Comparison between findings of saline infusion sonohysterography and office hysteroscopy in patients with recurrent implantation failure

Ahmed Reda, Ahmed Sherif Abdel Hamid, Rowaa Mostafa, Eman Refaei
Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Address for correspondence:
Dr. Ahmed Reda,
4 Abbas Elsherif Street,
Helmeyat Elzaitoon,
Cairo, Egypt.
E-mail: reda.ahmed@yandex.com

Received: 01.04.2016
Review completed: 15.06.2016
Accepted: 24.11.2016

Access this article online
Quick Response Code:

Website: www.jhrsonline.org

DOI: 10.4103/0974-1208.197661

ABSTRACT

AIM: This study aims to determine the accuracy of saline infusion sonohysterography (SIS) in the diagnosis of intrauterine pathologies in women with recurrent implantation failure (RIF). **SETTINGS AND DESIGN:** This is a prospective cross-over study which was carried out during the period between December 2013 and July 2014. **MATERIALS AND METHODS:** The study involved sixty subfertile women with a history of RIF. All cases underwent a transvaginal ultrasonography, SIS and then an office hysteroscopy (1 day after SIS) during early follicular phase. SIS was carried out by same sonographer, and then hysteroscopy was carried out by same gynecologist who was kept blind to findings at SIS. **STATISTICAL ANALYSIS:** Was done using IBM© SPSS© Statistics version 22. The sensitivity of SIS was calculated as it equals: True positive by SIS/all positive (true cases by hysteroscopy) and specificity was calculated as it equals: True negative by SIS/all negatives (normal by hysteroscopy). **RESULTS:** Overall uterine abnormalities were significantly less likely to be identified with SIS compared to hysteroscopy ($P = 0.002$), but analysis of each finding separately demonstrated a comparable difference between SIS and hysteroscopy ($P > 0.05$). We found that the sensitivity, specificity, positive predictive value, and negative predictive value of SIS to detect intrauterine pathology is 41.2%, 100%, 100%, and 81.1%, respectively. **CONCLUSION:** Our findings suggest a good role of SIS in the workup for RIF saving more invasive procedure for selected cases.

KEY WORDS: Hysterosonography, recurrent implantation failure, saline infusion sonohysterography, sonohysterography

INTRODUCTION

The use of assisted reproductive technologies (ART) has expanded worldwide after the reported birth in 1978 following the first successful *in vitro* fertilization (IVF) procedure.[1] With the evolution of ART protocols and availability of various diagnostic tools allowing good assessment of the genital tract and selection of high-quality embryos, the reported pregnancy rate after ART is still low.[2] Pregnancy rate is reported to be only one-third of IVF cycles started and with live birth rate of one-fourth.[3]

Embryo quality and receptivity of the uterus affect the success rate of IVF. Intrauterine pathology is one of the factors that may affect the success of IVF due to its effect on the endometrium receptivity.[4] Failure of IVF may also be due to various factors such as suboptimal laboratory culture conditions and faults in techniques of embryo transfer.[5]

Some couples have repeated IVF failures, even in successful units with high pregnancy and delivery rates.[5] Clinicians define

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Reda A, Hamid AS, Mostafa R, Refaei E. Comparison between findings of saline infusion sonohysterography and office hysteroscopy in patients with recurrent implantation failure. J Hum Reprod Sci 2016;9:236-40.

© 2016 Journal of Human Reproductive Sciences | Published by Wolters Kluwer - Medknow

recurrent implantation failure (RIF) as failure to achieve a pregnancy following 2–6 IVF cycles, in which more than 10 high-grade embryos were transferred to the uterus.[6]

More recently, RIF is defined as it refers to failure to achieve a clinical pregnancy after transfer of at least four good-quality embryos in a minimum of three fresh or frozen cycles in a woman under the age of 40 years.[7]

The etiology of RIF has not been fully elucidated but it can be broadly attributed to embryonic or uterine factors, but in most cases, the cause remains unexplained.[5] The incidence of Intrauterine pathologies in women with RIF is reported to be 25% of infertile patients.[8] In an observational study evaluating 1475 women with RIF, the reported incidence of uterine pathologies was 36.6%.[9]

Vaginal ultrasonography, hysterosalpingography, saline infusion sonohysterography (SIS), and hysteroscopy are tools that aid in the diagnosis of intrauterine lesions.[10]

