

Role of pre IVF hysteroscopy in women with unexplained infertility for detecting unsuspected intrauterine lesions and effect on pregnancy outcome

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Abstract

Objective: The relevance of routine hysteroscopy before IVF is debatable and there is no consensus on the effectiveness of routine pre IVF hysteroscopy in improving pregnancy outcome. The purpose of this study is to assess the role of pre IVF hysteroscopy in women with unexplained infertility in detecting unsuspected intrauterine lesions and its effect on pregnancy outcome. **Materials and Methods:** This was retrospective observational study conducted at Medicover Fertility Center, New Delhi, India. In the study group ($n = 60$), women with unexplained infertility of more than three years with normal transvaginal ultrasonography were included, where hysteroscopy was done in post-menstrual period, 1–2 months before starting IVF treatment. In the control group ($n = 60$), pre IVF hysteroscopy was not done. **Results:** The study and control group did not differ for age, body mass index, duration and type of infertility. There was a high prevalence (31.6%) of unsuspected intrauterine abnormalities in women with unexplained infertility with normal transvaginal ultrasound findings. The clinical pregnancy rate was 48.3% (29/60) in study group and 36.7% (22/60) in control group. The clinical pregnancy rate (CPR) was observationally higher in women with pre IVF hysteroscopy, but the difference was not statistically significant (P value = 0.193). **Conclusion:** There was high prevalence rate of unsuspected intrauterine lesions in women with unexplained infertility. Clinical pregnancy rates were not significantly higher in patients who underwent pre IVF hysteroscopy. Further larger studies and randomized controlled trials are needed to verify the positive outcome of use of hysteroscopy prior to IVF.

Keywords: Hysteroscopy, IVF, ICSI, intrauterine abnormalities, unexplained infertility

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INTRODUCTION

The cause of infertility is unexplained in up to one-third of all couples, undergoing in-vitro fertilization (IVF) treatment, where no specific contributors to infertility are detected after completing standard fertility

investigations.^[1] The assessment of intrauterine abnormalities is a core part of infertility evaluation as it impacts the complex process of embryo implantation.^[2]

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There has been seen high prevalence of (40%–50%) unsuspected intrauterine lesions like synechiae, septum, endometritis and polyps in asymptomatic women, diagnosed by pre IVF hysteroscopy, in numerous studies conducted in various IVF clinics.^[3-7] The presence of such intrauterine lesions can significantly compromise spontaneous fertility as well as pregnancy outcome in women after fertility treatment.^[2,8-11]

The gold standard technique for evaluating the uterine cavity is hysteroscopy.^[2,12] Compared to transvaginal ultrasonography (TVS), hysteroscopy allows for a direct visualization of the unsuspected lesions and treatment in the same sitting.^[7,13] According to the international guidelines of American Society for reproductive medicine (ASRM), hysteroscopy should be reserved for further evaluation after finding abnormalities on transvaginal ultrasonography and hysterosalpingography (HSG) considering cost effectiveness.^[14] However new endoscopic advancements have made diagnostic and operative hysteroscopy cost effective, safe, time saving and useful as fertility enhancing minimal invasive surgery.^[15]

The relevance of routine hysteroscopy before IVF is debatable and there is no consensus on the effectiveness of hysteroscopic surgery in improving pregnancy outcome. A number of studies have shown increased pregnancy rates after pre IVF hysteroscopy,^[3-5,10,16-18] whereas some have showed no potential benefits.^[19-21]

This study is aimed to assess the role of pre IVF hysteroscopy in women with unexplained infertility in detecting unsuspected intrauterine lesions and also to assess the effect of treating such lesions on pregnancy outcome.

AIMS AND OBJECTIVES

The purpose of this study is to determine the role of pre IVF hysteroscopy in women with unexplained infertility for detecting unsuspected intrauterine lesions and effect on pregnancy outcome.

MATERIALS AND METHODS

This is a retrospective observational study, conducted in women undergoing IVF treatment at Medicover Fertility Center, New Delhi over the period from January 2018 to January 2020. The study was approved by the institutional Ethics Board.

Inclusion criteria

Women with unexplained infertility of more than three years, age \leq 35 years, normal TVS findings, normal anti-Mullerian hormone (AMH) levels, normal stimulation responders, day 5 (blastocyst) fresh embryo transfer cycle.

