

Research Article

Impact on IVF Outcome Following Pre-IVF Hysteroscopy and Endometrial Scratching

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Abstract

Background: Transvaginal ultrasonography and hysteroscopy are the tools to assess the inner architecture of the uterus. Hysteroscopy is considered to be the gold standard for management of infertile women. The treatment of repeated implantation failure in spite of transfer of good-quality embryos continues to be a dilemma. In India as such very few studies were conducted to see the effect of endometrial injury on the pregnancy outcome, so the current study was conducted to assess the efficacy of hysteroscopy in identifying the uterine pathologies and to assess the pregnancy rate following the endometrial scratching.

Methodology: A prospective cohort study was conducted during June 2012 to may 2015 at KJK Hospital, Trivandrum. All patients undergoing IVF in the said duration are scheduled for Pre IVF Hysteroscopy prior to the onset of periods. All the study population had undergone a transvaginal USG and hysteroscopy. Half of the study population (n=175) had underwent endometrial scratching and the occurrence of clinical pregnancy was compared among the group who had not undergone the endometrial scratching.

Results: The uterine pathologies which were picked up by hysteroscopy was almost 4 times more than the uterine pathologies reported by USG. The sensitivity (100%) and specificity (85%) was much higher for hysteroscopy when compared with USG. There was a statistically significant difference in the occurrence of clinical pregnancy among the patients for whom endometrial scratching done when compared to those who had not undergone endometrial scratching ($p < .0001$).

Conclusion: Through hysteroscopy, the 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 and the clinical pregnancy and implantation rates significantly increase after endometrial scratching in same cycle in patients with good-quality embryos.

Keywords: IVF; Hysteroscopy; Endometrial scratching

Introduction

Despite the numerous advances in the field of *in vitro* fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI), the implantation rate per embryo transferred usually does not exceed 30%, although higher rates with the use of blastocysts have been reported, depending on female age [1,2].

Embryo quality, good conditions of the uterine environment, a skillful IVF laboratory and embryo transfer are essential in order to achieve a pregnancy in IVF. Unsuspected uterine cavity abnormalities, such as endometrial polyps, small submucous myomas, adhesions and septa are considered to have a negative impact on the chances to conceive through IVF [3].

Hysterosalpingography, transvaginal ultrasonography, saline infusion sonography and hysteroscopy are the tools to assess the inner architecture of the uterus [4]. Hysteroscopy is considered to be the gold standard; however, the World Health Organization (WHO) recommends Hysterosalpingography (HSG) alone for management

of infertile women [5]. The explanation for this discrepancy is that HSG provides information on tubal patency or blockage.

Office hysteroscopy is only recommended by the WHO when clinical or complementary exams (ultrasound, HSG) suggest intrauterine abnormality or IVF failure [6]. Nevertheless, many specialists feel that hysteroscopy is a more accurate tool because of the high false-positive and false negative rates of intrauterine abnormality with HSG [7-9]. This explains why many specialists use hysteroscopy as a first-line routine exam for infertility patients regardless of guidelines but, the validity of hysteroscopy may be limited in the diagnosis of endometritis and endometrial hyperplasia [5].

The prevalence of minor intrauterine abnormalities identified at hysteroscopy in cases with a normal transvaginal sonography has been recorded to be as high as 20-40%. Diagnosing and treating such pathology prior to initiating IVF/ICSI, has been widely advocated without high-quality evidence of a beneficial effect [5].

Table 1: Mean and SD of the demographic parameters among the study population.

Demographic parameter	Mean	SD
Age of mother (in years)	36.25	2.3
Duration of married life (in years)	5.75	1.4
Number of attempts (IVF)	1.25	0.35

Implantation failure, which is presently the major barrier in human fertility, is attributed, in many cases, to the failure of the uterus to acquire receptivity. The transition into a receptive uterus includes cellular changes in the endometrium and the modulated expression of different cytokines, growth factors, transcription factors, and prostaglandins. Embryo implantation is associated with an active Th1 inflammatory response while a Th2-humoral inflammation is required for pregnancy maintenance. The treatment of repeated implantation failure in spite of transfer of good-quality embryos continues to be a dilemma [10].

Barash et al. [11] were the first to study the effect of endometrial scratching on the pregnancy outcome [12]. They demonstrated a significant doubling of the implantation, clinical pregnancy, and live birth rates in patients who underwent endometrial scraping in the cycle immediately preceding the IVF cycle. They hypothesized that the injury inflicted on the endometrium could lead to a massive secretion of growth factors and cytokines during the process of wound healing, which could help in implantation.

Aims and Objectives

1. To assess the incidence of undiagnosed intrauterine pathology based on pre IVF Hysteroscopy findings and compares it with the findings of USG.
2. To assess the pregnancy rate following the endometrial scratching.

