Hysterosalpingo-Contrast Sonography With a Saline-Air Device Is Equivalent to Hysterosalpingography Only in the Presence of Tubal Patency

Isela M. Robertshaw, MD, Julie M. Sroga, MD, April E. Batcheller, MD, Alan M. Martinez, MD, Thomas C. Winter III, MD, Kristin Sinning, MD, MPH, Rose Maxwell, PhD, Steven R. Lindheim, MD, MMM

Objectives—To compare hysterosalpingo-contrast sonography with a saline-air device to hysterosalpingography for evaluating tubal patency.

Methods—Eighty women undergoing infertility evaluations were recruited for this prospective cohort study. All patients underwent both office-based hysterosalpingo-contrast sonography with a saline-air device and hysterosalpingography as the reference standard, and the fallopian tubes were individually assessed for tubal patency in each procedure. The Cohen κ coefficient was used to assess agreement between each procedure, and the Student *t* test and χ^2 test were used to compare differences in time, pain, and procedural preference.

Results—In total, 75 patients with 148 fallopian tubes were evaluated. Tubal patency on hysterosalpingo-contrast sonography with the saline-air device was noted in 85.8% (n = 127) of tubes compared to 92.5% (n = 137) on hysterosalpingography, with a positive predictive value of 95.2%. Tubal occlusion was noted in 21 tubes (14.2%) on hysterosalpingo-contrast sonography compared to 11 (7.4%) on hysterosalpingography, with a negative predictive value of 23.8% (24 of 28). Overall, hysterosalpingo-contrast sonography agreed with hysterosalpingography in 126 of 148 fallopian tubes (85.1%; $\kappa = 0.47$; $P < .001$). The procedural time and pain scores were significantly greater for hysterosalpingo-contrast sonography compared to hysterosalpingography.

Conclusions—There was a significant degree of agreement between hysterosalpingo-contrast sonography with a saline-air device and hysterosalpingography when the fallopian tube was patent but not when it was occluded. In the absence of patency, further evaluations with hysterosalpingography may be indicated to avoid false-positive results. Although the procedure time and degree of pain appear to be greater, avoidance of radiation exposure by using hysterosalpingo-contrast sonography with a saline-air device may outweigh the drawbacks.

Key Words—gynecologic ultrasound; hysterosalpingo-contrast sonography; hysterosalpingography; pain perception; predictive value; tubal patency

Received August 4, 2015, from the Department of Obstetrics and Gynecology, University of Cincinnati Medical Center, Cincinnati, Ohio USA (I.M.R., J.M.S., A.E.B.); Reproductive Science Center of New Jersey, Lawrenceville, New Jersey USA (A.M.M.); Department of Radiology, University of Utah, Salt Lake City, Utah USA (T.C.W.); and Department of Obstetrics and Gynecology, Wright State University, Boonshoft School of Medicine, Dayton, Ohio USA (K.S., R.M., S.R.L.). Revision requested August 25, 2015. Revised manuscript accepted for publication September 8, 2015.

This work was supported by Cooper Surgical, Inc (Trumbull, CT), and Femasys, Inc (Suwanee, GA).

Address correspondence to Steven R. Lindheim, MD, MMM, Department of Obstetrics and Gynecology, Wright State University, Boonshoft School of Medicine, 128 Apple St, Suite 3800, Weber CHE, Dayton, OH 45409 USA.

E-mail: steven.lindheim@wright.edu

Abbreviations

FDA, Food and Drug Administration; NPV, negative predictive value; PPV, positive predictive value

doi:10.7863/ultra.15.08008

Evaluation of the fallopian tubes is an essential part of the infertility workup, with abnormalities related to the fallopian tubes accounting for up to 40% of female subfertility.[1] Methods currently available include laparoscopy with chromopertubation, hysterosalpingography, and hysterosalpingo-contrast sonography. Previous investigations, using laparoscopy as the reference standard, demonstrated that hysterosalpingography had

sensitivity and specificity of 53% and 87%, respectively, for any tubal disorder and 46% and 95% for bilateral tubal disorders.[2] Hysterosalpingo-contrast sonography, which uses positive ultrasound-enhancing contrast media with transvaginal ultrasound to assess the status of the fallopian tubes as well as the uterine cavity, appears to be as accurate as hysterosalpingography when compared to laparoscopy, with diagnostic accuracy of 65% to 85% for establishing tubal patency.[3–5]

