ORIGINAL ARTICLE

Role of Hysteroscopy Prior to Assisted Reproductive Techniques in Patients with Previous IVF Failure

[1]Rutvij Jay Dalal, [2]Hrishikesh D Pai, [2]Nandita P Palshetkar

[1]Fellow of the National Board of Examinations (FNB) in the Subspecialty of Reproductive Medicine, Lilavati Hospital and Research Center Mumbai, Maharashtra, India

[2]Lilavati Hospital and Research Center, Mumbai, Maharashtra, India

Correspondence: Rutvij Jay Dalal, 20, Shreerang Society, Near Football Ground, Kankaria, Ahmedabad-380022, Gujarat India, Phone: 9930273377, 09537673993, e-mail: rutvij.dalal@gmail.com

ABSTRACT

Background: There have been numerous advances in the area of assisted reproduction. Among the various reasons of implantation failure, intrauterine lesions play an important role.

Objective: The aim of the present study is to evaluate the role of hysteroscopy prior to any assisted reproductive technique in patients who had previous one or more failed IVF cycle(s).

Materials and methods: It is a retrospective study of 248 women who attended our infertility clinic over a period of 18 months, who had a variable number of failed IVF cycles previously.

Results: Out of the 248 women studied, in 62 (25%) patients, intrauterine pathology was detected, which when rectified by hysteroscopy gave a considerable increase in pregnancy rate.

Conclusion: According to this study it can be concluded that evaluating the uterine cavity is an important step before any assisted reproductive procedure.

Keywords: Assisted reproduction, Hysteroscopy, Infertility, Intrauterine pathology, IVF failure.

INTRODUCTION

In the past few decades many assisted reproductive techniques have been invented raising the hopes of infertile couples. However, still many patients have remained without success even with these procedures. It has been known that the uterine factor plays about a 15 to 20% role in contributing to female infertility. Intrauterine pathologies like fibroids, polyps, septae, adhesions, etc. act by hindering the path of the ascending spermatozoa, preventing implantation of the embryo or by hindering the growth of the developing fetus. All of them have been shown to decrease the implantation rates and also take-home baby rates after assisted reproductive techniques. Hence, ruling out any evidence of any intrauterine pathology by hysteroscopy becomes an important step before subjecting the patient to any of the assisted reproductive techniques (ART).

With the invention of miniature hysteroscopes, it is possible to perform hysteroscopy in an office setup, with or without local or general anesthesia, for diagnostic and certain therapeutic interventions.[1]

In the present study, we have evaluated intrauterine pathologies with hysteroscopy and *in vitro* fertilization-embryo transfer (IVF-ET) outcome in patients with unexplained previous IVF cycle failures, after excluding all other possible etiological factors.

OBJECTIVE

The aim of the present study is to evaluate the importance of subjecting the patient to hysteroscopy prior to ART, to study the incidence of intrauterine pathology in the selected group, and to study the success of IVF posthysteroscopic procedures in women with previous IVF failures.

MATERIALS AND METHODS

This is a retrospective study of 248 women who attended our infertility clinic over a period of 18 months (January 2009 to June 2010).

The inclusion criteria for the study were the women who had one or more previous IVF cycle/cycles failure. All patients who had previous one or more cycle(s) of IVF failure were counseled and consented for undergoing hysteroscopy. All those who did not consent were excluded from the study. Only those patients meant for repeat IVF-ICSI cycle were chosen. Those for oocyte/embryo donation cycles and also those for frozen

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embryo transfer cycles were all excluded. Only those patients in whom hysteroscopy was not performed earlier for at least one year were included, for those in whom it was done within a year at any hospital were all excluded from the study. Also, those patients undergoing the short or antagonist protocol stimulation for IVF cycle were all excluded and all the selected patients in the study underwent a similar down-regulation and stimulation protocol.

Technique

All women in whom hysteroscopy was done were informed about the technique and the potential risks in the form of a written consent. All the selected women underwent the procedure of hysteroscopy under general anesthesia in the lithotomy position.

A rigid hysteroscope was put into the uterine cavity under visual control after cervical dilatation of 5 to 9 mm. Normal saline was used as the distension medium, keeping the uterine pressure between 100 and 150 mm of mercury.