Exclusion criteria

Women with abnormal menstrual history (menorrhagia, intermenstrual spotting, hypomenorrhea), any pre-existing intrauterine lesions on TVS or HSG, recurrent miscarriage (>2), previous failed IVF cycle, prior history of hysteroscopy.

During the period from January 2018 to January 2020, hysteroscopy reports were reviewed and 60 women were selected in the study group meeting the inclusion and exclusion criteria. The data was reviewed for the detailed history and basic infertility work up and those were selected for this study who had no obvious cause for infertility. The two-dimensional TVS, using Samsung SonoAce R7, EVN4-9 transvaginal probe (6.5 MHz) was performed by gynecologist trained in reproductive medicine. TVS examination done during the proliferative phase of menstrual cycle showed no intrauterine lesions like polyps, submucous myomas, septum or synechiae in the selected group of women. The endometrial thickness of at least 7 mm was included in this study. The hysteroscopy procedure was performed after patient counseling and written informed consent. The informed consent was also taken for data being used for training and research purposes.

In the study group, hysteroscopy was done in post menstrual period (day 5–day 10), 1-2 months before starting IVF treatment, under intravenous sedation or short general anaesthesia as required. 30 degree, forward oblique view, 2.9mm diameter Bettocchi hysteroscope was used and normal saline (0.9%) was used as distention medium, keeping the pressure between 80-100 mm Hg using a pressure adjustable cuff system, with the aim to use the lowest pressure required to distend the uterine cavity adequately. The hysteroscopy records were reviewed for detailed evaluation of endocervical canal, endometrial cavity, anterior, posterior and lateral walls and intrauterine findings were noted as normal cavity, endometrial polyp, septum, adhesions, narrow or tubular cavity or presence of any endometritis. In the same sitting if abnormalities were found then operative hysteroscopy was done. Endometrial polypectomy and adhesiolysis was done using hysteroscopy scissors. Fundal and lateral metroplasty was done if narrow or tubular cavity and septal resection were done using scissors or bipolar electrode. At the end of

procedure, an endometrial biopsy was obtained and sent for histological examination. The patients who had hysteroscopic evidence of endometritis (focal or diffuse hyperemia), received a course of doxycycline 100mg twice daily for 14 days. After septal resection and adhesiolysis, patients were given oral estradiol valerate 4–6 mg daily for 2–4 weeks, as required.

A control group of 60 women, with unexplained infertility, meeting inclusion and exclusion criteria, was taken who did not undergo hysteroscopy and wanted straightway IVF. All the women in study and control group were planned for controlled ovarian stimulation by gonadotropins (rFSH/ HMG) starting from day 2/3 of cycle and dose was given as per age and ovarian reserve test, average dose was 225 IU. The response was monitored with serial transvaginal ultrasound, the LH surge was suppressed by adding GnRH antagonist from day 6 of stimulation and once ovaries had at least three follicles of 17-18 mm in diameter, 250 mcg rhCG trigger was given. Transvaginal ultrasound-guided oocyte retrieval was done under general anaesthesia after 35–36 hours of trigger. IVF/ICSI was performed and embryos were cultured to day 3 or day 5 (blastocyst). In this study we included only blastocyst (day 5) cases and fresh embryo transfer was done. Luteal phase support consisted of vaginal micronized progesterone 400 mg twice daily. The serum beta HCG was done 14 days after embryo transfer and repeat level was done 48 hr later in those who had positive test. The early pregnancy transvaginal scan was scheduled after two weeks to check for gestational sac and cardiac activity. Clinical pregnancy was defined as a pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs and clinical pregnancy rate calculated as the number of clinical pregnancies per 100 embryo transfer cycles.

The outcome noted was the prevalence of intrauterine lesions in the study group and the comparison of clinical pregnancy rate between study group and control group. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) and the level of significance was set at *P* value less than 0.05. The two groups were analyzed using the Pearson Chi-square test, Student *t*-test, Mann-Whitney U test as indicated.

RESULTS

The baseline characteristics including age, body mass index (BMI), duration and type of infertility were similar in both study and control groups. The mean age of the women was 31.50 ± 6.30 years in study

group and 30.26 ± 5.89 years in control group (*P* value = 0.109). The mean BMI was 25.47 ± 5.64 in study group and 25.20 ± 4.32 in control group (*P*-value = 0.671). There was no significant difference between the groups regarding duration of infertility (*P*-value = 0.126). Majority of the women had primary infertility in both the groups [Table 1].

