Experience improves performance of hysterosalpingo-contrast sonography (HyCoSy): a comprehensive and well-tolerated screening modality for the subfertile patient

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Summary

Purpose: To investigate the clinical observations, provider experience, safety, and tolerance of the hysterosalpingo-contrast sonography (HyCoSy) procedure. *Materials and Methods:* A retrospective study design in which data was collected from ninety-six subfertile women who underwent the HyCoSy procedure at the University of Louisville over a 16-month interval. *Results:* Ninety-six HyCoSy procedures were performed by a single investigator and contained complete records for review. The authors observed significant decreases in the quantities of saline and air utilized per procedure over time ($p < 0.0001$ and $p = 0.0001$). Results from the HyCoSy studies were more often non-diagnostic or non-patent in women with a body mass index (BMI) > 30. Reported pain scores did not statistically differ over the course of the study interval. There were no procedure-related complications noted. *Conclusion:* The HyCoSy procedure is a timely and minimally invasive study that can be implemented in an office setting with minimal prior operator experience that improves over time.

Key words: HyCoSy; Hysterosalpingo-contrast sonography; Hysterosalpingogram; Infertility; Tubal patency.

Introduction

The current established diagnostic tests for tubal patency are regarded as accurate but have significant disadvantages [1-11]. Laparoscopy with chromopertubation is viewed as the "gold standard" test for tubal assessment and adding hysteroscopy to the procedure allows for concomitant evaluation of the intrauterine cavity [11-13]. These procedures, however, mandate regional and/or general anesthesia and incur operative costs and associated risks. An alternative and widely accepted screening test, hysterosalpingography (HSG), is regarded as an effective tool for assessing tubal patency and uterine cavity architecture; however, the HSG provides little information regarding myometrial or ovarian morphology [5]. Although the HSG is regarded as safe, the procedure exposes the patient to ionizing radiation and potentially allergenic contrast media [2, 7, 9, 14, 15]. Contrast sonohysterography, or saline-infusion sonography (SIS), accomplishes a simultaneous assessment of the uterine cavity and ovarian morphology, but the procedure fails to provide reliable information regarding tubal patency [16-20]. The introduction of hysterosalpingo-contrast sonography (HyCoSy) has become an increasingly popular alternative in countries outside of North America, combining the principles of SIS with those of HSG. This method has proven to be an acceptable, time-efficient, and well-tolerated alternative to HSG with comparable accuracy in the assessment of the uterine cavity and tubal patency [1, 8, 12-13, 21-27]. However, there is a paucity of data from the United States where obesity is more prevalent and may compromise the feasibility of performing the HyCoSy procedure. This paper examined the technical experiences, patient tolerability, and clinical outcomes of a newly implemented HyCoSy protocol at the University of Louisville from December 2009 through March 2011. Specifically, the authors investigated the parameters of the quantities of saline and air utilized per HyCoSy procedure as a marker of technical skill and procedure proficiency over time.

Materials and Methods

A comprehensive review of the literature regarding the HyCoSy procedure was completed to devise and implement a standardized protocol at the University of Louisville [21, 25, 28-30]. Initiated in December 2009, the HyCoSy procedures were completed in the Division of Reproductive Endocrinology and Infertility (REI) outpatient office setting utilizing the following methods:

Hysterosalpingo-Contrast Sonography (HyCoSy) protocol

Patients were selected as appropriate candidates for the HyCoSy procedure based on the clinical indications of irregular uterine bleeding, amenorrhea, suspected intrauterine synechiae, and/or infertility. Patients gave their signed informed consent for this clinically-indicated procedure.

Patients presented to the outpatient office during the follicular phase of a spontaneous menstrual cycle, typically cycle days 5-10 [31]. If patients reported a history of anovulation or irregular menses, they were placed on combination oral contraceptives, medroxyprogesterone acetate, or norethindrone acetate for 10-21 days prior to their procedure to prevent pregnancy. This also permitted endometrial uniformity and stabilization for improved ultrasonic visualization of the uterine cavity [31]. All patients had a negative urine pregnancy test prior to initiating pre-procedural hormone suppression and prior to the procedure.

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To date, there are no large studies that address the occurrence of post-HyCoSy pelvic infection. A review of the literature revealed inconsistencies in the use of prophylactic antibiotics [1, 16, 26, 30, 32-34]. Without a consensus opinion cited in the literature regarding the prevention of HyCoSy procedure-related infection, the decision was made to prophylactically treat all patients who underwent the HyCoSy procedure with Doxycycline, 100 mg administered orally twice daily for three days (initiated on the day prior to the procedure). If clinically indicated, patients were screened for neisseria gonorrhea and chlamydia trachomatis prior to the procedure.

