European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 01, 2022

ORIGINAL RESEARCH

Observational study about pre-art hysteroscopic findings and clinical outcomes post ICSI in infertile women who underwent controlled ovarian stimulation for IVF cycles

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ABSTRACT

Background: Hysteroscopy is a direct and definitive method of assessing intrauterine pathology. The present study was conducted to evaluate Pre-ART hysteroscopic findings and clinical outcomes post ICSI in infertile women who underwent controlled ovarian stimulation for IVF cycles.

Material and methods: It was a prospective observational study conducted among 80 women posted for pre-ART hysteroscopy in Nowrosjee Wadia Maternity Hospital. Detailed history followed by general and gynaecological examination of the patient was done. ICSI procedure was then performed and the fertilization check was done.

Results: In the present study atotal no. of patients posted were 80. In the present study singleton pregnancies were 16, twin gestation were 5, triplets were 1, missed abortions were 5 and ectopic gestations were 4. Maximum patients were having singleton pregnancies. Normal findings were found in 40 patients when diagnostic procedures were performed. Endometrial polyp was found in 11 patients when polypectomy was performed. Fundal septum was found in 10 patients when septal resection was performed. Intrauterine adhesions were found in 5 patients when adhesiolysis was performed. Blocked ostia was found in 7 patients. Submucosal fibroid was found in 3 patients when hysteroscopic myomectomy was performed. Unicornuate Uterus/ T-Shaped Uterus/ Narrow Uterine Cavity was found in 4 patients when lateral metroplasty was performed.7 patients were of age group 20-25yrs, 21 patients were of age group 26-30 yrs, 29 patients were of age group 31-35years, 23 patients were of age group 36-40 yrs. Primary infertility occurs in 53 patients and secondary infertility occurs in 27 patients. Normal findings found in 7 singleton pregnancy, 2 in missed abortion, 3 ectopic gestations. Endometrial polyps found in 3 singleton pregnancy, 1 in twins and triplets resp., 2 in missed abortion.Uterine septumfound in 3 singleton pregnancy, 2 in twins, 1 in missed abortionand ectopic gestation resp. Intrauterine adhesionsfound in 2 singleton pregnancy. Narrow uterine cavity, Uterine fibroid found in 1 singleton pregnancy respectively. Blocked ostia found in 1 singleton pregnancy and 1 in twins. In diagnostic procedure cases 30% patients conceived Post ICSI. In Polypectomy cases, 54.5% patients conceived Post ICSI. In septal resection 70% patients conceived Post ICSI. In adhesiolysis 40% patients conceived Post ICSI. In lateral metroplasty 25% patients conceived Post ICSI.

In hysteroscopic myomectomy 33% patients conceived Post ICSI. In blocked ostia 29% patients conceived Post ICSI. Maximum percentage of conception occurs in Septal resection cases.

Conclusion: The present study concluded that maximum percentage of conception occurs in Septal resection cases.

Keyword: Conception, ICSI procedure, fertilization

INTRODUCTION

About 7.5% of married couples experience infertility.[1] It has been reported that an abnormal uterine finding occurs in approximately 50% of infertile women.[2-4] Most endometrial pathologies implicated in infertility result in both structural and functional impairments.[5] Therefore, endometrial cavity assessment should be included in the evaluation of infertile couples. This can be done through transvaginal sonography, hysterosalpingography, sonohysterography and hysteroscopy.[6,7] The goal of uterine cavity evaluation is either to identify structural abnormalities such as polyps, myomas, or uterine septum or to obtain a sample of the endometrium (hyperplasia or neoplasia).[8] Hysteroscopic examination is probably superior to hysterography in evaluating the endometrial cavity.[8] Furthermore; abnormal hysteroscopic findings have been reported in patients with normal hysterography[9] or transvaginal ultrasonography.[10] Office hysteroscopy has been proven to have superior sensitivity and specificity in evaluating the endometrial cavity.[11-13] Mini-hysteroscopies allow for the performance of uterine cavity evaluation in an office setup, with or without local anesthetics, for diagnostic and certain therapeutic interventions.[14] However, the World Health Organization (WHO) recommends hysterosalpinography (HSG), alone, for management of infertile women probably because of its ability to provide information regarding tubal patency.[15] Nevertheless, hysteroscopy is a more accurate tool because of the high false-positive and false negative rates of intrauterine abnormality with HSG.[3,8,9] Furthermore, usage of OH can play an important role in detecting intrauterine pathologies in IVF patients. Therefore, it may have a positive impact on pregnancy outcome and treatment costs.[16,17] In addition, abnormal hysteroscopic findings 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.[18]This study aimed to analyse the outcome of hysteroscopy performed prior to start of IVF cycle in a group of 80 patients in Nowrosjee Wadia Maternity Hospital and to evaluate the outcome of office hysteroscopy on IVF cycle-whether performing hysteroscopy prior to starting an IVF cycle improves likelihood of achieving a clinical pregnancy in infertile women.

