

Assessment of uterine cavity by hysteroscopy in assisted reproduction programme and its influence on pregnancy outcome

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Abstract *Objective:* The aim of the study was to evaluate if the diagnosis and treatment of uterine cavity abnormalities by hysteroscopy in patients undergoing IVF programme is of any value in improving clinical pregnancy outcome. *Methods:* 520 patients participated in this prospective randomized study and were classified into two groups. Group I ($n = 265$) without office hysteroscopy. Group II ($n = 255$) had office hysteroscopy and was sub classified into Group II a and Group II b. Group II a ($n = 160$) had normal hysteroscopic findings whereas Group II b ($n = 95$) had abnormal office hysteroscopy findings, which were corrected at the same time. *Result:* There was no difference in the mean number of oocytes retrieved, fertilization rate, and number of embryos transferred among the patients in different groups. Statistically significant difference was observed in terms of clinical pregnancy rates between Group I and Group II a (26.2 and 44.44%, $P < 0.05$), and Group I and Group II b (26.2 and 39.55%, $P < 0.05$), respectively. *Conclusion:* Patients with recurrent IVF embryo transfer failures after normal hysterosalpingography findings should also be reevaluated using hysteroscopy prior to further commencing IVF-embryo transfer cycles in order to enhance the clinical pregnancy rates.

Keywords Infertility · Uterine cavity · Diagnosis · Hysteroscopy · In vitro fertilization

Introduction

The successful pregnancy outcome of patients undergoing ovarian stimulation for in vitro fertilization (IVF) or related advanced reproductive technologies depends on several factors. Among these, embryo quality and intra uterine environment plays a major role for the achievement and further continuation of pregnancy. It has been reported that an abnormal uterine finding occurs in approximately 50% of infertile women [1–3]. Due to this high prevalence, evaluation of uterine cavity is recommended to screen fibroids, polyps, adhesions, and uterine mullerian abnormalities. These abnormalities are commonly considered to have a negative impact on pregnancy outcome [4–6]. Uterine evaluation is usually accomplished with the help of hysterosalpingogram (HSG) or hysteroscopy (HSC).

Historically and till today, most of the clinicians prefer HSG as a first line approach to evaluate the intrauterine pathology in infertile patients, but it has been proven to have certain drawbacks. Studies by wang et al. and Golan et al. reported HSG has a false positive rate of 15.6% and false negative rate of 35.4% [7–9]. Hysteroscopic evaluation of uterine cavity for women with infertility has recently become a routine procedure. Hysteroscopy also offers great assistance for the interpretation of uncertain findings from other diagnostic methods. Further, it enables direct visualization of the cervical canal and uterine cavity, and in-

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creases the precision and accuracy in the diagnosis of intrauterine conditions. The main objective of the study is to assess the improvement in pregnancy outcome in patients scheduled to undergo IVF/other ART procedures by diagnosing and treating intra uterine abnormalities using hysteroscopy.

Materials and methods

Five hundred and twenty patients who had undergone two or more failed IVF cycles, in which two or more good quality embryos were transferred per procedure, participated prospectively in this study. They were investigated at the Krishna IVF clinic during the period Jan 2002–Feb 2005. This prospective randomized study was approved by Institutional Review Board (IRB), Krishna IVF Clinic. All the participating patients had primary infertility and normal appearance of the uterine cavity on hysterosalpingography. Informed consent was also taken from them prior to the study. The patient's age ranged from 26 to 30 years and duration of infertility ranged from 6 to 8 years. Patients were randomized into two groups using computer generated random numbers. Group I ($n = 265$) without office hysteroscopic evaluation prior to ovarian stimulation for IVF treatment. Group II ($n = 255$) had office hysteroscopy. Group II were subcategorized into Group II a and Group II b. Those in Group II a ($n = 160$) had normal hysteroscopic findings whereas Group II b ($n = 95$) had abnormal office hysteroscopy findings, which were corrected at the same time.

Hysteroscopy

Hysteroscopy was carried out at Krishna endoscopy on an outpatient basis without anesthesia. Midazolam 0.1 mg/kg was given intravenously as a sedative when needed. All hysteroscopies were performed in early proliferative phase using 1.9 mm miniature Karl Storz hysteroscope, which has a 30° view with a 3 mm Bettocchi continuous flow sheath. The flow sheath has a maximum 5 mm diameter with an incorporated 5 Fr working channel. Associated mechanical instruments used were grasping forceps with teeth and scissors. Uterine distention was accomplished with glycine and 80 mmHg constant intrauterine pressure was maintained using an electronic pump (hysteromat). At the end of the procedure, a sample of endometrium was taken for histological evaluation by aspiration using 4 mm cannula. The patients were discharged after 15–60 min of the procedure and no further complications were observed.

