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### Findings on hysteroscopy in patients with in vitro fertilization by intra cytoplasmic single sperm injection and embryo transfer failures

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Despite numerous developments in the field of assisted reproduction, the implantation rate remains low. Intrauterine and endometrial integrity abnormalities such as thin endometrium, altered expression of adhesive molecules and immunological factors may decrease endometrial receptivity, whereas chromosomal and genetic abnormalities of the male sperm or female ovarian defects, embryonic aneuploidy or zona hardening are embryonal reasons for the failure of implantation.<sup>1</sup> Among the various etiologies that were described, endometrial regularity played an important role in infertility and success of in vitro fertilization (IVF) programs. Hysterosalpingography, transvaginal sonography, and saline contrast hysterosonography are useful tools for detecting endometrial irregularity, however, hysteroscopy showed to be more accurate in the evaluation of intracavity pathology in comparison with any other paraclinical study.<sup>2</sup> Although the previous trials showed the usefulness of uterine reassessment by hysteroscopy in women with 2 IVF failures, but they did not exclude the other probable contribution factors such as thrombophilia, and immunological disorders. The objective of our study, was to evaluate the hysteroscopic abnormalities in patients with unexplained repeated in vitro fertilization by intra cytoplasmic single sperm injection and embryo transfer (IVF/ICSI-ET) failure after excluding all other possible ethological factors, with special concerns on age and duration of infertility.

This study was performed in a time period of 3 years (from July 2003 - October 2006), at the Avesina Infertility Clinic Tehran, Iran, in infertile women (25-38 years old) who referred with the history of more than 2 previous IVF/ICSI-ET failures despite transfer of a minimum 3 good-quality embryos in each attempt. After taking history, physical exam, routine hematological, biochemical, hormonal tests, spermiogram, also flow cytometry, autoantibodies profile like anti-Cardiolipin (aCL), Lupus Anticoagulant (LA), anti-Phosphatidylserine(aPS), anti-hosphatidylethanolamine (aPE), antinuclear antibodies (ANA), anti DNA, and thrombophilia profile like methylenetetrahydrofolate reductase (MTHFR) gene-prothrombin gene, factor V Leiden gene, serum homocystein, protein C, Protein S, anti-thrombin III, and karyotype have accomplished in all women. All infertile women underwent transvaginal ultrasonography (Pie Medical, Model 260

Corvus, Maastricht, The Netherlands) with convex 7.5 MHz transvaginal ultrasound probe. We excluded thrombophilia, immunological, genetic problems, and also severe male factor infertility in selected patients of our study. After obtaining informed consent, the selected patients underwent a diagnostic and/ or operative hysteroscopy (rigid hysteroscope, Olympus) in early follicular phase of the cycle (7th and 11th day of the cycle) under general anesthesia, using dextrose 5% as distention medium. After exclusion of other probable causes of ICSI /IVF-ET failures, the findings on hysteroscopy were compared with sonographic findings, then evaluated and analyzed with special concern to age and duration of infertility.

The data were analyzed using the Statistical Package for Social Sciences Version 11.5 and Fisher exact, chi-square, and MC-Nemar tests. A  $p < 0.05$  was considered statistically significant, 89 infertile women were selected for this study. The mean age was  $(31.02 \pm 3.28)$  years, the mean duration of infertility  $(8.56 \pm 2.91)$  years and mean numbers of previous embryo transfer (ET) attempts were  $(2.78 \pm 0.74)$ . Abnormal sonographic findings were observed in 47 cases (52.8%) in which endometrial irregularity, hyperplasia, and polyps were the most common. Abnormal hysteroscopic findings were observed in 53 cases (59.5%) in which intrauterine adhesions, endometrial hyperplasia, and polyps, were the most common (Table 1). Abnormal findings in patients with  $\leq 30$  years were not significantly more compared with older patients, using chi-square=0.44 ( $p=0.51$ ). However, significantly more hysteroscopic abnormalities were found in the infertile patients with more than 8 years infertility, (chi-square=4.7,  $p=0.03$ ). Also, single polyp and endometrial hyperplasia were not significantly more in patients with  $\leq 30$  years old, and  $\leq 8$  years infertility in comparison with older patients and longer duration of infertility using Fisher exact test (one tail) ( $p=0.27$ ). According to our results, using McNemar test ( $\chi^2=4$ ,  $p < 0.05$ ), sonography is more specific (100%) but not sensitive (88.6%) compared to the hysteroscopy, with false negative rate of 19.4%. However, hysteroscopy showed to be more sensitive and specific in the evaluation of intracavity pathology in comparison with sonography in selected patients. Structural abnormalities correlated with the presence of pathological abnormalities were seen in 94.3% ( $n=50$ ) of cases. Also in 13.2% ( $n=7$ ) of cases, nonspecific endometritis was reported. Previous studies reported a high incidence of intrauterine abnormalities related to IVF-ET failure.<sup>3</sup> It has been shown cervical abnormalities (synechia, polyp, and false passage) and intrauterine abnormalities (polyp, hyperplasia, adhesions and submucous myoma) in half of the cases after 2 implantation failures in IVF.<sup>4</sup> Also, uterine abnormalities have been shown in women (18%) with the history of  $\leq 3$  IVF-ET failures who had normal