Intrauterine lesions, such as synechiae, polyps, submucosal myomas, septae, and so on, were treated with scissors and resectoscope. Every hysteroscopy was followed by endometrial biopsy or curettage, and the material obtained was sent for histopathological examination. The purpose of that was to know about the phase of the ovarian cycle, health of the endometrium, and also to rule out any latent infection like tuberculosis that could be present in these group of patients.

Protocol of Stimulation in Subsequent IVF/ICSI Attempts

Depending upon the diagnosis and procedure done, the women were either stimulated immediately or after some period for IVF/ICSI cycle. The women were down-regulated with oral contraceptive pills and gonadotropin-releasing hormone (GnRH) analogues. Injection of HMG (human menopausal gonadotropin) or pure/recombinant FSH was started from the second day of menses and simultaneous follicular monitoring was done from the sixth day. Injection of hCG (human chorionic gonadotropin) was given when a minimum of three leading follicles were 16 to 18 mm in size. Thirty-six hours later, oocyte retrieval was performed followed by IVF/ICSI, and then the embryo transfer was finally carried out 2-3 days later. The dose of the gonadotropins were individualized by various parameters like the age of the patient, body mass index (BMI), day 2 FSH and Estradiol levels, Inhibin-B, AMH and day 2 Antral follicle count on ultrasound. To avoid bias, we have avoided selecting patients that underwent any other protocol in this study. Hence, all the patients in this study underwent the conventional long-protocol ovarian hyperstimulation.

RESULTS

Out of 248 patients, majority were in the age group of 31 to 35 years (Table 1). Patients were categorized into four groups on basis of period of infertility, ranging from 2 years to more than 10 years (Table 2). Maximum patients in our study had two previous IVF failures (Table 3). Out of the 248 women undergoing hysteroscopy, 186 (75%) had normal findings and 62 (25%) had intrauterine pathology (Table 4, Figs 1 to 4). The table also gives a review about the conception rate postprocedure, which varied from 19 to 72%, depending upon the pathology in the study group.

DISCUSSION

Despite advances in the field of assisted reproductive techniques over the past 20 years, implantation rates per embryo transferred

Table 1: Age distribution of the patients

Age group (years)	*No. of women studied*
< 30	93
31-35	106
> 35	49

Table 2: Duration of infertility

Duration (years)	*No. of women studied*
2-4	58
5-7	122
8-10	36
> 10	32

Table 3: Number of previous IVF attempts

No. of previous attempts	*No. of women studied*
One	46
Two	122
More than two	80

Table 4: Hysteroscopic findings

Hysteroscopy finding	*Procedure done*	*No. of cases*	*1 IVF cycle failure*	*2 IVF cycles failure*	*More than 2 IVF cycles failure*	*No. of pregnancies postprocedure*	*% of conception after procedure*
Normal	Diagnostic	186	39	91	56	72	38.70
Polyps	Polypectomy	08	01	03	04	06	75
Submucous fibroid	Myomectomy	18	02	09	07	12	66.6
Septa	Septum resection	09	02	03	04	04	44.4
Blocked ostia	Fallopian tube cannulation	06	0	03	03	02	33.3
Synechiae	Synechiolysis	14	02	08	04	03	21.4
Cervical stenosis	Dilatation	01	0	01	0	00	0
T-shaped uterus	Lateral metroplasty	06	0	04	02	03	50

still remains low at about 15 to 20%.[2] The two key factors in question for this problem are the quality of the embryo and the receptivity of the uterus. Although it is possible to assess the embryo quality by microscopy, and more recently by metabolic assessment, uterine receptivity cannot be fully evaluated. Some uterine factors that can be measured by transvaginal sonography are endometrial thickness, pattern, and blood flow in the uterine and subendometrial arteries.[3]

Structural abnormalities of the uterine endometrial cavity may affect the reproductive outcome adversely, by interfering with the implantation and causing spontaneous abortion. These abnormalities can have a negative effect on pregnancy in these women. The incidence of uterine abnormalities in patients undergoing hysteroscopy has been reported to be between 19 and 50%.[4]

In our study, as mentioned earlier, we found intrauterine pathologies in 25% of all patients. The clinical pregnancy rate of patients who were not carrying any intrauterine pathology after IVF treatment was 38.70%. This perhaps indicates that there are factors that are hitherto unknown into bringing about a successful pregnancy or that there are still some yet unknown intrauterine pathologies that inhibit implantation even with good quality embryos. Although the numbers are small, the pregnancy rate for the subgroup of patients who underwent IVF treatment after correction of the intrauterine pathologies is generally higher than those who did not have any in the first place. All except the subgroups of blocked ostia (33.3%) and synechiae (21.4%) have a higher clinical pregnancy rate than the normal uterus group. Most impressive result is seen after polypectomy (75% pregnancy rate).