Methodology

A prospective cohort study was conducted during June 2012 to May 2015 at KJK Hospital, Trivandrum. All patients undergoing IVF in the said duration are scheduled for Pre IVF Hysteroscopy prior to the onset of periods. A total of 362 women were included in the study.

Technique

All women in whom hysteroscopy was done were informed about the technique and the potential risks in the form of a written consent. 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 five to nine millimeters; 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 scratching with the scope itself and the material obtained was sent for histopathological examination.

In order to assess the impact of endometrial scratching, it was done on 50% of the study population.

Table 2: Comparison of the findings between hysteroscopy and ultrasonogram.

Findings	USG	Hysteroscopy	P value (Chi-square test)
Pathology detected	15	64	<.0001
No pathology	332	283	
Total	347	347	
Sensitivity of Hysteroscopy			100%
Specificity of hysteroscopy			85%

Protocol of stimulation in subsequent IVF/ICSI attempts

Depending upon the diagnosis and the procedure done, the women were either stimulated immediately or after some period for IVF/ICSI cycle. The women were downregulated with oral contraceptive pills and Gonadotropin-releasing hormone (GnRH) analogues. Injection HMG (Human Menopausal Gonadotrophin) was started from the second day of menses and simultaneous follicular monitoring was done from the sixth day. Injection HCG (Human Chorionic Gonadotrophin) was given when a minimum of three leading follicles were 16.18 mm size. Thirty-six hours later oocyte retrieval was performed followed by IVF/ICSI, and then the embryo transfer. Data entry and analysis was performed in SPSS version 17.0.

Results

Among the 362 women 15 were excluded from the study as embryo transfer was not done on them and so the sample size was 347. The demographic parameters among the study population shows that the mean age of the mothers was 36.25 years and their mean duration of marriage life was 5.75 years. For majority of the study population it was the 2nd attempt for IVF (Table 1). The uterine pathologies which were picked up hysteroscopy was almost 4 times more than the uterine anomalies reported by USG. The sensitivity (100%) and specificity (85%) was much higher for hysteroscopy when compared with USG (Table 2).

The most common pathology detected by hysteroscopy among the study population was polyp followed by adhesions. All the pathologies detected by hysteroscopy were corrected by various interventions. The various pathologies detected and the interventions done through hysteroscopy were highlighted under Table 3.

For assessing the impact of endometrial scratching the study

Table 3: Distribution of the study population based on the type of pathologies detected by hysteroscopy and the interventions done.

Type of pathologies	Number	Percentage	Type of interventions	Number	Percentage
Polyp	37	57.8%	Polypectomy	30	58.8%
Adhesions	6	9.3%	Biopsy	7	13.7%
Arcuate	6	9.3%	Adhesiolysis	6	11.7%
Partial septum	6	9.3%	Septal resection	6	11.7%
Atrophic	2	3.1%	SMF resection	2	3.9%
Bulge in anterior wall	2	3.1%	Total	51	100%
SMF	2	3.1%			
Thick endometrium	2	3.1%			
Bicornuate	1	1.5%			
Total	64	100%			

Table 4: Endometrial scratching and the impact of pregnancy.

Endometrial scratching	Urine pregnancy test positive	Urine pregnancy test negative	P value (Chi square test)
Done (n=175)	106 (60.5%)	69 (39.4%)	<.00001
Not done (n=172)	16 (9.3%)	156 (90.6%)	
Total	122	225	

population were divided into two groups for one group (n=175) the scratching was done and for the other group the scratching was not done (n=172). Among the patients for whom the scratching was done, in the follow up 106 had clinical pregnancy which was confirmed by urine pregnancy test. There was a statistically significant difference in the occurrence of clinical pregnancy among the patients for whom endometrial scratching was done when compared to those who had not undergone endometrial scratching ($p < .0001$) (Table 4).

Discussion

Several studies have compared the diagnostic values of transvaginal ultrasonography and hysteroscopy in diagnosing uterine pathologies. However, distributions of the uterine conditions vary in those samples. A recent study by vitner et al. found higher sensitivity and specificity for hysteroscopy in diagnosing uterine myomas, when compared to TVU; whereas, TVU had higher sensitivity for diagnosing the retained products of conception [13]. On the other hand, they failed to find a statistical difference between the two methods for the diagnosis of the polyps. In that study, the frequencies of endometrial polyps, uterine myomas and retained products of conception were close to each other: 27, 32 and 38% of the sample population, respectively. In contrast, uterine polyps comprised a great proportion of the patient sample in this study (n=37, 57.8%), and we found better sensitivity and specificity for diagnosing polyps with hysteroscopy.