Although laparoscopy is still considered the reference standard, and hysterosalpingography has long been recognized as complementary to laparoscopy for diagnostic evaluation of fallopian tubes, since tubal anatomy can be distinctly appreciated,[6] there has been a move away from these methods. Laparoscopy mandates regional or general anesthesia and incurs substantial surgical costs and risks.[7] In contrast, although hysterosalpingography obviates the need for hysteroscopy or laparoscopy, it is associated with exposure to ionizing radiation and the need for iodinated contrast material.[8–11]

Alternatively, the use of hysterosalpingo-contrast sonography for assessing tubal patency has increasingly been reported since the 1980s; however, its use in evaluating tubal patency has been limited, as the normal fallopian tube is a poor sonic reflector, devoid of the defined interfaces that produce clear organ outlines.[12–14] To enhance transvaginal sonographic visualization of tubal anatomy, a number of contrast agents have been used, including dextran-70 hypertonic fluid (Hyskon; Medisan Pharmaceuticals, Inc, Morristown, NJ), human albumin (Albunex; Mallinckrodt, St Louis, MO), soluble galactose microparticles in an aqueous solution (Echovist; Bayer Schering Pharma AG, Berlin, Germany), perflutren lipid microspheres (Definity; Lantheus Medical Imaging, North Billerica, MA), and newer second-generation agents, including a nontoxic gel containing hydroxyethylcellulose and glycerol (ExEm-Gelw; GynaecologIQ, Delft, the Netherlands).[15–18] Multiple studies comparing hysterosalpingo-contrast sonography (using both 2- and 3-dimensional sonography) to hysterosalpingography have been performed,[19–25] but cost, the need for refrigerated storage, and lack of US Food and Drug Administration (FDA) approval have negated their routine use in the office setting.

Others have substituted a mixture of saline and/or air for more elaborate distending media: some vigorously shake a syringe of saline and air, creating air bubbles immediately before infusion, whereas others have described filling a syringe with both air and saline and tilting the syringe with the intermittent infusion of air, followed by saline in increments of 1 to 3 mL.[26–28] However, air bubble hysterosalpingo-contrast sonography, particularly with 2-dimensional imaging, has limitations, as it is highly observer dependent and is only accurate in the hands of experienced investigators. Recently the FDA approved a saline-air device, which creates and delivers a constant alternating pattern of filtered saline and air as a continuous stream in a controlled fashion, allowing for fallopian tube evaluation under ultrasound guidance.[29,30] Our objective was to determine whether hysterosalpingo-contrast sonography with the saline-air device is equivalent or superior to hysterosalpingography for evaluation of fallopian tube patency and its tolerability in those undergoing hysterosalpingography for infertility evaluations.

Materials and Methods

This study was a prospective clinical trial conducted under an Institutional Review Board–approved protocol. Informed consent was obtained from all patients before their involvement in the trial, and the study was compliant with the Health Insurance Portability and Accountability Act of 1996. The manuscript was designed according to the Standards for the Reporting of Diagnostic Accuracy Studies guidelines.

Patient Selection

Eighty patients undergoing hysterosalpingography for infertility evaluation were recruited to participate between August 2012 and August 2013. Inclusion criteria included all women of childbearing age and undergoing fertility testing. Exclusion criteria included undiagnosed abnormal uterine bleeding, current urogenital disease, history of iodinated contrast agent allergy, abnormal pap smear results, and positive urine pregnancy test results.

Hysterosalpingo-Contrast Sonographic and Hysterosalpingographic Procedures

All procedures were performed by a single physician (S.R.L.) experienced in these techniques. Both procedures, first hysterosalpingo-contrast sonography with the saline-air device (office) followed by hysterosalpingography (radiology suite) approximately 2 to 3 hours later, were performed by the same physician either during the follicular phase of a spontaneous menstrual cycle or after a progestin withdrawal bleed. This decision was for patient convenience and in an attempt to keep the physicians unbiased on the read of the hysterosalpingo-contrast sonographic test given that hysterosalpingography was deemed the reference standard. To quantify pain perception during the procedure, an 11-point (0–10) Likert pain scale numerical

rating schema, on which 0 corresponded to no pain at all and 10 indicated severe pain, was completed before, during, and at the completion of each study.

