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REPRODUCTIVE MEDICINE

# Hysteroscopic findings in women with recurrent IVF failures and the effect of correction of hysteroscopic findings on subsequent pregnancy rates

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**Abstract**
*Introduction* Our aim is to evaluate the incidence of unrecognized uterine abnormalities in cases with recurrent IVF failure by screening office hysteroscopy (OH), and impacts of treatment of hysteroscopic findings on the success rate of IVF.
*Materials and methods* The retrospective and descriptive study was conducted at assisted reproduction unit in a tertiary medical center. One hundred and fifty-seven patients with a history of recurrent IVF failures underwent hysteroscopy between May 2009 and March 2012. Hysteroscopy (diagnostic or operative, as appropriate) was performed to evaluate the endometrial cavity in patients with two or more IVF failures and Incidence of abnormal hysteroscopic findings and the clinical pregnancy rate (CPR) in subsequent IVF cycles were assessed.
*Results* In all, 44.9 % of the patients included in this study had abnormal hysteroscopic findings and 75 women (48.1 %) became pregnant following hysteroscopy. Of these pregnancies, 36 occurred in women with corrected endometrial pathology, the majority of which was identified as endometrial polyps. Implantation rate and clinical pregnancy rate were statistically significant increased after polipectomy.
*Conclusion* Abnormal findings on hysteroscopy are significantly higher in patients with previous ART failure and hysteroscopy could be seen as a positive prognostic factor for achieving pregnancy in subsequent IVF procedure in women with a history of RIF.

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## Introduction

Despite advances in the field of assisted reproductive techniques (ART), several IVF cycles fail to achieve pregnancy. Specific identified factors associated with repeated IVF failures (RIF) include decreased endometrial receptivity such as uterine cavity abnormalities, inadequate endometrial thickness, the medical condition of the mother (e.g. thrombophilia and abnormal immunologic response), defective embryonic development such as genetic abnormalities affecting partners, gametes, or embryos, increased thickness/hardening of the zona pellucida, and multifactorial (e.g. endometriosis, presence of hydrosalpinges) [1].

Repeated implantation failure occurs when transferred embryos fail to implant after several IVF treatment procedures [2]. Implantation after in vitro fertilization (IVF) depends on the oocyte biology, embryonic development and endometrial receptivity or a combination of all [3]. However, structural abnormalities of the uterus may adversely affect the ART outcomes using the high-quality embryos for transfer due to the implantation failure or spontaneous abortion. Therefore, recurrent implantation failure may be due to unrecognized uterine pathology. Intrauterine pathologies are present in 25 % of infertile patients [4]. Evaluation of the uterine cavity may become an important step before ART procedures and it might be routinely performed in the basic evaluation of infertile women, especially women with RIF. Structural abnormalities of the uterus are also known risk factors for recurrent spontaneous miscarriages [5]. Bohlmann et al. investigated hysteroscopic results in women with a history of two or

more consecutive miscarriages and did not find significant differences in the rates of uterine anomalies and prevalence of acquired (adhesions, polyps, fibroids) and congenital uterine anomalies (septate or bicornuate uterus, etc.). However, uterine anomalies are frequently found in patients with recurrent spontaneous miscarriages. Due to the high rate of uterine anomalies in patients with recurrent miscarriages and a possible therapeutic approach, hysteroscopy might be a diagnostic option for these patients [6].

Transvaginal ultrasonography, hysterosalpingography, saline infusion sonography and hysteroscopy could be used as tools to evaluate the uterine cavity [7]. Hysteroscopy is especially performed in cases with suspected intrauterine pathology and recurrent IVF failure because uterine cavity abnormalities can be easily assessed by hysteroscopy. Diagnostic hysteroscopy is currently considered to be the gold standard for the evaluation of the endometrial cavity [8].

The aim of the present study was to evaluate the incidence of unrecognized uterine abnormalities in cases with recurrent IVF failure by screening with office hysteroscopy (OH), and impacts of treatment of hysteroscopic findings on the success rate of IVF.