Similar to the findings in this study, Mukhopadhyay et al. found a high sensitivity (71.4%) and specificity (100.0%) for hysteroscopy for diagnosing polyps [14]; with strong agreement with biopsy findings ($k=0.81$). Soguktas et al. found better diagnostic value for hysteroscopy when compared to both saline infusion sonography and transvaginal ultrasonography in detecting uterine polyps; however, for detection of any uterine pathology, hysteroscopy and saline infusion sonography had similar efficacy but better than transvaginal ultrasonography [15]. Similarly, Mathlouthi et al. [16] and Yela et al. [17] found diagnostic values in favor of hysteroscopy for the diagnosis of uterine pathologies. In the study by Yela et al., the specificity of TVU in particular was remarkably low (7.4%) for the detection of uterine disease [17]. Kasraeian et al. examined the diagnostic value of transvaginal ultrasonography in non-bleeding postmenopausal women and found only moderate accuracy to diagnose uterine pathologies [18].

The place of routine hysteroscopy in the management of infertile women without other diagnosed or doubtful intrauterine pathologies is still a matter of debate [19]. The two main problems 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 [20]. Nevertheless, in a study by Shoker *et al.*, it was suggested that 26% of the patients with normal Hysterosalpingography were with abnormal

hysteroscopic findings [21].

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.* [22] 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. Women who had myomectomies for myomas more than two centimeters had significantly higher pregnancy and live birth rates than women in whom myomectomy was not done [23].

The role of hysteroscopic septum resection in patients with septate uterus has also been studied extensively [24]. 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.

The local injury of the endometrium in IVF patients substantially increased the incidence of pregnancy and more than doubled the rate of live birth rates. Moreover, this protocol that increased the implantation rate did not enhance the risk of multiple pregnancies.

The evidence is strongly in favour of inducing local endometrial injury in the preceding cycle of ovarian stimulation to improve pregnancy outcomes in women with unexplained RIF. However, large randomized studies are required before iatrogenic induction of local endometrial injury can be warranted in routine clinical practice.

Some women undergoing IVF treatment fail to conceive despite several attempts with good-quality embryos and no identifiable reason. We call this "recurrent implantation failure" (RIF) where the embryo fails to embed or implant within the lining of the womb. Studies have shown that inducing injury to the lining of the womb in the cycle before starting ovarian stimulation for IVF can help improve the chances of achieving pregnancy. Injury can be induced by either scratching the lining of the womb with biopsy cannula or through hysteroscopy. Inducing injury is 70% more likely to result in a clinical pregnancy as opposed to no treatment.

Furthermore, scratching of the lining was 2-times more likely to result in a clinical pregnancy compared with hysteroscopic evaluation of the uterus. In women with RIF, inducing local injury to the womb lining in the cycle prior to starting ovarian stimulation for IVF can improve pregnancy outcomes [25]. So, endometrial scratching in a systematic manner by non traumatizing instrument is associated with higher implantation potential.

Conclusion

The role of hysteroscopy in patients undergoing IVF seems to be vital for patients in whom an IVF is being contemplated, for 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. The clinical pregnancy and implantation rates significantly increase after endometrial scratching in same cycle in patients with good-quality embryos. This phenomenon could be due to the injury-induced endometrial decidualization secondary to upregulation of genes encoding for locally acting mediators.