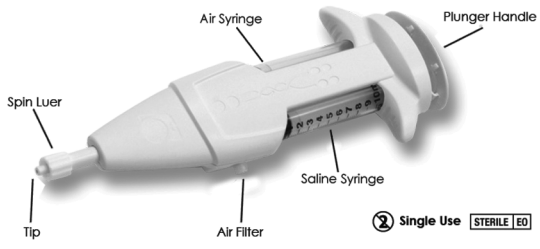
All patients were instructed to take nonsteroidal anti-inflammatory medications of up to 800 mg 1 hour before both the hysterosalpingo-contrast sonography and hysterosalpingography. A preliminary transvaginal sonographic examination was performed in all patients to determine the basic anatomy and uterine and ovarian positions. Subsequently, with the patients in the standard lithotomy position, a speculum examination was performed. The cervix was identified, and the speculum was used to optimally orient the cervix. The cervix was cleansed with a povidone-iodine solution. A 2-lumen 5F balloon catheter (Cooper Surgical, Inc, Trumbull, CT) was flushed with sterile saline before placement. Subsequently, the cervix was canalized with the catheter, with the goal of placing the catheter into the lower uterine segment. After the balloon was inflated with sterile saline, the speculum was removed, and a sterile covered transvaginal ultrasound transducer was inserted (LOGIQ E9; GE Healthcare, Waukesha, WI). During continuous transvaginal imaging, sterile saline was administered through the catheter until an adequate evaluation of the uterine cavity was obtained. Transvaginal sonograms in orthogonal planes were recorded and saved to a picture archiving and communication system (Horizon Medical Imaging; McKesson, San Francisco, CA). The hysterosalpingographic catheter was deflated to further assess the lower uterine segment and then reinflated before the hysterosalpingo-contrast sonographic portion of the study. To evaluate tubal patency, a saline-air device (FemVue; Femasys, Inc, Suwanee, GA; Figure 1) was attached to the catheter.[31] It is designed to simultaneously introduce filtered air and saline in a controlled fashion, creating a constant alternating pattern of saline and air to be used as contrast and allowing visualization of the fallopian tubes. The volume and time for the saline infusion and hysterosalpingo-contrast sonographic portions of the study were documented. If fallopian tube patency was indeterminate for either tube, the patient was repositioned into a 45° oblique position to better visualize the fallopian tube. At the completion of the study, the balloon was deflated and removed. The fallopian tube was considered patent by: (1) visualization of the air bubble and displacement of air within it by the saline solution; (2) detection of air bubbles moving around the ovary; observation of flow around the ovaries may be possible even without visualization of the whole course of the tube; and (3) detection of the fluid and air bubbles in the pouch of Douglas (Figure 2).[26]

For hysterosalpingography, patients were placed in the lithotomy position; the cervix was identified and cleansed; the same 2-lumen 5F balloon catheter (Cooper Surgical, Inc) was flushed; and the cervix was canalized with the catheter, with the goal of placing the catheter into the lower uterine segment and inflating the balloon. The speculum was then removed; iopamidol contrast material (Isovue 250; Bracco Pharmaceuticals, Princeton, NJ) was infused through the catheter; and a fluoroscopic examination was performed during the injection. The hysterosalpingographic findings were considered normal if the uterine cavity and both tubes were well visualized, and the contrast material flowed freely into the peritoneal cavity. If fallopian tube patency was indeterminate for either tube, the patient was repositioned into a 45° oblique position to better visualize the fallopian tube. At the completion of the study, the balloon was deflated and removed. Similarly, the volume and time for the hysterosalpingography were documented.

Patients were asked to assess their level of pain by using a 11-point Likert visual analog pain scale. This pain assessment was performed before each procedure, at the time the balloon catheter was initially inflated, and after completion. Patients were monitored for 10 minutes in the supine position after the procedure.

The primary outcome of interest was the agreement between hysterosalpingo-contrast sonography and hysterosalpingography in evaluating tubal patency. Secondary outcome measures included the degree of agreement with respect to the uterine cavity, time required and total volume required for each procedure, subjective assessment of pain for both procedures, complications, and the preferred diagnostic test. Baseline demographics recorded included age, gravidity, parity, and body mass index, and infertility risk factors, including previous pelvic-cervical surgery, pelvic inflammatory disease endometriosis, and infertility diagnosis, were recorded.

Figure 1. Saline-air device for hysterosalpingo-contrast sonography.[31]