Ovarian stimulation

After hysteroscopy, down regulation was initiated using intramuscular injection of Decapeptide 3.75 mg (Triptoreline) on day 21 of the cycle. Adequacy of down regulation was confirmed by measuring E2 (< 50 pg/ml) and LH levels (< 1 ng/ml). Controlled ovarian stimulation was achieved using recombinant FSH (Recagon, Organon) and the dose was adjusted on the basis of individual response. Human chorionic gonadotropin (hCG) at a dose of 10,000 IU was given after two follicles of 18 mm or more were visualized in the ultrasound scan. Oocyte retrieval was scheduled 36 h later by transvaginal ultrasonography (TVS). After fertilization, embryo transfer was performed on day 3 and the number of embryos transferred is kept constant in all patient groups. Luteal support was given by progesterone vaginal suppositories (Uterogestan). Two weeks after embryo transfer, serum human chorionic gonadotropin (hCG) was measured for confirmation of pregnancy, and a diagnosis of clinical pregnancy was made after visualization of fetal heart pulsation four weeks later by transvaginal sonography (TVS).

Statistical analysis

Patient's age, body mass index (BMI), duration of infertility, number of oocytes, fertilization rate (%), and number of embryos transferred were compared by one way analysis of variance (ANOVA). Mean number of failed transfer cycles, clinical pregnancy (%), and live births (%) were compared using chi-squared analysis. A P value of < 0.05 was considered statistically significant.

Results

There was no significant difference in the mean age, body mass index (BMI), duration of infertility, number of failed cycles, number of IVF and ICSI cycles in either group (Table 1). Among the 255 patients (Group II) who had office hysteroscopy, 95 patients (37.25%) were found to have uterine cavity abnormalities (Tables 2, 3). Among these, 32 had polyps (33.68%), 30 had cervical stenosis (31.57%), 12 had endometrial hyperplasia (12.63%), 12 had synechiae (12.63%), 8 had septate uterus (8.42%), and 1 had fibroids (1.05%) (Table 3). All these abnormalities were treated during office hysteroscopy without any difficulty.

There was no difference in the mean number of oocytes retrieved, fertilization rate, and number of

Table 1 Mean age, BMI, duration of infertility, number of failed transfer cycles, number of IVF and ICSI cycles among the groups

Variables	Group I (<i>n</i> = 265)	Group II a (<i>n</i> = 160)	Group II b (<i>n</i> = 95)	<i>P</i> value
Age	26.72 ± 0.46	27.40 ± 0.60	29.04 ± 0.92	NS
Body mass index	26.74 ± 0.12	22.71 ± 0.41	23.10 ± 0.71	NS
Duration of infertility	7.01 ± 0.10	6.94 ± 0.72	7.12 ± 0.52	NS
Mean number of failed transfer cycles	2.6 ± 0.1	2.8 ± 0.3	2.4 ± 0.4	NS
Number of IVF (%)	61.0	61.25	60	NS
Number of ICSI (%)	39.0	38.75	40.0	NS

Values are expressed as mean ± SEM

IVF in vitro fertilization, ICSI intra cytoplasmic sperm injection, NS not significant

Table 2 Cause of infertility (%)

	Group I	Group II a	Group II b	<i>P</i> value
Female infertility (%)				
Number of IVF	61	61.25	60	NS
Ovulatory	46.25	44.89	45.61	NS
PCOD (% of ovulatory)	83.78	81.81	84.61	NS
Ovarian reserve (% of ovulatory)	16.21	18.18	15.38	NS
Endometriosis (%)	35.62	38.77	38.5	NS
Tubal factor (%)	18.12	16.32	15.78	NS
Uterine factor	Not performed	Nil	95	–
Male infertility (%)				
Number of ICSI (%)	39.0	38.75	40	NS
Male factor (%)	80.9	77.4	78.9	NS
Combined male and female factor (%)	19.04	22.58	21.05	NS

NS not significant

embryos transferred among the patients in different groups (Table 4). Of the 520 patients, five were not included in the analysis due to poor quality of embryos (Three in Group I, one in Group II a and one in Group II b), which were not transferred. Clinical pregnancy rates in Group I, Group II a, and Group II b were 26.2, 44.44, and 39.55%, respectively. Significant difference was found in the clinical pregnancy rates between patients in Group I and Group II a (26.2 and 44.44%, $P < 0.05$) and Group I and Group II b (26.2 and 39.55%, $P < 0.05$). There was no significant difference in the clinical pregnancy rates in patients in Group II a and Group II b (Table 4). There were no significant differences observed in terms of miscarriage rates in all groups.