Hysteroscopy has become an important tool in the evaluation of infertility as it provides visualizing the uterine cavity and identifying any pathology.[11] also, uterine cavity assessment by hysteroscopy has been demonstrated to be useful in women with two IVF failures.[12,13] Hence, hysteroscopy has become one of the common investigations proposed after RIF.[14]

SIS is a technique in which a catheter is placed into the endometrial cavity, and sterile saline is instilled to separate the walls of the endometrium.[15] Sonohysterography, hysterosonography, transvaginal sonography with fluid contrast augmentation and SIS are used synonymously for this technique.[16,17] SIS has been shown to be an accurate and safe method in uterine cavity assessment.[18] It is also less invasive, less costly, and less painful.[19]

The aim of the current work is to determine the accuracy of SIS in the diagnosis of intrauterine pathologies in women with RIF.

MATERIALS AND METHODS

This study is a prospective cross-over study which was carried out from December 2013 to July 2014. The study protocol was in agreement with the Helsinki Declaration for Ethical Medical Research (last updated in Seoul, South Korea, 2008). A written informed consent was signed by each woman before enrollment in the study after detailed explanation of the objectives and protocol of the study.

The study involved sixty subfertile women with a history of RIF. RIF is defined as failure to achieve a clinical pregnancy after three IVF cycles despite transfer of at least four good-quality embryos.[7] Women aged 40 years or more and patients with chronic pelvic disease or chronic systemic illness were excluded from the study.

All cases underwent a transvaginal ultrasonography, SIS and then an office hysteroscopy during early follicular phase of the same cycle. Women were scheduled for hysteroscopy during early follicular phase of their menstrual cycle (between day 7 and 11). A transvaginal ultrasonography and SIS were carried out 1 day before hysteroscopy.

SIS was done by the same sonographer and was carried out using SonoAce X4 ultrasound system (Samsung Medison) with a 5 MHZ transvaginal probe.

The patient was examined in lithotomy position, an initial transvaginal ultrasound scan was done then a sterile speculum was inserted into the vagina, and the cervix is visualized and cleaned, and the anterior lip was grasped with a single-toothed tenaculum if needed. A pediatric Foley's catheter sized 6 Fr was threaded into the cervical canal with a ring forceps after being flushed with saline to remove air bubbles. The catheter was fixed by inflating its balloon with 1.5–2 ml saline. The speculum was removed carefully so as not to dislodge the catheter and the vaginal probe was reinserted, and the scan was done after uterine cavity distention by injection of 10 ml of sterile isotonic saline through the catheter.

Office hysteroscopy was carried out 1 day after SIS using Karl Storz (KARL STORZ GmbH and Co. KG, Tuttlingen, Germany) telescope: Rigid 30° Harmou II Hysteroscope model 26157 BT with a 3.5 mm outer diameter of the sheath. The procedure was carried out by the same gynecologist who was kept blind to findings at SIS.

After vaginal disinfection, the tip of the hysteroscope was positioned in the vaginal introitus and the labia being slightly separated with the examiner fingers and the vagina was distended using normal saline. The scope was directed to the posterior fornix until portiovaginalis of the uterine cervix was visualized then the scope was withdrawn slowly to visualize the external os, then it was moved through it to the uterine cavity. The uterine cavity was then systematically examined and any pathology found was recorded.

Statistical analysis was done using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA). Assuming that hysteroscopy is the gold standard for identification of intrauterine pathologies. The sensitivity of SIS was calculated as it equals: True positive by SIS/all positive (true cases by hysteroscopy) and specificity was calculated

as it equals: True negative by SIS/all negatives (normal by hysteroscopy).

RESULTS

The mean ± standard deviation (SD) of age of the studied patients was 30.55 ± 3.62 years (range from 22 to 35), and the mean ± SD of the duration of infertility was 6.32 ± 3.24 years with a range between 2 and 17 years. Of the included cases in this study, 49 patients (81.7%) had primary infertility whereas 11 patients (18.3%) had secondary infertility.

Initial transvaginal ultrasonography showed abnormalities in 4 patients (6.7%); 2 cases (3.3%) with endometrial polyp and the other 2 cases (3.3%) had a submucosal myoma. SIS was carried out in the same setting with abnormalities were detected in 7 cases (11.7%); endometrial polyp was detected in 5 patients (8.3%) and the remaining 2 cases (3.3%) had submucosl myoma [Table 1].