Statistical Analyses

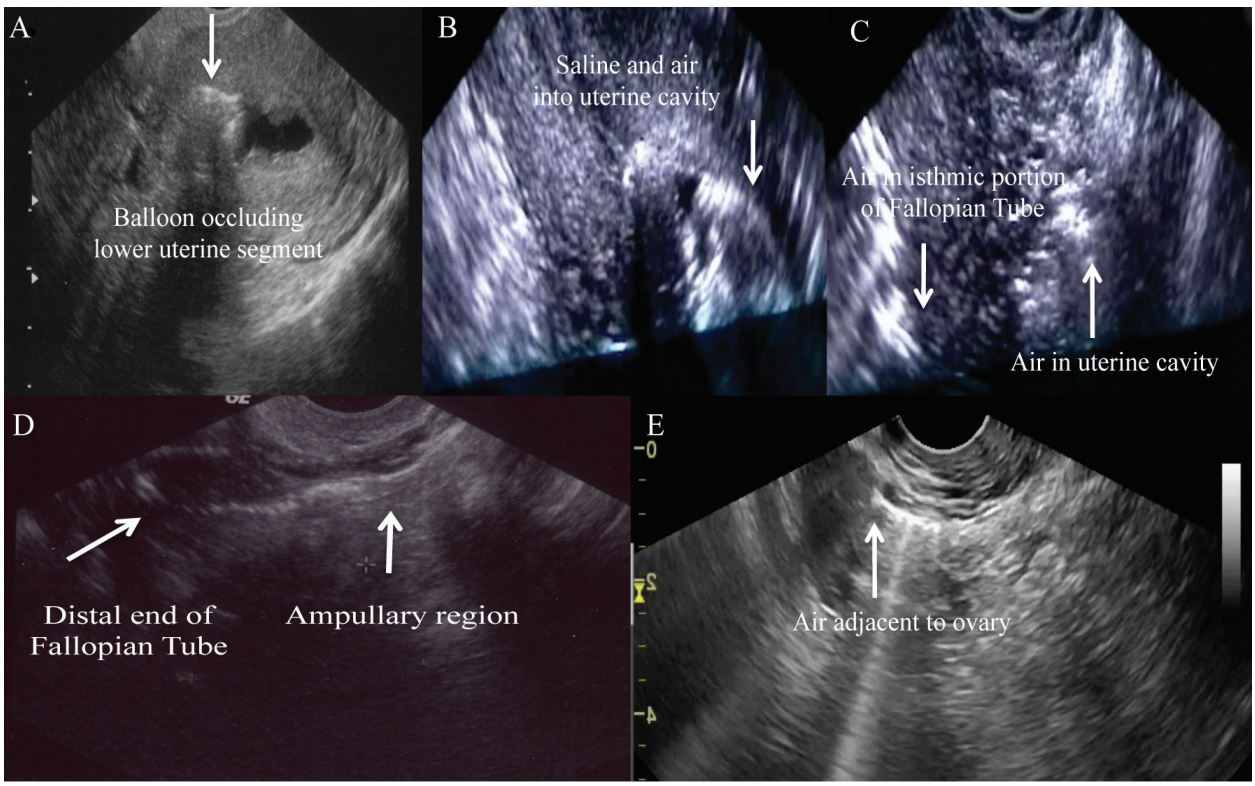
Statistical analyses were performed with SPSS version 18 software (IBM Corporation, Armonk, NY). The sensitivity, specificity, diagnostic accuracy, positive predictive value (PPV), and negative predictive value (NPV) of hysterosalpingo-contrast sonography with the saline-air device were calculated with respect to findings on hysterosalpingography (considered the reference standard). Agreement between each study evaluation was measured by the κ statistic. For this purpose, both studies indicated normal uterine cavity, tubal patency or nonpatency, or an inconclusive result. The κ statistic is similar to a correlation statistic, in that $\kappa = 1$ corresponds to perfect agreement, and $\kappa = 0$ corresponds to no greater agreement than would be expected due to chance. A hypothesis test of $\kappa = 0$ versus $\kappa > 0$ was performed to assess agreement between the study procedures, with a 5%-level result being regarded as significant. The κ statistic itself measured the strength of agreement. The Student *t* test, χ^2 test for categorical comparisons, and Spearman bivariate regression were used to assess secondary measurements. Significance was defined as $P < .05$.

Results

From August 2012 to August 2013, 80 patients were enrolled in the study. Seventy-five patients completed the study: 53 (71%) had primary infertility, and 22 (29%) had secondary infertility, without differences noted between the groups. Two patients refused to undergo the hysterosalpingography because of "significant pain" after the saline infusion sonohysterography and air bubble hysterosalpingo-contrast sonography; 1 had an extreme emotional response due to a previous stillborn fetus while observing the saline infusion sonohysterography and withdrew from the study; and 2 were lost to follow-up. Baseline characteristics are presented in Table 1. No differences were noted between those with primary and secondary infertility (data not shown).