References

- Andersen AN, Goossens V, Ferraretti AP, Bhattacharya S, Felberbaum R, de MJ, et al. Assisted reproductive technology in Europe, 2004: results generated from European registers by ESHRE. *Hum Reprod*. 2008; 23: 756-771.
- Stillman RJ, Richter KS, Banks NK, Graham JR. Elective single-embryo transfer: a 6-year progressive implementation of 784 single blast cyst transfers and the influence of payment method on patient choice. *Fertil Steril*. 2009; 92: 1895-1906.
- Rogers PA, Milne BJ, Trounson AO. A model to show human uterine receptivity and embryo viability following ovarian stimulation for in vitro fertilization. *J In Vitro Fert Embryo Transf*. 1986; 3: 93-98.
- Bozdag G, Aksan G, Esinler I, Yarali H. What is the role of office hysteroscopy in women with failed IVF cycles? *Reprod Biomed Online*. 2008; 17: 410-415.
- Koskas M, Mergui JL, Yazbeck C, Uzan S, Nizard J. Office hysteroscopy for infertility: a series of 557 consecutive cases. *Obstet Gynecol Int*. 2010.
- Brown SE, Coddington CC, Schnorr J, Toner JP, Gibbons W, Oebninger S. Evaluation of outpatient hysteroscopy, saline infusion hysterosonography, and hysterosalpingography in infertile women: a prospective, randomized study. *Fertil Steril*. 2000; 74: 1029-1034.
- Golan A, Eilat E, Ron-El R, Herman A, Soffer Y, Bukovsky I. Hysteroscopy is superior to hysterosalpingography in infertility investigation. *Acta Obstet Gynecol Scand*. 1996; 75: 654-656.
- Roma Dalfo' A, Ubada B, Ubada A, Monzon M, Rotger R, Ramos R, et al. Diagnostic value of hysterosalpingography in the detection of intrauterine abnormalities: a comparison with hysteroscopy. *AJR Am J Roentgenol*. 2004; 183: 1405-1409.
- Pundir J, El Toukhy T. Uterine cavity assessment prior to IVF. *Women's Health*. 2010; 6: 841-848.
- Wael S, Nossair, Manal M. El Behery, Mohamed Al S, Farag. Endometrial Scratch-Suction and Implantation Failure. *Open Journal of Obstetrics and Gynecology*. 2014; 4: 217-227.
- Barash A, Dekel N, Fieldust S, Segal I, Schechtman E, Granot I. Local Injury to the Endometrium Doubles the Incidence of Successful Pregnancies in Patients Undergoing *in Vitro* Fertilization. *Fertility and Sterility*. 2003; 79: 1317-1322.
- Granot I, Gnainsky Y, Dekel N. Endometrial Inflammation and Effect on Implantation Improvement and Pregnancy Outcome. *Reproduction*. 2012; 144, 661-668.
- Vitner D, Filmer S, Goldstein I, Khatib N, Weiner Z. A comparison between ultrasonography and hysteroscopy in the diagnosis of uterine pathology. *Eur J Obstet Gynecol Reprod Biol*. 2013; 171: 143-145.
- Mukhopadhyay S, Bhattacharyya SK, Ganguly RP, Patra KK, Bhattacharya N, Barman SC. Comparative evaluation of perimenopausal abnormal uterine bleeding by transvaginal sonography, hysteroscopy and endometrial biopsy. *J Indian Med Assoc* 2007; 105: 624, 626, 628.
- Soguktas S, Cogendez E, Kayatas SE, Asoglu MR, Selcuk S, Ertekin A. Comparison of saline infusion sonohysterography and hysteroscopy in diagnosis of premenopausal women with abnormal uterine bleeding. *Eur J Obstet Gynecol Reprod Biol*. 2012; 161: 66-70.
- Mathlouthi N, Slimani O, Ferchichi A, Ben Temime R, Makhlof T, Attia L et al. [Postmenopausal bleeding. Comparison between ultrasonography, hysteroscopy and histology results]. *Tunis Med*. 2013; 91: 99-103.
- Yela DA, Ravacci SH, Monteiro IM, Pereira KC, Gabiatti JR. [Comparative study of transvaginal sonography and outpatient hysteroscopy for detection of pathologic endometrial lesions in postmenopausal women]. *Rev Assoc Med Bras*. 2009; 55: 553-556.
- Kasraeian M, Asadi N, Ghaffarpasand F, Karimi AA. Value of transvaginal ultrasonography in endometrial evaluation of non-bleeding postmenopausal women. *Climacteric*. 2011; 14: 126-131.
- De Placido G, Clarizia R, Cadente C, Castaldo G, Romano C, Mollo A, et al. Ongoing debate the real significance of the observed uterine pathology on fertility. *Eur J Reprod Biol*. 2007; 135: 83-87.
- Crosignani PG, Rubin BL. Optimal use of infertility diagnostic tests and treatments: The ESHRE Capri Workshop Group. *Hum Reprod*. 2000; 15: 723-732.
- Shokeir TA, Shalan HM, El Shafei MN. Significance of endometrial polyps detected hysteroscopically in infertile women. *J Obstet Gynecol*. 2004; 30: 84-89.
- Lass A, Williams G, Abusheikha N, Brinsden P. The effects of endometrial polyps on *in vitro* fertilisation. *J Assist Reprod Genet*. 1999; 16: 410-415.
- Pritts EA. Fibroids and Infertility: A systematic review of the evidence. *Obstet Gynecol Surv*. 2001; 56: 483-491.
- Grimbizis GF, Camus M, Tarlatzis BC, Bontis JN, Devroey P. Clinica implications of uterine malformations and hysteroscopic treatment results. *Hum Reprod Update*. 2001; 7: 161-174.
- Potdar N, Gelbaya T, Nardo LG. Endometrial Injury to Overcome Recurrent Embryo Implantation Failure: A Systematic Review and Meta-Analysis. *Reproductive BioMedicine Online*. 2012; 25: 561-571.