As regards hysteroscopy, intrauterine abnormalities were detected in a total of 16 cases (26.6%); endometrial polyp was identified in 5 cases (11.7%), submucosal myoma in 2 cases (3.3%), abnormal shape of uterine cavity in 1 case (1.7%), uterine septum and intrauterine adhesions (IUA) were identified in 4 cases (6.7%) each [Table 1].

As shown in Table 1, overall uterine abnormalities were significantly less likely to be identified with SIS compared to hysteroscopy ($P = 0.002$), but analysis of each finding separately demonstrated a comparable difference between SIS and hysteroscopy ($P > 0.05$).

Table 1: Comparison between saline infusion sonohysterography and hysteroscopy in detection of intrauterine abnormalities

	Saline infusion sonohysterography	Hysteroscopy	*P*
Polyp	5 (8.3)	5 (8.3)	1.00
Abnormal shape	0	1 (1.7)	1.00
Septum	0	4 (6.7)	0.125
Intrauterine adhesions	0	4 (6.7)	0.125
Submucosal myoma	2 (3.3)	2 (3.3)	1.00
Total	7 (11.7)	16 (26.6)	0.002*

Data presented as *n* (%), analysis done using McNemar test, *= significant

We found that the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of SIS to detect intrauterine pathology is 41.2%, 100%, 100%, and 81.1%, respectively. Validity of SIS to detect each pathology is listed in Table 2.

DISCUSSION

Intrauterine pathologies revealed during hysteroscopy are diagnosed in about 50% of women with RIF.[20] Makris *et al*.[21] reported that 40.5% of cases with RIF included in their study had an intrauterine abnormality detected with hysteroscopy. Higher incidence was also reported by Arefi *et al*.[22] who reported abnormalities in 59.5% of their patients. In the current study, we detected intrauterine abnormalities in 26.6% of our patients which is somewhat lower than what reported which may be due to we did not exclude other causes of RIF before enrollment.

With direct visualization of the uterine cavity, hysteroscopy is considered as the gold standard for diagnosis of any intrauterine lesion. However, due to its high cost and need for expertise gynecologist to carry out the procedure besides patients discomfort encountered during the procedure, clinicians may need an alternative accurate tool aiding in the detection of intrauterine pathologies.

Transvaginal ultrasonography is reported to be more accurate than hysterosalpingography in intrauterine lesions detection. The reported sensitivity and specificity for transvaginal sonography is 81.8% and 96.3% respectively with a PPV of 73.8% and NPV of 97.6%.[23,24] SIS is reported to be superior to transvaginal ultrasonography in detecting such abnormalities.[25]

In a systematic review and meta-analysis, de Kroon *et al*.[18] demonstrated that SIS is an accurate and safe method in detection of intrauterine abnormalities. SIS was also demonstrated to be as accurate as hysteroscopy in detecting intrauterine abnormalities.[26]

In this study, the overall accuracy of SIS in detecting intrauterine abnormalities was significantly less than hysteroscopy although analysis of the accuracy in detecting

Table 2: Validity of saline infusion sonohysterography in detection of intrauterine abnormalities

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Polyp	100	100	100	100
Abnormal shape	0	100	0	98.3
Septum	0	100	0	93.3
Intrauterine adhesions	0	100	0	93.3
Submucosal myoma	100	100	100	100
Total	41.2	100	81.13	100

a specific pathology separately showed a nonsignificant difference between both procedures.

Our finding is supported by Qazizadeh *et al*.[19] who reported that SIS is significantly less accurate than hysteroscopy in detecting intrauterine lesions and stated that small lesions may be unnoticed with SIS.

The defect of SIS in detecting intrauterine lesion in our study was in detecting uterine septum and IUA. Hysteroscopy identified septum in 4 cases, 3 of them had a small septum <0.5 cm and the 4th had a subseptate uterus. All cases with IUA detected in this study were peripheral adhesions. This may explain that SIS could not detect these cases.

We found the diagnostic accuracy of SIS in detecting endometrial polyp and submucosal myoma to be 100%. In agreement with our results, Shokeir and Abdel-Shaheed[27] reported that SIS correctly detected 6 cases with submucosal myoma identified with hysteroscopy.