In total, 75 patients and 148 fallopian tubes were evaluated (2 patients had a previous unilateral salpingectomy for an ectopic pregnancy). Tubal patency on hysterosalpingo-contrast sonography with the saline-air device was noted in 85.8% (n = 127) of tubes compared to 92.5% (n = 137)

Figure 2. Hysterosalpingo-contrast sonograms obtained with the saline-air device. **A**, Balloon occluding the lower uterine segment. **B**, Saline and air in the uterine cavity. **C**, Air in the isthmic portion of the fallopian tube. **D**, Air contrast in the ampullary region and distal end of the fallopian tube. **E**, Air adjacent to the ovary.



on hysterosalpingography, with a PPV of 95.2%. Tubal occlusion was noted on 21 (14.2%) hysterosalpingo-contrast sonographic studies compared to 11 (7.4%) on hysterosalpingography, with an NPV of 23.8% (Table 2). Proximal tubal occlusion in 10 studies and mid-distal or distal occlusion in 11 studies was noted on hysterosalpingo-contrast sonography.

A comparison of the saline infusion sonohysterography showed a normal cavity in 59% (n = 44) compared to hysterosalpingography, on which a normal cavity was seen in 64% (n = 48). Abnormal cavity findings included 11 with polyps, 2 with an arcuate uterus, 2 with a septum, 3 with submucosal myomas, 1 with intrauterine adhesions, and 8 with unclear-poorly defined findings. Five saline infusion sonohysterographic studies revealed intramural myomas (considered a normal finding), which hysterosalpingography was unable to show (Table 3).

As expected, the overall concordance for evaluation of the uterine cavity was excellent, at 90.6% (68 of 75 studies), with a κ coefficient of 0.80 ($P < .001$). In contrast, although hysterosalpingo-contrast sonography with the saline-air device and saline infusion sonohysterography were in agreement with hysterosalpingography, at 85.1% (126 of 148) by tube and 81.3% (61 of 75) by patient, the κ coefficient was only 0.47 ($P < .001$). These findings were attributed to the lack of agreement when an abnormal study was seen on hysterosalpingo-contrast sonography with the saline-air device.

Table 1. Baseline Demographics (n = 75)

Characteristic	Value
Age, y	34.1 ± 5.0
Gravidity	1.3 ± 0.4
Parity	0.5 ± 0.1
Body mass index, kg/m^2	26.3 ± 7.0
Duration of infertility, mo	21.3 ± 22.5
Polycystic-appearing ovary	24 (32)
Pelvic inflammatory disease	5 (6)
Pelvic surgery	25 (32)
Chronic pelvic pain/dysmenorrhea	14 (19)
Cervical stenosis	13 (18)
Uterine fibroids	7 (47)
Müllerian anomaly	11 (15)
Endometriosis	4 (5)
Polycystic ovary syndrome	14 (19)
Diminished ovarian reserve	8 (6)
Unexplained	22 (14)
Male factor	11 (14)

Data are presented as mean ± SD and number (percent).

There were no differences in baseline age, gravidity, parity, body mass index, or risk factors, including cervical stenosis, endometriosis, previous surgery, or history of pelvic inflammatory disease, when analyzed by the *t* test and χ^2 test. A nonsignificant trend for discordance between hysterosalpingo-contrast sonography with the saline-air device and hysterosalpingography was seen for cervical stenosis (–0.21; $P = .07$), diminished ovarian reserve (–0.21; $P = .07$), and polycystic-appearing ovaries (0.19; $P = .10$). Of 5 studies read as patent for both hysterosalpingo-contrast sonography and hysterosalpingography, however, 3 had a delayed spill, whereas 2 had a loculated spill on hysterosalpingography.

The procedural time was significantly longer for hysterosalpingo-contrast sonography with the saline-air device compared to hysterosalpingography (mean ± SD, 5.03 ± 2.4 versus 3.12 ± 2.2 minutes, respectively; $P < .001$). The volume of the infused contrast material was also greater for hysterosalpingo-contrast sonography compared to hysterosalpingography but failed to achieve statistical significance (17.6 ± 12.0 mL versus 9.9 ± 6.5 mL; $P = .14$). Pain scores were higher for hysterosalpingo-contrast sonography compared to hysterosalpingography (3.4 ± 2.5 versus 2.8 ± 2.1; $P < .01$). Two cases of vasovagal reactions occurred, 1 from each group, which were self-

Table 2. Agreement Between Air Bubble Hysterosalpingo-Contrast Sonography (HyCoSy) and Hysterosalpingography (HSG)

	HSG		
HyCoSy	Patent	Occluded	Total
Patent	121	6	127
Occluded	16	5	21
Total	137	11	148

Sensitivity = 121/(121 + 16) = 89.4%; specificity = 5/(5 + 6) = 45.5%; PPV = 121/(121 + 6) = 95.2%; NPV = 5/(5 + 16) = 23.8%; overall concordance = 126/148 = 85.1% (κ = 0.47; $P < .001$).