Different hypotheses have been suggested to define the mechanism of infertility due to intrauterine pathologies. Polyps may cause infertility by virtue of their location, thereby causing mechanical block (e.g. tubocornual polyp), by their association with endometriosis or by expression of the enzyme aromatase, thereby inhibiting embryo implantation. Myomas that protrude into the cavity may decrease vascular supply to the trophoblastic tissue when implantation takes place on the overlying endometrium. Most septa are relatively avascular, and hence result in implantation failure when implantation takes place over them. Other pathologies like synechiae, endometritis, cervical stenosis, and chronic cervicitis can be causes of subfertility.

The place of routine hysteroscopy in the management of infertile women without other diagnosed or doubtful intrauterine pathologies is still a matter of debate.[5] The two main problems

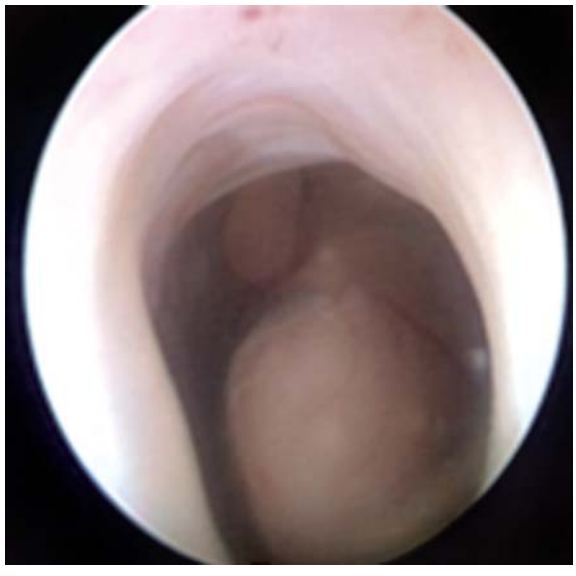

Fig.1: Endometrial polyp

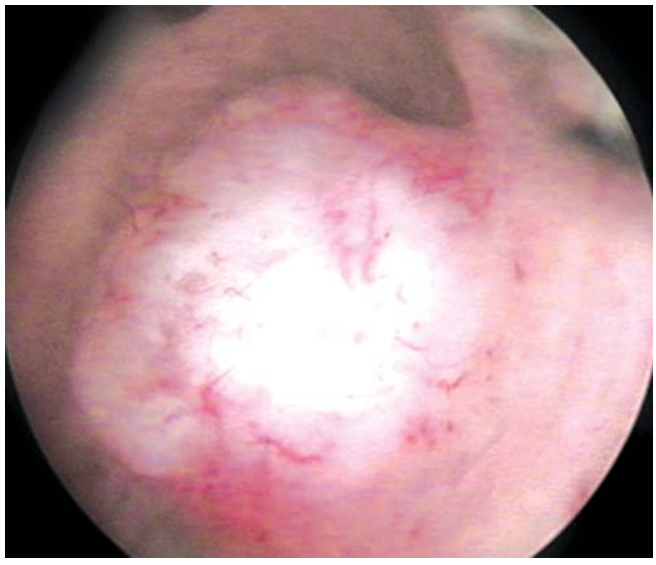

Fig. 2: Submucous fibroid

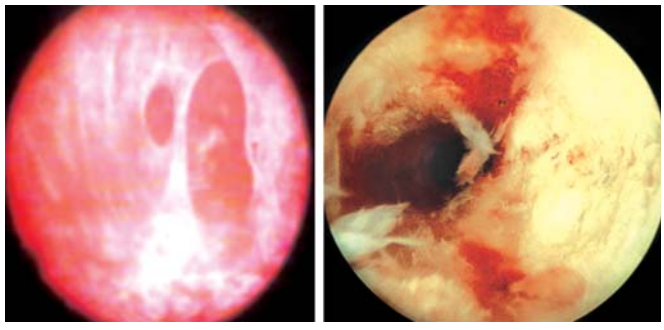

Fig. 3: Intrauterine adhesions

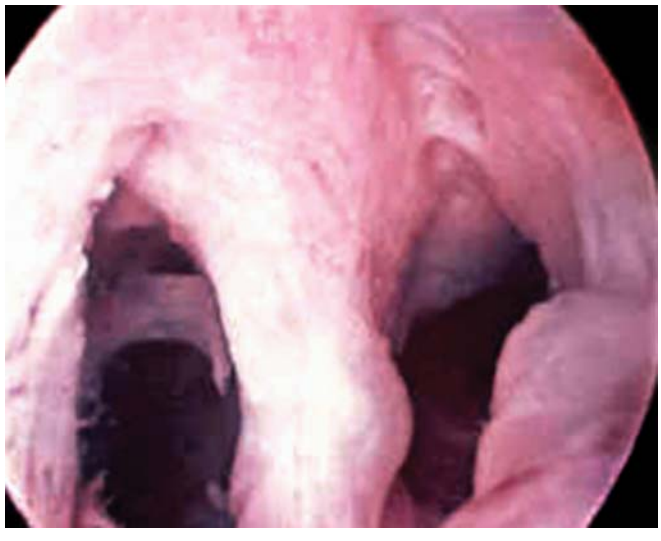

Fig. 4: Uterine septum

that argue against the case of hysteroscopy are: First, it is an invasive procedure, and second, there is still an ongoing debate about the real significance of the observed intrauterine pathology on fertility.[6] 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.[6] Nevertheless, in a study by Shoker et al it was suggested that 26% of the patients with normal hysterosalpingography were with abnormal hysteroscopic findings.[7]

The impact of polyps on infertility is mainly dependent on their size and location. A prospective randomized study of the impact of polyps on an IVF program by Lass et al[8] concluded that small endometrial polyps (less than two centimeters) do not decrease the pregnancy rate after IVF, but a trend toward increased pregnancy loss exists.