Bingol *et al*.[28] in their study demonstrated that SIS detected endometrial polyp and submucosal myoma in 121 cases (35%) and 101 cases (29.2%) respectively which was confirmed with hysteroscopy in 109 cases (31.5%) and 102 cases (29.5%) respectively. The accuracy in detecting submucosal myoma is nearly 100% and small false positive rate in detecting endometrial polyp. The same study disagrees with our finding in that SIS detected IUA in all cases identified with hysteroscopy. The nature of these adhesions was not specified.

In the current study, SIS has sensitivity, specificity, PPV and NPV of 41.2%, 100%, 100%, and 81.1%, respectively. Qazizadeh *et al*.[19] agree with our results as they reported sensitivity, specificity, PPV, and NPV of 30%, 100%, 100%, and 30%, respectively.

In disagreement with these results, some studies reported SIS to be more sensitive. Ragni *et al*.[29] reported sensitivity, specificity, PPV and NPV of 98%, 94%, 95%, and 98%, respectively. Furthermore, Alborzi *et al*.[30] reported that SIS had sensitivity of 94.1%, specificity of 95%, PPV of 96%, and NPV of 90%.

A weak point in our study is the small proportion of patients identified with intrauterine abnormality which may have an impact on the presented results. SIS detected all cases with endometrial polyp and submucosal myoma which makes it an accurate tool to identify such cases also with its high specificity; SIS may confirm uterine cavity normality. Thus, hysteroscopy may be indicated in selected cases.

CONCLUSION

SIS was accurate in detecting endometrial polyp and submucosal myoma but defective to diagnose septum and IUA. This suggests a good role of SIS in the workup for RIF saving more invasive procedure for selected cases.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Steptoe PC, Edwards RG. Birth after the reimplantation of a human embryo. Lancet 1978;2:366.
2. Andersen AN, Gianaroli L, Felberbaum R, de Mouzon J, Nygren KG; European IVF-Monitoring Programme (EIM), European Society of Human Reproduction and Embryology (ESHRE). Assisted reproductive technology in Europe, 2001. Results generated from European registers by ESHRE. Hum Reprod 2005;20:1158-76.
3. Society for Assisted Reproductive Technology; American Society for Reproductive Medicine. Assisted reproductive technology in the United States: 2001 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology registry. Fertil Steril 2007;87:1253-66.
4. Moini A, Kiani K, Ghaffari F, Hosseini F. Hysteroscopic findings in patients with a history of two implantation failures following *in vitro* fertilization. Int J Fertil Steril 2012;6:27-30.
5. Margalioth EJ, Ben-Chetrit A, Gal M, Eldar-Geva T. Investigation and treatment of repeated implantation failure following IVF-ET. Hum Reprod 2006;21:3036-43.
6. Tan BK, Vandekerckhove P, Kennedy R, Keay SD. Investigation and current management of recurrent IVF treatment failure in the UK. BJOG 2005;112:773-80.
7. Coughlan C, Ledger W, Wang Q, Liu F, Demirol A, Gurgan T, *et al*. Recurrent implantation failure: Definition and management. Reprod Biomed Online 2014;28:14-38.
8. Levi Setti PE, Colombo GV, Savasi V, Bulletti C, Albani E, Ferrazzi E. Implantation failure in assisted reproduction technology and a critical approach to treatment. Ann N Y Acad Sci 2004;1034:184-99.
9. Ly KD, Aziz N, Safi J, Agarwal A. Evidence- based management of infertile couples with repeated implantation failure following IVF. Curr Womens Health Rev 2010;6:200-18.
10. Oliveira FG, Abdelmassih VG, Diamond MP, Dozortsev D, Nagy ZP, Abdelmassih R. Uterine cavity findings and hysteroscopic interventions in patients undergoing *in vitro* fertilization-embryo transfer who repeatedly cannot conceive. Fertil Steril 2003;80:1371-5.
11. Nayak PK, Mahapatra PC, Mallick J, Swain S, Mitra S, Sahoo J. Role of diagnostic hystero-laparoscopy in the evaluation of infertility: A retrospective study of 300 patients. J Hum Reprod Sci 2013;6:32-4.
12. Dicker D, Ashkenazi J, Feldberg D, Farhi J, Shalev J, Ben-Rafael Z. The value of repeat hysteroscopic evaluation in patients with failed *in vitro* fertilization transfer cycles. Fertil Steril 1992;58:833-5.
13. Noyes N. Hysteroscopic cervical canal shaving: A new therapy for cervical stenosis before embryo transfer in patients undergoing *in vitro* fertilization. Fertil Steril 1999;71:965-6.
14. El-Toukhy T, Campo R, Sunkara SK, Khalaf Y, Coomarasamy A. A multi-centre randomised controlled study of pre-IVF outpatient hysteroscopy in women with recurrent IVF implantation failure: Trial of