Table 3. Sensitivity, Specificity, and Degree of Agreement Between Saline Infusion Sonohysterography (SIS) and Hysterosalpingography (HSG)

	HSG		
SIS	Normal Cavity	Abnormal Cavity	Total
Normal cavity	44	3	47
Abnormal cavity	4	24	28
Total	48	27	75

Sensitivity = 44/(44 + 4) = 91.6%; specificity = 24/(24 + 3) = 88.8%; PPV = 44/(44 + 3) = 93.6%; NPV = 24/(24 + 4) = 85.7%; overall concordance = 68/75 = 90.6% (κ = 0.80; $P < .001$).

limited events treated with observation, and the patients returned home after a period of observation. No other complications, including no postprocedural infections, were noted. Sixty-three percent (n = 47) of the women preferred hysterosalpingography compared to hysterosalpingo-contrast sonography with the saline-air device (41 had less pain; 5 preferred hysterosalpingography because it was faster; and 2 thought hysterosalpingography was more informative). In contrast, 23% (n = 17) preferred hysterosalpingo-contrast sonography (3 had less pain; 3 liked the idea of no radiation exposure; 6 thought it was more convenient; and 5 thought it was more informative). Fifteen percent (n = 11) preferred neither study. No changes over time were noted in provider efficiency and technical improvement with respect to procedure time, contrast material volume, pain, or patient preferences.

Discussion

Our findings reveal that hysterosalpingo-contrast sonography with a saline-air device and hysterosalpingography had a significant degree of agreement with respect to tubal patency in contrast to tubal occlusion. However, hysterosalpingo-contrast sonography with the saline-air device required a significantly longer time to complete, resulted in higher pain scores, and overall, more patients preferred hysterosalpingography. Inaccurate hysterosalpingo-contrast sonographic reads tended to be associated with those who had cervical stenosis, as air bubbles may have been more likely to egress out of the cervix instead of upward toward the fallopian tubes and diminished ovarian reserve, where smaller ovaries may have made it harder to track the air bubbles.

The allure of hysterosalpingo-contrast sonography with a saline-air device is that it is a relatively quick and noninvasive procedure, can be done in the office setting, and does not require exposure to ionizing radiation. A number of studies, including a meta-analysis, have demonstrated concordance rates of 83% to 100% between hysterosalpingo-contrast sonography with a saline-air device, laparoscopy, and hysterosalpingography when detecting tubal disorders.[3–6] Various agents to enhance contrast in the fallopian tubes have been described; however, storage issues, expense, and lack of FDA approval have obviated their routine use in the office setting.

A simpler method that has been described includes a mixture of saline and air for distending media, in which one vigorously shakes a syringe of saline and air, creating air bubbles immediately before infusion, or fills a syringe with both air and saline and tilting the syringe, with the intermittent infusion of air followed by saline in increments of 1 to 3 mL.[26–28] The low cost of air and saline solutions makes this particular hysterosalpingo-contrast sonographic procedure attractive for determining tubal patency (price points range from US$10–$40 for the saline infusion catheter and US$90–$150 for the saline-air device). The PPV and NPV for air bubble hysterosalpingo-contrast sonography have been reported to be similar to those for other contrast materials in detecting both tubal patency and occlusion when compared to both laparoscopy and hysterosalpingography. In cases of nonvisualization, attempts to combine Doppler flow to improve the depiction of the tube might prove beneficial, but this process adds another layer of sonographic complexity.[21–25]

Unlike the distinct tubal anatomy seen on hysterosalpingography, distinct tubal architecture cannot be delineated with sonography unless a hydrosalpinx is present. Moreover, the challenge of air bubbles is that they disappear quickly, since the fallopian tube is not linear and lies in different planes. Therefore, proficient operator skills are required to make rapid movements of the probe to visualize the entire tubal course during infusion, limiting tubal assessment, particularly in distinguishing the tubal lumen from air moving in the bowel. To help with this issue, hysterosalpingo-contrast sonography with the saline-air device creates and delivers a constant alternating pattern of saline and air as a continuous stream in a controlled fashion, allowing for fallopian tube infusion.[29] The air also goes through a microfilter within the device, eliminating any risk of bacterial infection, although the risk of insufflation of bacteria with room air is considered small. Two other studies with smaller sample sizes evaluated the feasibility of office hysterosalpingo-contrast sonography with the saline-air device.[29,30] Tubal patency appeared to be comparable to hysterosalpingography in those studies, and similarly, one reported an increase in patient discomfort compared to hysterosalpingography.