OBJECTIVES

To study different hysteroscopic findings and post ICSI outcomes.

PRIMARY OUTCOME

Clinical pregnancy rate

SECONDARY OUTCOME

Multiple pregnancy rates, ectopic pregnancy rates, miscarriage rate, failure rate of the cycle.

MATERIAL AND METHODS

It was a prospective observational study conducted among 80 women posted for pre-ART hysteroscopy in Nowrosjee Wadia Maternity Hospital from 1 March 2019 to 31 December 2019 for a period of 10 months.Women undergoing ART treatment cycle with ICSI who may or may not have had previous IUI/ICSI cycles posted for hysteroscopy, women of age

between 21-39 yrs, women with Tubal factor infertility, Unexplained infertility, Male factor infertility were included in the study. A written, valid, informed consent was taken from every patient prior to the procedure.Women above age of 40 years were not included as the primary factor for failure in this age group is related to embryo quality which is unlikely to be corrected by uterine or endometrial anomaly correction.

METHODOLOGY

Detailed history followed by general and gynaecological examination of the patient was done. Serum AMH levels, transvaginal sonography and hysterosalpingography was done for all patients as a part of basic infertility workup. After confirming anaesthetic fitness, patient was posted for hysteroscopy post menstrually. Per vaginal prostaglandin tablet of 200mcg was used as cervical softening agent prior to hysteroscopy, kept 1 hour prior to procedure. A rigid hysteroscope (2.9mm/30 degree BETTOCHHI) was put into the uterine cavity under visual control after minimal cervical dilatation, 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. Every hysteroscopy was followed by endometrial curettage, and the material obtained was sent for histopathological examination, TB-PCR and rapid AFB culture. Patients were discharged from the ward on complete recovery and reffered back to the IVF centre on second day of menses.The patients were downregulated using combined oral contraceptive pills for 21 days COS was done using the antagonist protocol starting from the second day of the subsequent menses. The drugs used for stimulation were intramuscular injections of highly purified human menopausal gonadotropin (Injection Menotas, Intas Pharmaceuticals Ltd) starting with dose of 300 IU and increasing up to 450 IU as per the patient response. Serial transvaginal ultrasound was performed to monitor follicle growth. The antagonist used was subcutaneous injections of cetrorelix in a dose of 0.25mg (InjCetrolix, Intas Pharmaceuticals Ltd.), using the flexible protocol i.e. when the leading follicle >14mm. The drug used for triggering final maturation of follicles was subcutaneous injection of leuprolide acetate (InjLupride, Intas Pharmaceuticals Ltd) in a dose of 2mg (Agonist trigger). Trigger was given once the leading follicles were in the range of 18 mm while others in ranges of 14-15mm. Oocyte retrieval was performed 34 hours after the trigger by standard transvaginal method.

The follicular fluid was scanned for oocytes. The retrieved oocytes were maintained in culturemedium (Global® for fertilisation, LifeGlobal, Connecticut, USA) supplemented with 10% protein supplement (LGPS, LifeGlobal, Connecticut, USA) and covered with paraffin oil (Paraffin oil P.G., LifeGlobal, Connecticut, USA) for two to three hours before the removal of cumulus cells. Thesurrounding cumulus cells were removed after exposure toa HEPES-buffered medium containing hyaluronidase. (80IU/mL, LifeGlobal, Connecticut, USA). The remaining cumuluscells were gently removed with a denuding pipette. Before performing ICSI, the oocytes were examined for their morphology under Olympus Inverted Microscope. The grading of the oocytes according to the nuclear maturity was done.