The HyCoSy procedure was performed with the patient placed supine in the lithotomy position. A baseline transvaginal pelvic ultrasound, utilizing the General Electric Voluson E8 system (General Electric Healthcare, Milwaukee, WI) was completed to assess for uterine size, myometrial composition, hydrosalpinges, antral follicle count, and ovarian morphology. The vaginal transducer was then removed and an open-sided vaginal speculum inserted. Cervical preparation was completed utilizing povidone-iodine solution; chlorhexidine gluconate was an available alternative for patients with iodine allergy. Occasionally, when needed, a tenaculum was positioned slowly on the cervix for stabilization and uterine positioning. A standard 5 Fr, latex-free Redi-HSG catheter (Redi Medical, Goldsboro, NC) was inserted through the endocervix, with or without the aid of the stabilizing sheath. In rare cases, at the discretion of the provider, the balloon tip was slowly inflated to limit efflux of media and spontaneous expulsion of the catheter. Prior to insertion of the HSG catheter, the catheter lumen was flushed with sterile saline utilizing a pre-filled 30 ml syringe secured to the end of the catheter. This step was done to avoid insertion of air bubbles during the initial uterine cavity assessment. The speculum was then removed and the vaginal ultrasound transducer re-inserted. Sterile saline was instilled into the uterine cavity during simultaneous ultrasound imaging. Images were obtained and stored to document uterine cavity architecture in both two- and three-dimensional fields. Once the uterine cavity assessment was completed, the 30 ml syringe was removed from the HSG catheter, filled with approximately 15 ml air and 15 ml saline, and re-fastened to the catheter. The syringe was intermittently tilted to allow an alternating, slow infusion of air and saline in small increments (1-3 ml at a time) [21, 25, 28-29]. Hyperechoic "scintillations" were made possible on real time (b-mode) ultrasound imaging by the positive pressure flow of echogenic air bubbles as they traversed the path of least resistance, from the uterine cavity into the pelvis via patient Fallopian tubes. In a few cases, the catheter balloon was inflated to prevent excessive vaginal efflux of air and saline. Tubal patency was distinguished by visualization of proximal intratubal flow of echogenic contrast for at least five to ten seconds, followed by flow extending from the distal end of the Fallopian tube and the adjacent ovary.

For standardization purposes, real time ultrasound imaging was first directed to document bilateral proximal scintillations, accomplished best while viewing the uterine fundus in a transverse plane (Figure 1). The vaginal transducer was then guided to the right adnexa while real time ultrasound imaging continued with simultaneous instillation of the air and saline mixture. Once desired imaging was obtained, the transducer was redirected to the left adnexa and the same procedure was performed to complete the tubal patency evaluation (Figure 2). Thirty-second ultrasound video clips were obtained throughout the procedure to document the presence or absence of proximal and distal scintillations. The amounts of instilled saline and air required to complete the uterine cavity and tubal patency assessment were noted.

Once the HyCoSy procedure was completed, all vaginal instruments were removed. Patients were monitored for the occurrence of adverse symptoms for at least 15 minutes prior to discharge. Patients completed a Wong-Baker FACE and/or numerical 1-10 pain scale evaluation, noting the duration of experienced pain or other side-effects [35-37]. Patients were contacted within seven to ten days to review the results of their study and address any procedure-related side effects or concerns.

Statistical analysis of data

A retrospective review was conducted of all HyCoSy procedures performed between December 2009 and March 2010 under the approval of the University of Louisville institutional review board (IRB). The study conclusions were made upon analysis of the entire group and the goal was to provide data for improvements in evidence-based practice. Data of 96 patients was collected and analyzed in the current study. Demographic data included age, gravidity, parity, body mass index (BMI), experienced pain score, and clinical indication for the HyCoSy procedure. Outcome variables included the total amount of saline (ml) and air (ml) utilized during each HyCoSy procedure.

Information on the total amount of saline and air required for each procedure was investigated to determine if the utilized quantities decreased over time. Initially, the patients (n = 96) were stratified into tertiles (the first 33 women, the second 32 women, and the last 31 women) to investigate if the mean amount of saline/air used in the procedure decreased over time. Subsequently, the amount of saline/air used in the procedure was made a function of case number (first patient was case #1, second patient was case #2, up until the last patient that was case #96) to predict the effect experience had on amount of saline/air used in the procedure.

The data in each tertile group was tested for normality (α = 0.05). One-way analysis of variance (ANOVA) techniques were used to test for differences in patient age and BMI between the tertiles. The mean quantities of utilized air (ml) and saline (ml) between the three tertiles were also compared using one-way ANOVA techniques. This was done separately for both air and saline. When a statistical difference was noted, post-hoc comparisons (Tukey's pairwise comparisons) were performed to identify where the group differences existed. Additionally, two separate linear regression models were developed to evaluate if the quantities of air (ml) and saline (ml) per HyCoSy procedure decreased over time (with increased experience); adjusting for age, gravidity, and BMI.