A limitation of our study was that we performed hysterosalpingo-contrast sonography with the saline-air device first in all patients, which may have affected the pain scores, as the women knew what to expect when undergoing the subsequent hysterosalpingographic procedure. The large bubbles created and extra saline volume infused by the saline-air device may have played a role in the increased pain perceived by the patient. In addition, we did not look at conception rates after hysterosalpingo-contrast sonography. We recognize that a κ value of greater than 0.6 is regarded as good[32]; however, our lower κ can be explained by the low number of abnormal findings for both the hysterosalpingo-contrast sonographic and hysterosalpingographic studies

and perhaps would improve with greater numbers of patients and more experience with the procedure. Additionally, the time needed to perform detailed imaging of myometrial echoes and the ovaries made the longer time to completion of the hysterosalpingo-contrast sonographic study not unexpected.

In conclusion, our results confirm those of other studies in the literature, which demonstrate that hysterosalpingo-contrast sonography with a saline-air device has good predictive value when the fallopian tube is patent and may be the first-step procedure of choice for assessment of tubal patency in those with minimal risk factors. Hysterosalpingography should be considered in patients with cervical stenosis, small ovaries, and proximal tubal occlusion shown on hysterosalpingo-contrast sonography, due to the high tubal spasm rates. Although this saline-air device allows for a simple and continuous delivery of saline and filtered air as a continuous stream in a controlled fashion, other FDA-approved devices (ABBI; Cooper Surgical, Inc; and SonoFlow; CrossBay Medical, Inc, San Rafael, CA) and continued refinement of the system with smaller air bubbles may further enhance the accuracy of the device for evaluation of tubal patency.

References

1. Bradshaw KD, Carr BR. Modern diagnostic evaluation of the infertile couple. In: Carr BR, Blackwell RE (eds). *Textbook of Reproductive Medicine.* 2nd ed. East Norwalk, CT: Appleton & Lange; 1998:443–452.
2. Okonofua FE, Essen UI, Nimalaraj T. Hysterosalpingography versus laparoscopy in tubal infertility: comparison based on findings at laparotomy. *Int J Gynaecol Obstet* 1989; 28:143–147.
3. Exacoustos C, Zupi E, Carusotti C, Lanzi G, Marconi D, Arduini D. Hysterosalpingo-contrast sonography compared with hysterosalpingography and laparoscopic dye pertubation to evaluate tubal patency. *J Am Assoc Gynecol Laparosc* 2003; 10:367–372.
4. Deichert U, Schleif R, van de Sandt M, Juhnke I. Transvaginal hysterosalpingo-contrast-sonography (Hy-Co-Sy) compared with conventional tubal diagnostics. *Hum Reprod* 1989; 4:418–424.
5. Hamed HO, Shahin AY, Elsamman AM. Hysterosalpingo-contrast sonography versus radiographic hysterosalpingography in the evaluation of tubal patency. *Int J Gynaecol Obstet* 2009; 105:215–217.
6. Al-Badawi IA, Fluker MR, Bebbington MW. Diagnostic laparoscopy in infertile women with normal hysterosalpingograms. *J Reprod Med* 1999; 44:953–957.
7. Musich JR, Behrman SJ. Infertility laparoscopy in perspective: review of five hundred cases. *Am J Obstet Gynecol* 1982; 143:293–303.
8. Siegler AM. Hysterosalpingography. In: Wallach E, Zacur H (eds). *Reproductive Medicine and Surgery.* 1st ed. St Louis, MO: Mosby-Year Book; 1995:481–508.
9. Karande VC, Pratt DE, Balin MS, Levrant SG, Morris RS, Gleicher N. What is the radiation exposure to patients during a gynecoradiologic procedure? *Fertil Steril* 1997; 67:401–40.
10. Strandell A, Bourne T, Bergh C, Granberg S, Asztely M, Thorburn J. The assessment of endometrial pathology and tubal patency: a comparison between the use of ultrasonography and X-ray hysterosalpingography for the investigation of infertility patients. *Ultrasound Obstet Gynecol* 1999; 14:200–204.
11. Darby SC, Wall BF. The genetically significant dose from diagnostic radiology in Great Britain. *Radiography* 1981; 47:200—202.
12. Nannini R, Chelo E, Branconi F, Tantini C, Scarselli GF. Dynamic echohysteroscopy: a new diagnostic technique in the study of female infertility. *Acta Eur Fertil* 1981; 12:165–171.
13. Richman TS, Viscomi GN, deCherney A, Polan ML, Alcebo LO. Fallopian tubal patency assessed by ultrasound following fluid injection: work in progress. *Radiology* 1984; 152:507–510.
14. Mitri FF, Andronikou AD, Perpinyal S, Hofmeyr GJ, Sonnendecker EW. A clinical comparison of sonographic hydrotubation and hysterosalpingography. *Br J Obstet Gynaecol* 1991; 98:1031–1036.
15. Session DR, Lerner JP, Tchen CK, Kelly AC. Ultrasound-guided fallopian tube cannulation using Albunex. *Fertil Steril* 1997; 67:972–974.
16. Holz K, Becker R, Schurmann R. Ultrasound in the investigation of tubal patency: a meta-analysis of three comparative studies of Echovist-200 including 1007 women. *Zentralbl Gynakol* 1997; 119:366–373.
17. Lanzani C, Savasi V, Leone FP, Ratti M, Ferrazzi E. Two-dimensional HyCoSy with contrast tuned imaging technology and a second-generation contrast media for the assessment of tubal patency in an infertility program. *Fertil Steril* 2009; 92:1158–1161.
18. Reis MM, Soares SR, Cancado ML, Camargos AF. Hysterosalpingo contrast sonography (HyCoSy) with SH U 454 (Echovist) for the assessment of tubal patency. *Hum Reprod* 1998; 13:3049–3052.
19. Kiyokawa K, Masuda H, Fuyuki T, et al. Three-dimensional hysterosalpingo--contrast sonography (3D-HyCoSy) as an outpatient procedure to assess infertile women: a pilot study. *Ultrasound Obstet Gynecol* 2000; 16:648–654.
20. Taechakraichana N, Wisawasukmongchol W, UerpairojkijB, Suwajanakorn S, Limpaphayom K, Phaosawasdi S. Assessment of tubal patency by transvaginal sonographic hydrotubation with color Doppler flow. *J Obstet Gynaecol Res* 1996; 22:473–479.
21. Kleinkauf-Houcken A, Huneke B, Lindner C, Braendle W. Combining B-mode ultrasound with pulsed wave Doppler for the assessment of tubal patency. *Hum Reprod* 1997; 12:2457–2460.
22. Yarali H, Gurgan T, Erden A, Kisnisci HA. Colour Doppler hysterosalpingosonography: a simple and potentially useful method to evaluate fallopian tubal patency. *Hum Reprod* 1994; 9:64–66.
23. Allahbadia GN. Colour-coded duplex sonography for the assessment of fallopian tube patency. *Ann Acad Med Singapore* 1994; 23:98–101.
24. Kalogirou D, Antoniou G, Botsis D, Kassanos D, Vitoratos N, Zioris C. Is color Doppler necessary in the evaluation of tubal patency by hysterosalpingo- contrast sonography? *Clin Exp Obstet Gynecol* 1997; 24:101–103.