**Table 1** - Findings on hysteroscopy in the study group

Characteristics	Total n (%)	Age		Infertility	
		≥30 years (N=54)	<30 years (N=35)	≥8 years (N=55)	<8 years (N=34)
Findings on hysteroscopy (%)	53 (59.5)	34	19	37	16
Submucosal myoma	5 (9.8)	5	0	4	1
Single large polyp	11 (20.7)	8	3	9	2
Polypoid endometrium	10 (18.8)	6	4	6	4
Endometrial hyperplasia	10 (18.8)	8	2	7	3
Uterine cavity hypoplasia	4 (7.8)	3	1	2	2
Adhesions	7 (13.7)	3	4	5	2
Endocervical polyp	3 (5.8)	1	2	0	3
Multiple lesions	3 (5.8)	2	1	3	0
Without any finding	36 (40.44)	20	16	18	18

initial hysteroscopy.<sup>5</sup> According to the results of our study, abnormal hysteroscopic findings were observed in 59.5% of the cases with repeated IVF failures which are higher than the result of previous studies due to the exclusion of the other possible reasons of repeated ET failures. We showed sonography as specific, but not sensitive method compared to the hysteroscopy. The sensitivity and specificity of sonography in comparison with hysteroscopy were 91% and 83% with the false positive rate of 9.2%, and false negative rate of 5.1% in Ragni study.<sup>2</sup> We treated the structural abnormalities at the time of hysteroscopy, and we had no early, late, major, or even minor complications in our series. The pathological reports confirmed the observed lesions in 94.7%, with nonspecific endometritis in 13.2 % (n= 7) of cases.

It has been shown that in elderly women, age-related uterine pathology such as submucous myoma, endometrial hyperplasia, and polyps were more prominent, other than in younger patients, other uterine lesions such as adhesions, and tubal ostia occlusion were more common.<sup>5</sup> In our experiences, we have seen single polyp and endometrial hyperplasia more (but not significant) in the patients with ≤30 years old rather than the younger group (*p*-value= 0.78). Also there were more (but not significant) abnormalities especially single polyp, polypoid endometrium, and hyperplasia in group of the patient with more than 8 years infertility (*p*=0.08, *p*=0.06, and *p*=0.12).

This communication, emphasis the need of hysteroscopy in patients with unexplained repeated IVF/ICSI-ET failure According to our experience, it seems legitimate to perform hysteroscopy in women who had 2 IVF-ET failures before trying any other procedure after excluding all other possible etiological or accompanying factors. The results were significant in the group with longer duration of the infertility. Our study showed that the direct view of the uterine cavity by hysteroscopy was more sensitive and specific, and

more accurate in the evaluation of intracavity pathology in comparison with sonography in patients with unexplained repeated IVF failures. Also, hysteroscopy proved to be a very useful, accurate and safe method of assessing uterine and endometrial functional status in patients with repeated IVF/ICSI-ET failures after excluding other possible reason for implantation failure, although it couldn't evaluate uterine and endometrial functional status.

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