Table 3 Findings of office hysteroscopy

Variables	Abnormal findings of patients (%)
Normal	160 (62)
Polyps	32 (33.68)
Stenosis	30 (31.57)
Endometrial hyperplasia	12 (12.63)
Synechiae	12 (12.63)
Septate uterus	8 (8.42)
Fibroids	1 (1.05)

Discussion

The evaluation of the couple with recurrent implantation failure is very complex and to a large extent it mainly depends on two important factors which include embryo quality and uterine integrity. At present, ovarian stimulation and predictive outcome of embryo quality have developed in a standardized manner whereas reliable parameters for uterine receptivity are still in the infancy. One such parameter for uterine receptivity is the morphological assessment of the uterine cavity by hysteroscopy. A thorough evaluation of the uterine cavity forms an important part of screening process before starting any assisted reproduction technique. Further, it is also mandatory particularly in patients with good quality embryos who fail to conceive.

Hysterosalpingogram (HSG) has been most commonly used for the evaluation of uterine cavity before undergoing IVF treatment. Since last decade, its sensitivity and specificity have been questioned by several studies. Studies by Kessler and Lancet reported that more than two third of the cases diagnosed by HSG did not correlate with hysteroscopic findings and results show that 54.3% of intrauterine adhesions diagnosed on HSG were not found on hysteroscopic examination

Table 4 Results of IVF outcome in patients

Variables	Group I (n = 265)	Group II a (n = 160)	Group II b (n = 95)	P value
Number of oocytes	9.21 ± 4.75	10.67 ± 5.6	9.44 ± 5.51	NS
Fertilization rate (%)	63.10 ± 6.1	59.25 ± 4.2	66.01 ± 6.2	NS
Number of embryos transferred	4.20 ± 1.0	4.33 ± 1.24	4.10 ± 1.5	NS
Clinical pregnancy (%)	26.2	44.44*	39.55*	P < 0.05
Miscarriages rate (% of clinical pregnancies)	36.2	32.3	35.13	NS
Live birth rate (%)	16.6	30*	25*	P < 0.05
Singleton (%)	79.4	79.1	79.0	NS
Multiple pregnancies (%)	20.4	21.0	20.8	NS

Values are expressed as mean ± SEM

NS not significant

*P < 0.05, when compared to Group I

[10]. Another study comparing the diagnostic value of HSG and HSC by Wang et al. reported HSG has false negative rate of 35.4 % and false positive rate of 15.6% [8]. This study is further supported by Valle, Golan et al. and Prevedourakis et al. [2, 7, 11]. Therefore, HSG interpreted as normal in more than one third of the cases gives a false reassurance.

Small intrauterine lesions such as adhesions, polyps, and submucous myomas, which may be of greater significance in causing implantation failure, are diagnosed more accurately by using HSC in comparison with HSG. A recent study by Cicinelli et al. reported that HSG has a false negative rate of 59% in case of intrauterine abnormalities, which is higher than that reported by others [12]. This is further supported by studies done by Shokeir et al. [13]. These data further strengthen the role of hysteroscopy in the management of infertile patients in detecting endometrial pathologies that were never revealed by HSG.

The present study demonstrated that 37.25% of patients with normal HSG had abnormal hysteroscopy findings. In all patient groups, there was no significant difference in the parameters regarding age, duration of infertility, and BMI (Table 1), whereas significant difference was observed in the pregnancy rates among the patients in Groups I, II a, and II b (26.2, 44.44, and 39.5%), respectively. There was no significant difference in miscarriages rate observed between the groups. Results from this prospective randomized study show that pregnancy outcome can be improved by treating small intrauterine lesions effectively using office hysteroscopy which has a significant role in altering the uterine environment, ultimately improving the pregnancy outcome. Further, the results also support the findings of the various authors who have reported hysteroscopy as a better alternative to HSG for assessment of endometrial cavity.

In conclusion, our study revealed that hysteroscopy is a reliable diagnostic tool to evaluate uterine cavity abnormalities and it should be used as a first

line infertility investigation. Further, repeat hysteroscopy evaluation may also be considered in patients with repeated IVF failures as the multiple embryo transfer procedures may by themselves induce certain endometrial pathologies like adhesions producing an unfavorable endometrial bed. Correction of these lesions reduces the implantation failure and enhances the clinical pregnancy outcome.

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