ICSI procedure was then performed and the fertilization check was done at 22, 44, 72 and 96 hours post ICSI. All embryos were frozen by vitrification and transfer was performed in the subsequent cycle. Endometrial preparation for frozen-thawed embryo transfer (FET) cycle was done with standard protocol of oral estradiol valerate 6mg daily (gradually increased up to 12mg daily). Serial monitoring for endometrial thickness was done till a thickness of 8-9mm was achieved. Intramuscular injections of 100mg natural micronized progesterone were added for appropriate number of days depending on the stage of embryos being transferred. Pregnancy was confirmed by estimation of serum beta human chorionic gonadotropin levels

17 days after the embryo transfer procedure. Clinical pregnancy was defined as the presence of an intrauterine gestational sac on trans-vaginal ultrasound.

RESULTS

In the present study atotal no. of patients posted were 80.

Table 1: Distribution of patients according to type of pregnancy

Type of pregnancy	N
Singleton Pregnancies	16
Twin Gestation	5
Triplets	1
Missed Abortion	5
Ectopic Gestation	4

In the present study singleton pregnancies were 16, twin gestation were 5, triplets were 1, missed abortions were 5 and ectopic gestations were 4. Maximum patients were having singleton pregnancies.

Table 2: Hysteroscopic Findings

Hysteroscopic Findings	Procedure Done	No. Of Patients
Normal Findings	Diagnostic	40
Endometrial Polyp	Polypectomy	11
Fundal Septum	Septal Resection	10
Intra Uterine Adhesions	Adhesiolysis	5
Blocked Ostia	-	7
Sub Mucosal Fibroid	Hysteroscopic Myomectomy	3
UnicornuateUterus/ T-Shaped Uterus/ Narrow Uterine Cavity	Lateral Metroplasty	4

Normal findings were found in 40 patients when diagnostic procedures were performed. Endometrial polyp was found in 11 patients when polypectomy was performed. Fundal septum was found in 10 patients when septal resection was performed. Intrauterine adhesions were found in 5 patients when adhesiolysis was performed. Blocked ostia was found in 7 patients. Submucosal fibroid was found in 3 patients when hysteroscopic myomectomy was performed. Unicornuate Uterus/ T-Shaped Uterus/ Narrow Uterine Cavity was found in 4 patients when lateral metroplasty was performed.

Table 3: Distribution according to age group

Age Group (Years)	Total No. Of Patients
20-25	7
26-30	21
31-35	29
36-40	23

7 patients were of age group 20-25yrs, 21 patients were of age group 26-30 yrs, 29 patients were of age group 31-35years, 23 patients were of age group 36-40 yrs.

Table 4: Distribution according to type of infertility

Type Of Infertility	Total No. Of Patients
Primary	53
Secondary	27

Primary infertility occurs in 53 patients and secondary infertility occurs in 27 patients.

Table 5: Hysteroscopic findings in relation to type of pregnancy

Hysteroscopic findings	Procedure done	Singleton pregnancy	Twins	Triplets	Missed abortion	Ectopic gestation
Normal findings	Diagnostic	7	0	0	2	3
Endometrial polyps	Polypectomy	2	1	1	2	0
Uterine septum	Septal resection	3	2	0	1	1
Intrauterine adhesions	Adhesiolysis	2	0	0	0	0
Narrow uterine cavity	Lateral metroplasty	1	0	0	0	0
Uterine fibroid	Hysteroscopic myomectomy	1	0	0	0	0
Blocked ostia	-	1	1	0	0	0

Normal findings found in 7 singleton pregnancy, 2 in missed abortion, 3 ectopic gestations.Endometrial polyps found in 3 singleton pregnancy, 1 in twins and triplets resp., 2 in missed abortion.Uterine septumfound in 3 singleton pregnancy, 2 in twins, 1 in missed abortionand ectopic gestation resp. Intrauterine adhesionsfound in 2 singleton pregnancy. Narrow uterine cavity, Uterine fibroid found in 1 singleton pregnancy respectively.Blocked ostiafound in1singleton pregnancy and 1 in twins.