## Materials and methods

This retrospective study was based on the analysis of the medical records of all patients that underwent diagnostic office hysteroscopy to evaluate the endometrial cavity by the same operator (C.F.) due to a history of at least two consecutive implantation failures despite the transfer of high-quality embryos in our IVF unit between May 2009 and March 2012. It was conducted at the Department of Obstetrics and Gynecology, Yeditepe Univesity School of Medicine, Istanbul, Turkey. The study protocol was approved by the Ethical Committee of the Yeditepe University. 157 women were included in the present study. Inclusion criteria were primary infertile patients undergoing IVF treatment, with normal uterine finding according to HSG, BMI $\leq$ 25 kg/m$^2$ and between 18 to 44 years-old. Patients were excluded from the study if they had uterine factor of infertility, abnormal findings on HSG or abnormal transvaginal ultrasonography, previous intrauterine surgery, or contraindication for hysteroscopy. Routine infertility investigations were performed in all patients. In our IVF unit, evaluation of the patients, hysteroscopic procedures and the embryo transfer are performed by the same operator (C.F.) and we routinely recommend office hysteroscopy to assess the endometrial cavity in patients with a history of at least two consecutive implantation failures before further IVF cycles.

All patients underwent OH in the early follicular phase, between the 7th and 11th day of the cycle. Hysteroscopy was performed under general anesthesia using office and operative hysteroscope (Karl Storz, Tuttlinger, Germany). Hysteroscopic findings were classified as normal hysteroscopic findings in 86 patients (absence of uterine anomaly, $N = 86$) or abnormal pathology in 70 patients (endometrial polyp, polypoid endometrium, arcuate uterus, endometrial adhesion). In patients with detected abnormal pathology, appropriate surgical management was performed. Adhesiolysis was performed with the use of microscissors and also endometrial polyps were excised with the use of the bipolar resectoscope electrosurgery system.

The following controlled ovarian stimulation protocols were used: luteal leuprolide acetate down regulation (long) or antagonist protocol and stimulation with recombinant follicle stimulating hormone (recFSH). HCG was administered when at least two follicles reached a mean diameter of >17 mm. Transvaginal ultrasound-guided oocyte retrieval was performed 36 h after hCG administration. Fertilization of the oocytes was performed using the standard ICSI techniques. Patients with three or more eight-cell embryos on day three were offered blastocyst transfer. Transfers were performed with the Wallace catheter (Smiths medical international Ltd., Hythe, Kent, UK) using after load transfer technique under abdominal ultrasonographic guidance. Luteal phase support was achieved using vaginal crinone gel (Crinone 8 %, 90 mg; Merck Serono, Central Pharma Ltd., Bedfordshire, UK) daily. Serum quantitative β-hCG levels were obtained 12 days after ET. A clinical pregnancy was defined as the presence of a fetal sac visualized by transvaginal ultrasound examination.

### Statistical analysis

Analyses were done using the statistical package for the Social Sciences, version 20 (SPSS, Chicago, IL). Data were reported as mean ± SD or number and percentage. The Chi-square test was used to compare categorical variables. $P < 0.05$ was considered significant.

## Results

156 subjects were included in the analysis. The patient demographics including mean age (years), mean duration of infertility (years), mean number of previous ART trials and etiology of infertility are presented in Table 1. Abnormal hysteroscopic findings, including endometrial polyp, polypoid endometrium, arcuate uterus and endometrial adhesion, were observed in 70 of 156 patients (44.9 %) (Table 2). 86 patients (55.1 %) did not have any uterine pathology on hysteroscopy. Endometrial polyp (25 %) and intrauterine adhesions (9 %) were the most common hysteroscopic abnormalities. 75 women (48.1 %)

**Table 1** Patients' characteristics

| Parameters | Values ($N = 156$) |
|---|---|
| Age (years) | 33.04 ± 5.13 |
| Duration of infertility (years) | 6.01 ± 4.33 |
| Etiology of infertility | |
| Male factor | 69 (44.2 %) |
| Ovulatory disorder | 29 (18.6 %) |
| Tubal/peritoneal factor | 12 (7.7 %) |
| Combined factors | 1 (0.6 %) |
| Unexplained | 45 (28.8 %) |
| Number of previous ART trials | 2.31 ± 0.2 |