Additional analysis was performed to detect differences in patient-reported pain scores between and among tertiles utilizing one-way ANOVA techniques. A separate analysis was completed comparing HyCoSy procedure patency results, "patent" or "non-patent," to patient BMI using the Mann-Whitney U (i.e., Rank-Sum Test) to test for differences.

All statistical calculations were computed using IBM SPSS, version 19, (IBM Corps, Armonk, New York) and GraphPad Prism-5 statistical software (GraphPad, La Jolla, CA, USA).

Results

Ninety-six total HyCoSy procedures were initiated at the University of Louisville between December 2009 and March 2011. These procedures were performed by a single, primary investigator and contained complete records for review. Two of the 96 procedures were aborted sec-

Table 1. — *Mean patient demographics and characteristics among tertiles*.

Variable	1st Tertile	2nd Tertile	3rd Tertile	*p* value*
Age (years)	33 (4.886)	32 (5.034)	31 (5.192)	0.339
BMI	29.4 (8.369)	28.9 (8.083)	29.4 (8.183)	0.967
Pain Score (1-10)	5 (2.401)	5.5 (1.934)	6 (2.874)	0.232

* The mean difference is significant at the 0.05 level.

Table 2. — *Mean quantity of saline and air utilized per HyCoSy procedures*.

Contrast media	1st Tertile	2nd Tertile	3rd Tertile	*p* value*
Saline (ml)	39.04 (2.2)	31.17 (2.0)	26.11 (2.2)	< 0.001
Air (ml)	33.27 (3.3)	29.73 (3.1)	18.04 (2.4)	< 0.002

* The mean difference is significant at the 0.05 level.

Table 3. — *Linear regression analysis of saline and air quantities utilized per HyCoSy procedure*.

Contrast media	β	95% Confidence interval		*p* value*
		Lower bound	Upper bound	
Saline (ml)	-0.189	-0.395	-0.110	< 0.001
Air (ml)	-0.252	-0.289	-0.089	0.001

* The mean difference is significant at the 0.05 level.

ondary to cervical stenosis and data from the remaining 94 studies were examined. Table 1 demonstrates the patient characteristics stratified by tertile of completed HyCoSy procedures. As seen in Table 2, no differences existed in these variables across the tertiles (all p values > 0.05). Test for differences between ethnicity were not performed since a vast majority of patients (over 85%) were Caucasian and no difference was noted across tertiles of the small proportion of Asian, African American, or other ethnicities. Eleven of the 94 patients (12%) were anovulatory and pre-treated with combination oral contraceptive pills or progestin as outlined in the HyCoSy protocol. These patients were evenly distributed across the tertiles. Likewise, a statistical comparison of nulliparity status was not computed as patient nulliparity was constant at 45 percent per tertile.

Using one-way ANOVA statistical analysis, a statistically significant decrease was observed in the quantity of saline utilized per HyCoSy procedure across the tertiles (Table 2). The post-hoc comparisons showed that significant decreases in the amount of saline utilized between the first and second tertiles (C.I. 1.72 - 15.03, $p = 0.028$) and the first and third tertiles (C.I. 5.59 – 20.26, $p < 0.001$), while there was no statistically significant difference in the quantities of saline utilized between the second and third tertiles (C.I. -2.03 – 12.14, $p = 0.210$). The mean quantities of saline required to complete the HyCoSy procedure per tertile declined from 39 ml in the first tertile, to 31 ml in the second tertile, and 26 ml in the third tertile. A similar declining trend was noted in the quantity of air utilized per procedure in the first and third tertiles (C.I. 4.97 – 25.50, $p = 0.002$) and second and third tertiles (C.I. 1.79 – 21.61, $p = 0.017$), with no significant difference between the first and second tertiles ($p = 0.677$). A mean quantity of 33 ml of air was utilized in the first tertile, 29 ml in the second tertile, and 18 ml in the third tertile. Figures 3 and 4 display the mean quantities of saline and air utilized over time, stratified by tertile.

Table 3 displays the results of the two linear regressions models in which quantities of utilized saline and air declined with time/provider experience (e.g., case number). The results in Table 3 show that experience significantly impacts the amount of saline and air used per procedure. The amount of saline ($\beta = -0.189$, $p < 0.001$) and air ($\beta = -0.252$, $p = 0.001$) used per procedure significantly decreased over time. While the authors assumed a linear relationship, one can easily imagine that the decrease in the amount of saline/air used plateaus. As such, a non-linear relationship may exist. The current data does not support a non-linear relationship hypothesis since a linear model fit the data the best. Further studies showing were a plateau begins is warranted and needed.