Table 6: Percentage of Patients Conceived Post ICSI

Procedure	No. of Patients Underwent Procedure	No. of Patients Conceived Post ICSI	Percentage of Conception Post Procedure
Diagnostic	40	12	30%
Polypectomy	11	6	54.5%
Septal resection	10	7	70%
Adhesiolysis	5	2	40%
Lateral metroplast	4	1	25%
Hysteroscopic myomectomy	3	1	33%
Blocked ostia	7	2	29%

In diagnostic procedure cases 30% patients conceived Post ICSI. In Polypectomy cases, 54.5% patients conceived Post ICSI. In septal resection 70% patients conceived Post ICSI. In adhesiolysis 40% patients conceived Post ICSI. In lateral metroplast 25% patients conceived Post ICSI. In hysteroscopic myomectomy 33% patients conceived Post ICSI. In blocked ostia 29% patients conceived Post ICSI. Maximum percentage of conception occurs in Septal resection cases.

DISCUSSION

The uterine cavity is considered to play an important role in successful implantation. Faghali et al., have also recommended screening the uterus by hysteroscopy before proceeding with IVF, to minimize implantation failures.21 The availability of hysteroscopes with smaller diameter has made the use of outpatient or office hysteroscopy feasible as a routine examination.[19]

The prevalence of unsuspected intrauterine abnormalities, diagnosed by hysteroscopy prior to IVF, has been reported to be 11–45%.[20,21]Easier embryo transfer, more accurate embryo placement and enhanced endometrial receptivity secondary to endometrial stimulation have been considered as plausible explanations for the improved IVF outcome after normal hysteroscopy.[22] Evidence exists that performing hysteroscopy before IVF treatment significantly increases the chance of pregnancy in the subsequent IVF cycle in women who had one or more failed IVF cycles.[5]Karayalcin et al reported on a total of 2500 consecutive office-based diagnostic hysteroscopies in an IVF population enrolled prospectively prior to treatment. Endometrial pathology on hysteroscopy which may have impaired the success of IVF was identified in 22.9%.[23]

Karayalcın et al enrolled 1258 patients attending an IVF clinic with normal hysteroscopic findings in an attempt to establish the impact of timing of office hysteroscopy before embryo transfer on pregnancy rate. The implantation, pregnancy, and clinical pregnancy rates were significant when office hysteroscopy was performed 50 days or less before embryo transfer.[24]

Another recent study included 157 women with a history of recurrent IVF failures (two or more) who underwent hysteroscopy (diagnostic or operative, as appropriate) to evaluate the endometrial cavity. Abnormal hysteroscopic findings were found in 44.9% of the patients in this study 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.[25]

The benefit of hysteroscopic surgery was further corroborated in a retrospective matched control study by Tomazevic et al. These authors evaluated the influence of septate, subseptate, and arcuate uterus on pregnancy and live birth rates in 2481 in conventionally stimulated IVF/intracytoplasmic sperm injection (ICSI) cycles. Pregnancy rates after embryo transfer before hysteroscopic surgery were significantly lower, both in women with subseptate and septate uterus and in women with arcuate uterus compared with controls. When live birth rates were considered, differences were more evident. The differences disappeared upon hysteroscopic resection.[26]

The TROPHY trial aimed to assess whether hysteroscopy improves the livebirth rate following IVF treatment in women with recurrent failure of implantation. It concluded that outpatient hysteroscopy before IVF in women with a normal ultrasound of the uterine cavity and a history of unsuccessful IVF treatment cycles does not improve the livebirth rate. Further research into the effectiveness of surgical correction of specific uterine cavity abnormalities before IVF was warranted.[27]

Another latest study in Italy by Di SpiezioSardo et al concluded that robust and high-quality RCTs are still needed before hysteroscopy can be regarded as a first-line procedure in all infertile women, especially during the basal clinical assessment of the couple.[28] This study showed improvement in clinical pregnancy rate after hysteroscopy was done in patients prior to ICSI cycle,especially in cases of recurrent implantation failure.

CONCLUSION

The position of hysteroscopy in the management of the infertile female remains under debate. Although a variety of studies demonstrate that the procedure is well tolerated and effective in the treatment of intrauterine pathologies, there is no consensus on the effectiveness of hysteroscopic surgery in improving the prognosis of subfertile women. There are not enough prospective randomized trials to clearly demonstrate that surgical removal of all intrauterine abnormalities improves fertility or IVF outcomes. However, published observational results suggest a benefit for resection of submucosal leiomyomas, adhesions, and at least a subset of polyps in increasing pregnancy rates. So in a country like India with limited resources, definitely hysteroscopy should be utilized as a tool to diagnose uterine anomalies prior to

ICSI cycles, correct them in the same sitting and then attempt ICSI cycle so as to improve implantation rate and clinical pregnancy rate.

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