The available data on the role of submucous myomas in infertility and the impact of hysteroscopic myomectomy on pregnancy outcome shows encouraging results. Authors have reported clinical pregnancy rates ranging from 31 to 77% post-myomectomy.[9] Women who had myomectomies for myomas more than 2 cm had significantly higher pregnancy and live birth rates than women in whom myomectomy was not done.[9] Hysteroscopic resection is said to be the gold standard for the treatment of submucous or intracavitary myomas.[10]

The role of hysteroscopic septum resection in patients with septate uterus has also been studied extensively.[11] A meta-analysis of retrospective data comparing pregnancy outcome before and after hysteroscopic septoplasty indicated a marked improvement after surgery in increasing the pregnancy rate and decreasing the miscarriage rate.[12]

Several studies have also been performed to find out if hysteroscopic treatment of intrauterine pathologies increases the success of IVF-ET. Kirsop et al suggested that intrauterine abnormalities may be a cause for failure of IVF-ET or gamete intrafallopian transfer (GIFT) and therefore hysteroscopy should be part of the infertility work-up for all patients, prior to undergoing IVF treatment.[13]

Faghali et al have also recommended screening the uterus by hysteroscopy before proceeding with IVF, to minimize implantation failures.[14]

The role of hysteroscopy in patients with previously failed IVF cycles has also been studied. A recent systematic review and meta-analysis of two randomized and three non-hysteroscopy control trials on 1691 patients concluded that hysteroscopy before a subsequent IVF attempt significantly increases the odds for conception in patients with at least two failed IVF attempts.[15]

CONCLUSION

Hysteroscopy seems to be vital for patients in whom an IVF is being contemplated for evaluation and treatment of infertility. Intrauterine pathologies and structural uterine abnormalities, that may be responsible for the failure of IVF, can be detected and treated, resulting in improved pregnancy rates. This would also save the patient additional costs of IVF cycles where failures occur because the intrauterine pathology is missed on other screening investigations like hysterosalpingography. This is especially true in women with one or more prior failed IVF cycles.

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