25. Deichert U, Schlief R, van de Sandt M, Daume E. Transvaginal hysterosalpingo-contrast sonography for the assessment of tubal patency with gray scale imaging and additional use of pulsed wave Doppler. *Fertil Steril* 1992; 57:62–67.
26. Volpi E, Zuccaro G, Patriarca A, Rustichelli S, Sismondi P. Transvaginal sonographic tubal patency testing using air and saline solution as contrast media in a routine infertility clinic setting. *Ultrasound Obstet Gynecol* 1996; 7:43–48.
27. Chenia F, Hofmeyr GJ, Moolla S, Oratis P. Sonographic hydrotubation using agitated saline: a new technique for improving fallopian tube visualization. *Br J Radiol* 1997; 70:833–836.
28. Jeanty P, Besnard S, Arnold A, Turner C, Crum P. Air-contrast sonohysterography as a first-step assessment of tubal patency. *J Ultrasound Med* 2000; 19:519–527.
29. Malik S, Always SM, Gustafson K, Sanfillippo JS. Evaluation of tubal patency with the FEMVUE™ saline-air device: are we ready to move back to the office [abstract]? *Fertil Steril* 2013; 100(suppl):P-817.
30. Singh M, Diamond MP, Awonuga A, Shavell V, Bolnick J, Puscheck EE. An office-based observational study of 10 female infertility evaluations performed using sono HSG with the FemVue saline-air device [abstract]. *Fertil Steril* 2013; 100(suppl):P-818.
31. FemVue saline-air device information website. http://www.femvue.com/femvue_device.php. Accessed July 19, 2015.
32. Brennan P, Silman A. Statistical methods for assessing observer variability in clinical measures. *Br Med J* 1992; 304:1491–1494.