outpatient hysteroscopy – [TROPHY] in IVF. Reprod Health 2009;6:20.
15. Berridge DL, Winter TC. Saline infusion sonohysterography: Technique, indications, and imaging findings. J Ultrasound Med 2004;23:97-112.
16. Syrop CH, Sahakian V. Transvaginal sonographic detection of endometrial polyps with fluid contrast augmentation. Obstet Gynecol 1992;79:1041-3.
17. Goldstein RB, Bree RL, Benson CB, Benacerraf BR, Bloss JD, Carlos R, *et al*. Evaluation of the woman with postmenopausal bleeding: Society of radiologists in ultrasound-sponsored consensus conference statement. J Ultrasound Med 2001;20:1025-36.
18. de Kroon CD, de Bock GH, Dieben SW, Jansen FW. Saline contrast hysterosonography in abnormal uterine bleeding: A systematic review and meta-analysis. BJOG 2003;110:938-47.
19. Qazizadeh SH, Nezhad AQ, Rashidi BH, Aqsa MM, Sohrabvand F, Tehraninejad S, *et al*. Comparison of sonohysterography and hysterosalpingography with hysteroscopy in the diagnosis of intrauterine lesions. Iran J Radiol 2006;4:37-41.
20. 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;17:410-5.
21. Makris N, Xygakis A, Michalas S, Dachlythras M, Prevedourakis C. Day clinic diagnostic hysteroscopy in a state hospital. Clin Exp Obstet Gynecol 1999;26:91-2.
22. Arefi S, Soltanghoraee H, Zarnani AH, Tabaei AS, Novin MG, Zeraati H, *et al*. Repeated IVF/ICSI-ETs failures and impact of hysteroscopy. Iran J Reprod Med 2008;6:19-24.
23. Shalev J, Meizner I, Bar-Hava I, Dicker D, Mashiach R, Ben-Rafael Z. Predictive value of transvaginal sonography performed before routine diagnostic hysteroscopy for evaluation of infertility. Fertil Steril 2000;73:412-7.
24. Hauge K, Flo K, Riedhart M, Granberg S. Can ultrasound-based investigations replace laparoscopy and hysteroscopy in infertility? Eur J Obstet Gynecol Reprod Biol 2000;92:167-70.
25. Alborzi S, Dehbashi S, Khodaee R. Sonohysterosalpingographic screening for infertile patients. Int J Gynaecol Obstet 2003;82:57-62.
26. Kelekci S, Kaya E, Alan M, Alan Y, Bilge U, Mollamahmutoglu L. Comparison of transvaginal sonography, saline infusion sonography, and office hysteroscopy in reproductive-aged women with or without abnormal uterine bleeding. Fertil Steril 2005;84:682-6.
27. Shokeir T, Abdelshaheed M. Sonohysterography as a first-line evaluation for uterine abnormalities in women with recurrent failed *in vitro* fertilization-embryo transfer. Fertil Steril 2009;91 4 Suppl: 1321-2.
28. Bingol B, Gunenc Z, Gedikbasi A, Guner H, Tasdemir S, Tiras B. Comparison of diagnostic accuracy of saline infusion sonohysterography, transvaginal sonography and hysteroscopy. J Obstet Gynaecol 2011;31:54-8.
29. Ragni G, Diaferia D, Vegetti W, Colombo M, Arnoldi M, Crosignani PG. Effectiveness of sonohysterography in infertile patient work-up: A comparison with transvaginal ultrasonography and hysteroscopy. Gynecol Obstet Invest 2005;59:184-8.
30. Alborzi S, Parsanezhad ME, Mahmoodian N, Alborzi S, Alborzi M. Sonohysterography versus transvaginal sonography for screening of patients with abnormal uterine bleeding. Int J Gynaecol Obstet 2007;96:20-3.