Among 60 women who underwent hysteroscopy, intrauterine abnormalities were found in 19 (31.6%) of them. Intrauterine adhesions were present in 6 women (10%), tubular cavity in 3 (5%), septum in 3 (5%), endometritis in 2 (3.3%) and endometrial focal thickening/ polyp was present in 5 (8.3%) of them [Table 2]. Adhesions noted were mild and flimsy, septum was partial (1.5–3 cm) and size of endometrial polyps varied from 5 to 7mm. Operative hysteroscopy procedure was done to correct intrauterine abnormalities accordingly. The procedure was well tolerated in almost all the patients. No intraoperative complication occurred. The majority of women didn't feel any significant pain after the procedure, only five women (8.3%) had mild lower abdominal cramps like pain and managed with oral analgesics. Two (3.3%) women had irregular mild bleeding per vaginum for one to two weeks that was managed with oral tranexamic acid.

The clinical pregnancy rate was 48.3% (29/60) in study group and 36.7% (22/60) in control group. The clinical pregnancy rate (CPR) was observationally higher in women with pre IVF hysteroscopy, but the difference was not statistically significant (*P*-value = 0.193) [Table 3]. This difference was seen in women who underwent operative hysteroscopy for correction of intrauterine abnormalities as well as who had normal findings after

Table 1: Demographic characteristics

Characteristics	Study group (N = 60) Mean ± SD	Control group (N = 60) Mean ± SD	<i>P</i> value
Age (years)	31.50 ± 6.30	30.26 ± 5.89	0.109
BMI (kg/m ²)	25.47 ± 5.64	25.20 ± 4.32	0.671
Duration of infertility (years)	6.34 ± 6.26	5.23 ± 5.12	0.126
Type of infertility	Primary-72.4% Secondary-27.6%	Primary-78.6% Secondary-21.4%	0.303

Table 2: Hysteroscopy findings in the study group

Hysteroscopy findings	Number (N = 60)	Percentage
Normal cavity	41	68.3%
Adhesions	6	10%
Polyp/focal thickening	5	8.3%
Septum	3	5%
Tubular cavity	3	5%
Endometritis	2	3.3%

Table 3: The comparison of clinical pregnancy rate between study and control group

Clinical pregnancy rate	Study group (N = 60)	Control group (N = 60)	P value
	29 (48.3%)	22 (36.7%)	0.193

Table 4: Clinical pregnancy rate in study (Hysteroscopy) group (N=60)

Hysteroscopy findings	No. of women conceived	No. of total cases	Percentage
Normal cavity	20	41	48.8%
Adhesions	2	6	33.3%
Polyp	3	5	60%
Septum	2	3	66.7%
Tubular cavity	1	3	33.3%
Endometritis	1	2	50%

hysteroscopy. 29 women (48.3%) out of 60 conceived after hysteroscopy. 9/19 (47.3%) pregnancies occurred in women with corrected intrauterine abnormalities [Table 4]. In the study group, out of 29 women who conceived, 14 (48.2%) have delivered, 4 (13.8%) aborted, and 11 (37.9%) have ongoing pregnancy. In the control group, among 22 who conceived, 11 (50%) have delivered, 3 (13.6%) aborted and 8 (36.3%) have ongoing pregnancy. [Table 5]

DISCUSSION

A variety of factors can influence success rates after IVF. The uterine cavity is considered to be one of the key factors influencing the outcome of the fertility treatment.^[2] Hysteroscopy is the gold standard for the assessment of uterine cavity with an advantage to treat any detected uterine pathology.^[2,12] Elsetohy *et al.*^[3] and Bakas *et al.*^[7] have concluded that TVS is specific but not sensitive compared to hysteroscopy. In a study by Apirakviriyaya *et al.*^[22] 3D-TVUS in comparison with hysteroscopy had 84.1% diagnostic accuracy, 68.2% sensitivity and 91.5% specificity. Several intrauterine lesions like intrauterine adhesions, septum and endometritis cannot be satisfactorily detected by transvaginal ultrasound.