**Table 2** Distribution of hysteroscopic findings

| Hysteroscopic findings | No. of cases (%) |
|---|---|
| Normal hysteroscopic findings | 86 (55.1) |
| Abnormal hysteroscopic findings | 70 (44.9) |
| Endometrial polyps | 39 (25) |
| Polypoid endometrium | 13 (8.3) |
| Endometrial adhesions | 14 (9) |
| Arcuat uterus | 4 (2.6) |

became pregnant following hysteroscopy. Of these pregnancies, 36 occurred in women with corrected endometrial pathology, the majority of which was identified as endometrial polyps. Although implantation rate and clinical pregnancy rate were significantly increased after polipectomy ($p = 0.001$), in patients with endometrial adhesion after adhesiolysis, the increase was not statistically significant ($p > 0.05$). Of the 69 infertile patients with male factor etiology, 28 had also an uterine abnormality on hysteroscopy (endometrial polyp in 21 of patients, endometrial adhesion in one, polypoid endometrium in six, arcuate uterus in two) and 20 of these patients became pregnant after corrected endometrial pathology.

## Discussion

Clearly, there are many factors that contribute to the success or failure of an IVF cycle. Therefore, recurrent IVF failure may result from multiple causes related to oocyte, embryo and/or endometrium. The uterine abnormalities may be one of these reasons. The causative role of unrecognized uterine in recurrent IVF failure and the impact of the treatment of the uterine pathology on pregnancy rates after ART are still not clear. The European Society of Human Reproduction and Embryology (ESHRE) guidelines indicate that the hysteroscopy is unnecessary, unless it is used for confirmation and treatment of a doubtful intrauterine pathology [9].

Hysteroscopy is generally considered in basic clinical practice as the gold standard procedure to evaluate uterine cavity and identify uterine abnormalities with the ability to allow direct visualization of the uterine cavity [4, 10–13]. Hysteroscopy should be a part of the basic routine investigation of women with RIF to evaluate uterine cavity and correct uterine cavity abnormalities to potentially improve pregnancy rates. A prospective randomized study demonstrated that hysteroscopy should be a basic tool for first line infertility investigation to evaluate uterine cavity abnormalities, because detection and treatment of intrauterine lesions by office hysteroscopy can improve the pregnancy outcome [14].

The presence of uterine pathology was 10–62 % of women with infertility and in 19–50 % of women who failed to achieve pregnancy with assisted reproductive technologies [15–17]. Several studies demonstrated that hysteroscopic correction of the uterine abnormality including endometrial polyps, submucous fibroids, intrauterine adhesions and uterine septum improves the spontaneous pregnancy rates [18]. In addition, Elmorsy et al. [19] found that of 23 patients (45 %) with abnormal hysteroscopy finding, 15 patients (65.2 %) achieved pregnancy after correction of their uterine abnormalities. Aletebi (2010) also indicated that of 132 patients with a history of repeated implantation failures, 50 patients (38 %) had abnormal findings on hysteroscopy and 55 % of patients with abnormal hysteroscopic findings got pregnant in subsequent IVF cycles after hysteroscopy [20]. Likewise, a recent systematic review including 1,691 patients with two or more failed IVF attempts demonstrated that office hysteroscopy is highly beneficial in patients with a history of RIF and significantly improve the pregnancy rate (PR) in the subsequent IVF cycle [21].

The results of current study were similar to literature and revealed that 44.9 % of patients with a history of RIF had uterine abnormalities detected with hysteroscopy, while endometrial polyp was the most common hysteroscopic abnormality in patients with recurrent IVF failure. Moreover, the significantly improved implantation and clinical pregnancy rates were detected in patients with endometrial polyp after polypectomy. Of 69 infertile patients with male factor, 40.5 % had concomitantly an uterine abnormality, detected on hysteroscopy. Therefore, abnormal uterine pathology could be considered in patients with RIF and male factor infertility. On the other hand, because hysteroscopy is an invasive procedure, there is an ongoing debate about the real significance of it on detecting and correcting intrauterine pathologies. Despite the debates, hysteroscopy is the gold standard for the

evaluation of the endometrial cavity and cost-effective when compared to the cost of RIF.

In conclusion, according to our results and the current literature, abnormal findings detected with hysteroscopy are significantly higher in patients with previous ART failure and hysteroscopy could be regarded as a positive prognostic factor for achieving pregnancy in subsequent IVF treatment in women with a history of RIF. The evaluation of the uterine cavity may routinely be considered as part of the assessment of women with RIF. In addition, the surgical treatment of uterine abnormalities, especially endometrial polyps, could be helpful to improve pregnancy rates. On the other hand, well-designed randomized controlled trials are needed before firm conclusions can be made.

