccurate effects on fertility [17]. Shokeir *et al.* [18] reported that 26% of the patients with normal hysterosalpingography had abnormal hysteroscopic findings. A meta-analysis of six studies also showed that the incidence of uterine abnormalities in patients undergoing hysteroscopy ranges between 10 and 59% [12]. Data presented in this meta-analysis indicates that hysteroscopy performed in the cycle preceding the ovarian stimulation cycle could improve IVF outcome in asymptomatic patients who were undergoing their first IVF cycle and who had normal transvaginal ultrasonography findings. Both the clinical pregnancy and live birth rates were found to be higher in the hysteroscopy group than the control group. On the other hand, these data should be interpreted carefully as there was considerable methodological and statistical heterogeneity among the reviewed studies. In addition, only one of the six studies was randomized and was published as a conference abstract [12].

As for the present study, nearly 30% of the women who were to undergo their first IVF/ICSI cycle were diagnosed with an intrauterine pathology and only 35.5% of the pregnancies conceived by first IVF/ICSI attempt occurred in women who had intrauterine pathologies that were corrected by hysteroscopy. These findings suggest that hysteroscopy may not be as effective as it has been anticipated in women who would have their first IVF/ICSI treatment. The relatively narrow extent of improvement in IVF outcome after hysteroscopy may be attributed to the lower burden of intrauterine pathology expected in those having their first IVF cycle. That is, the women having their first IVF cycle probably have different fertility potentials compared to those who have gone through one or more failed IVF attempt. Therefore, the degree of improvement in IVF outcome observed after hysteroscopy prior to the first IVF cycle seems to be lower than that observed after hysteroscopy following previous IVF failure. This may consequently result in a higher number of women who should undergo hysteroscopy in order to achieve an additional clinical pregnancy [19, 20].

Office hysteroscopy is a simple, safe and minimally invasive procedure that could be readily integrated into IVF programs in most assisted reproduction centers. The possible benefits of hysteroscopy include the correction of intrauterine pathologies, procurement of easier embryo transfer, provision of more accurate embryo placement and enhancement of endometrial receptivity secondary to endometrial stimulation [21].

The limitations of the study

Despite the statistical similarities in demographic and clinical characteristics of the normal and abnormal hysteroscopy groups, there was a significant increase in the implantation, clinical pregnancy and live birth rates. This increase implies that the utilization of hysteroscopy before the first IVF cycle improves the pregnancy rates. However, the power of these findings is limited by its retrospective design, relatively small and heterogeneous cohort, absence of standardization in ovulation induction protocols and lack of longitudinal data related with the ultimate fertility outcome of the women who had hysteroscopic treatment of intrauterine pathologies.

Conclusions

The utilization of hysteroscopy before the first IVF cycle would also allow the detection and treatment of intrauterine pathologies and structural uterine abnormalities that may be responsible for the failure of IVF and, thus, result in improved pregnancy rates. This would also protect the infertile couples from additional costs of IVF cycles, where failures occur because an intrauterine pathology is missed on other screening tools such as hysterosalpingography.

Further research is warranted to clarify the benefits of hysteroscopy in asymptomatic women who would undergo their first IVF/ICSI cycle.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

References

[1] Coughlan C, Ledger W, Wang Q, Liu F, Demirol A, Gurgan T, et al. Recurrent implantation failure: definition and management. Reprod Biomed Online 2014;28:14-38.
[2] Timeva T, Shterev A, Kyurkchirev S. Recurrent implantation failure: the role of the endometrium. J Reprod Infertil 2014;15:173-83.
[3] Fatemi HM, Popovic-Todorovic B. Implantation in assisted reproduction: a look at endometrial receptivity. Reprod Biomed Online 2013;27:530-8.
[4] Moini A, Kiani K, Ghaffari F, Hosseini F. Hysteroscopic findings in patients with a history of two implantation failures following in vitro fertilization. Int J Fertil Steril 2012;6:27-30.
[5] Cenksoy P, Ficicioglu C, Yildirim G, Yesiladali M. Hysteroscopic findings in women with recurrent IVF failures and the effect of correction of hysteroscopic findings on subsequent pregnancy rates. Arch Gynecol Obstet 2013;287:357-60.
[6] Pundir J, El Toukhy T. Uterine cavity assessment prior to IVF. Womens Health (Lond) 2010;6:841-7; quiz 847-8.
[7] Papathanasiou A, Bhattacharya S. Prognostic factors for IVF success: diagnostic testing and evidence-based interventions. Semin Reprod Med 2015;33:65-76.
[8] Bosteels J, Weyers S, Puttemans P, Panayotidis C, Van Herendael B, Gomel V, et al. The effectiveness of hysteroscopy in improving pregnancy rates in subfertile women without other gynaecological symptoms: a systematic review. Hum Reprod Update 2010;16:1-11.
[9] Bettocchi S, Achilarre MT, Ceci O, Luigi S. Fertility-enhancing hysteroscopic surgery. Semin Reprod Med 2011;29:75-82.
[10] Bosteels J, Kasius J, Weyers S, Broekmans FJ, Mol BW, D'Hooghe TM. Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities. Cochrane Database Syst Rev 2015;2:CD009461.
[11] Makrakis E, Pantos K. The outcomes of hysteroscopy in women with implantation failures after in-vitro fertilization: findings and effect on subsequent pregnancy rates. Curr Opin Obstet Gynecol 2010;22:339-43.
[12] Pundir J, Pundir V, Omanwa K, Khalaf Y, El-Toukhy T. Hysteroscopy prior to the first IVF cycle: a systematic review and meta-analysis. Reprod Biomed Online 2014;28:151-61.
[13] Coughlan C, Ledger W, Wang Q, Liu F, Demirol A, Gurgan T, et al. Recurrent implantation failure: definition and management. Reprod Biomed Online 2014;28:14-38.
[14] Vlachadis N, Vrachnis N, Economou E, Siristatidis C. Zooming in on the definition of "recurrent implantation failure". Reprod Biomed Online 2014;29:144-5.
[15] Evans-Hoeker EA, Young SL. Endometrial receptivity and intrauterine adhesive disease. Semin Reprod Med 2014;32:392-401.
[16] Campo S, Campo V, Benagiano G. Adenomyosis and infertility. Reprod Biomed Online 2012;24:35-46.
[17] Crosignani PG, Rubin BL. Optimal use of infertility diagnostic tests and treatments: The ESHRE Capri Workshop Group. Hum Reprod 2000;15:723-32.
[18] Shokeir TA, Shalan HM, EI Shafei MN. Significance of endometrial polyps detected hysteroscopically in eumenorrheic infertile women. J Obstet Gynecol 2004;30:84-9.
[19] Fatemi HM, Kasius JC, Timmermans A, van Disseldorp J, Fauser BC, Devroey P, et al. Prevalence of unsuspected uterine cavity abnormalities diagnosed by office hysteroscopy prior to in vitro fertilization. Hum Reprod 2010;25:1959-65.
[20] Yu HT, Wang CJ, Lee CL, Huang HY, Chen CK, Wang HS. The role of diagnostic hysteroscopy before the first in vitro fertilization/intracytoplasmic sperm injection cycle. Arch Gynecol Obstet 2012;286:1323-8.
[21] Di Spiezio Sardo A, Di Carlo C, Minozzi S, Spinelli M, Pistotti V, Alviggi C, et al. Efficacy of hysteroscopy in improving reproductive outcomes of infertile couples: a systematic review and meta-analysis. Hum Reprod Update 2016;22:479-96.