Our results suggested a high prevalence (31.6%) of unsuspected intrauterine abnormalities in women with unexplained infertility with normal 2D-TVUS findings who underwent pre IVF hysteroscopy. These intrauterine abnormal findings were intrauterine adhesions (10%), endometrial polyps (8.3%), uterine septum (5%), tubular cavity (5%) and endometritis (3.3%). Elsetohy *et al.*^[3] (43.3%), Cenksoy *et al.*^[4] (44.9%), Doldi *et al.*^[5] (40%), Ajayi *et al.*^[6] (61.1%) and Bakas *et al.*^[7] (31.8%)

Table 5: Outcome of pregnancy among all women who conceived

Outcome	Study group (N = 29)	Control group (N = 22)
Aborted	4 (13.8%)	3 (13.6%)
Ectopic	0 (0%)	0 (0%)
Delivered	14 (48.2%)	11 (50%)
Ongoing pregnancy	11 (37.9%)	8 (36.3%)

have also reported high prevalence of unsuspected intrauterine lesions like synechiae, septum, endometrial polyps in asymptomatic women undergoing infertility treatment. The evidence on the effectiveness of hysteroscopic surgeries in women with intrauterine abnormalities indicates a potential benefit. A Cochrane review by Bosteels *et al.*^[9] showed that hysteroscopic polypectomy prior to IUI increases clinical pregnancy rate. Perez-Medina *et al.*^[11] also demonstrated that hysteroscopy removal of endometrial polyps increases chance of pregnancy, suggesting its possible association with implantation failure. Bakas *et al.*^[16] found that hysteroscopy metroplasty in women with septate uterus and unexplained infertility improve clinical pregnancy rates and live births. A retrospective matched-control study by Tomazevic *et al.*^[23] evaluated the effect of uterine anomalies on pregnancy rates after 2481 embryo transfers and concluded that pregnancy rates after embryo transfer before hysteroscopy metroplasty were significantly lower in women with arcuate, subseptate and septate uterus compared with embryo transfer after corrected surgeries.

In this study, it was found that clinical pregnancy rate was higher (48.3% vs. 36.7%) in women with unexplained infertility who underwent hysteroscopy prior to first IVF cycle than who did not undergo hysteroscopy, but this difference was not statistically significant (P value = 0.193). 48.3% of women conceived after hysteroscopy, 47.3% pregnancies occurred in women with corrected intrauterine abnormalities. A systematic review and meta-analysis by Di Spiezio *et al.*^[17] showed beneficial effect of hysteroscopy for women undergoing their first IVF/ ICSI cycle and also for women with one or more implantation failures. A meta-analysis by Pundir *et al.*^[18] showed increased live birth rates when hysteroscopy was performed prior to first IVF cycle. The increased pregnancy rates after pre IVF hysteroscopy was also seen in studies by Elsetohy *et al.*^[3] Cenksoy *et al.*^[4] and Doldi *et al.*^[5] The higher pregnancy rates in even those women who had normal findings after hysteroscopy can be because of immunological mechanism triggered by hysteroscopic mechanical manipulation or by the effect of distension

medium on the endometrium. Irrigation of cavity with saline removes harmful anti-adhesive glycoprotein molecules (cyclooxygenase-2, mucin-1 & integrin $\alpha V\beta 3$) on the endometrium thus improving endometrial receptivity.^[24-26] Sometimes visual assessment of cervical canal and adhesiolysis in case of cervical stenosis also helps further in embryo transfer. Some studies didn't recommend hysteroscopy as a routine practice before ART, as the significance of treating unsuspected intrauterine lesions are not yet fully proven.^[19-21] The findings from a multicenter randomized clinical inSIGHT^[19] trial showed that hysteroscopy does not improve live birth rate in women with normal transvaginal ultrasound of uterine cavity before first IVF cycle. Another randomized controlled trial, TROPHY trial on the role of hysteroscopy in women with two to four failed IVF cycles also reported no improvement in live birth rates after hysteroscopy.^[20]

There is no consensus on the routine use of hysteroscopy before IVF, although many observational studies and meta-analysis suggest increased pregnancy rates after the hysteroscopic removal of such lesions.^[3-5,10,16-18] Hence, the importance of hysteroscopy as a routine in the management of infertile women still remains a matter of debate.

CONCLUSION

This study concluded that there was high prevalence rate of unsuspected intrauterine lesions in women with unexplained infertility diagnosed by pre IVF hysteroscopy. Pre IVF hysteroscopy increased clinical pregnancy rate, though the difference was not statistically significant. Limitation of this study was small sample size, further larger studies and randomized controlled trials are needed to verify the positive outcome of routine use of hysteroscopy prior to IVF.

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Conflicts of interest

There are no conflicts of interest.

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