**Conflict of interest** None.

## References


1. Margalioth EJ, Ben-Chetrit A, Gal M, Eldar-Geva T (2006) Investigation and treatment of repeated implantation failure following IVF–ET. Hum Reprod 21:3036–3043
2. Alex S, Neri L (2012) Repeated implantation failure: clinical approach fertility and sterility, vol 97, No. 5
3. Fatemi HM, Kasius JC, Timmermans A, van Disseldorp J, Fauser BC, Devroey P et al (2010) Prevalence of unsuspected uterine cavity abnormalities diagnosed by office hysteroscopy prior to in vitro fertilization. Hum Reprod 25:1959–1965
4. Levi Setti PE, Colombo GV, Savasi V, Bulletti C, Albani E, Ferrazzi E (2004) Implantation failure in assisted reproduction technology and a critical approach to treatment. Ann N Y Acad Sci 1034:184–199
5. Rai R, Regan L (2006) Recurrent miscarriage. Lancet 368(9535): 601–611
6. 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 original research article. Reprod Biomed Online 21(2):230–236
7. Bozdag G, Aksan G, Esinler I, Yarali H (2008) What is the role of office hysteroscopy in women with failed IVF cycles? Reprod Biomed Online 17:410–415
8. Soares SR, Barbosa dos Reis MM, Camargos AF (2000) Diagnostic accuracy of sonohysterography, transvaginal sonography, and hysterosalpingography in patients with uterine cavity diseases. Fertil Steril 73:406–411
9. Crosignani PG, Rubin BL (2000) Optimal use of infertility diagnostic tests and treatments. The ESHRE Capri Workshop Group. Hum Reprod 15:723–732
10. Golan A, Eilat E, Ron-El R, Herman A, Soffer Y, Bukovsky I (1996) Hysteroscopy is superior to hysterosalpingography in infertility investigation. Acta Obstet Gynecol Scand 75(7):654–656
11. Bosteels J, Weyers S, Puttemans P, Panayotidis C, Van Herendael B, Gomel V et al (2010) The effectiveness of hysteroscopy in improving pregnancy rates in subfertile women without other gynaecological symptoms: a systematic review. Hum Reprod Update 16:1–11
12. Bettocchi S, Ceci O, Nappi L, Di Venere R, Masciopinto V, Pansini V et al (2004) Operative office hysteroscopy without anesthesia: analysis of 4,863 cases performed with mechanical instruments. J Am Assoc Gynecol Laparosc 11:59–61
13. Siristatidis C, Chrelias C, Salamalekis G, Kassanos D (2010) Office hysteroscopy: current trends and potential applications: a critical review. Arch Gynecol Obstet 282:383–388
14. Rama Raju GA, Shashi Kumari G, Krishna KM, Prakash GJ, Madan K (2006) Assessment of uterine cavity by hysteroscopy in assisted reproduction programme and its influence on pregnancy outcome. Arch Gynecol Obstet 274:160–164
15. Gaglione R, Valentini AL, Pistilli E, Nuzzi NP (1996) A comparison of hysteroscopy and hysterosalpingography. Int J Gynecol Obstet 52:151–153
16. (2004) National institute for clinical excellence guidelines tools to optimize the IVF–ET procedure and its cost effectiveness, RCOG Press, London
17. Oliveria FG, Abdelmasih VG, Diamond MP, Dozortezef D, Nagy ZP, Abdelmassih R (2003) Uterine cavity findings and hysteroscopy interventions in patients undergoing in vitro fertilization–embryo transfer who repeatedly cannot conceive. Fertil Steril 80:1371–1375
18. Taylor E, Gomel V (2008) The uterus and fertility. Fertil Steril 89(1):1–15
19. Hossam ES, Mahmoud E, Mostafa K (2012) Eissa routine office hysteroscopy prior to ICSI and its impact on assisted reproduction program outcome: a randomized controlled trial. Middle East Fertil Soc J 17:14–21
20. Fatma A (2010) Hysteroscopy in women with implantation failures after in vitro fertilization: findings and effect on subsequent pregnancy rates. Middle East Fertil Soc J 15:288–291
21. El-Toukhy T, Sunkara SK, Coomarasamy A, Grace J, Khalaf Y (2008) Outpatient hysteroscopy and subsequent IVF cycle outcome: a systematic review and metaanalysis. Reprod Biomed Online 16:712–719