Patient tolerability and side-effects

Over the 16-month study interval, a mean reported pain score value of five was noted utilizing the Wong-Baker FACE and numerical 1-10 pain rating scales. The duration of experienced pain ranged from 15 to 120 seconds of maximum discomfort which rapidly subsided to a reported "mild cramping" or "menstrual-like feeling" following the procedure. Using one-way ANOVA statistical analysis, the mean pain scores and duration of reported pain did not differ significantly between or among tertiles ($p = 0.232$). Moderate side-effects included two reported episodes of nausea with emesis and 19 reported incidences, or 20 percent, of shoulder discomfort immediately following the procedures. One patient experienced a vasovagal reaction with near syncope. She was monitored for approximately 35 minutes post-procedure with complete resolution of symptoms. There were no uterine perforations, post-procedure infections, post-procedure hospitalizations, or other severe side-effects reported throughout the study interval.

Effect of BMI on HyCoSy procedure results

Fallopian tube assessment during the HyCoSy procedure was stated to have unilateral or bilateral "non-patency" if distal scintillations were unable to be visualized in one or both tubes, respectively. The term "non-patency" represented both true tubal occlusions as well as non-diagnostic results (when patency could not be determined) due to poor visibility. Anecdotally, the HyCoSy investigator noted increased difficulty in determining tubal patency in obese patients secondary to poor ultrasound visibility. Thus, further analysis of the data was undertaken to examine trends in HyCoSy patency results compared to patient BMI.

In this study population, obesity (BMI ≥ 30) was noted in 38 percent of patients and morbid obesity (BMI ≥ 40) in 13.5 percent of patients. The mean patient BMI for patients with patent tubal findings was 28; whereas, the mean patient BMI for all non-patent results was 32.

Fig. 1

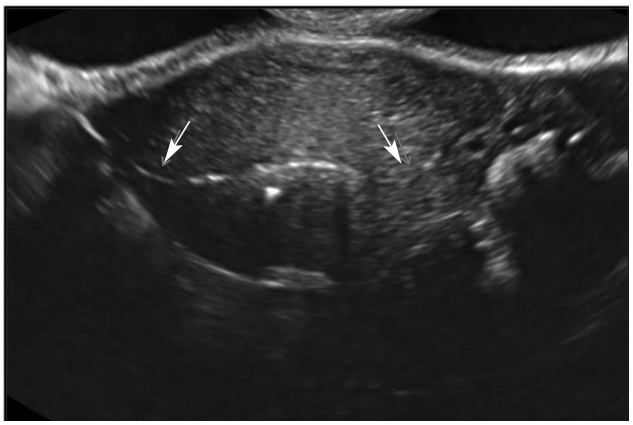

Fig. 2

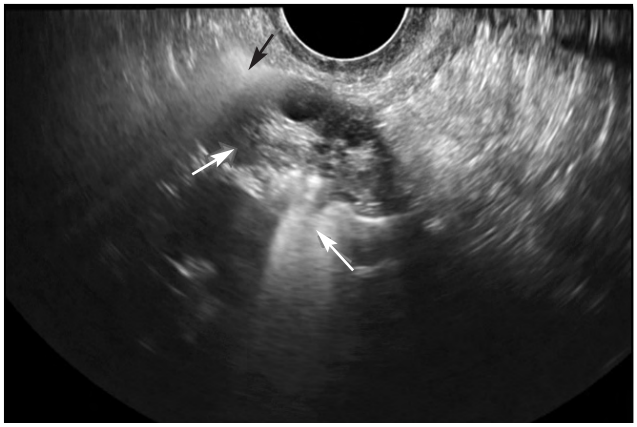

Fig. 3

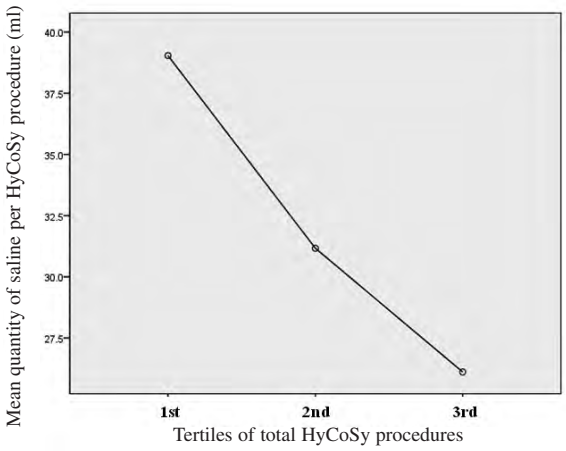

Fig. 4

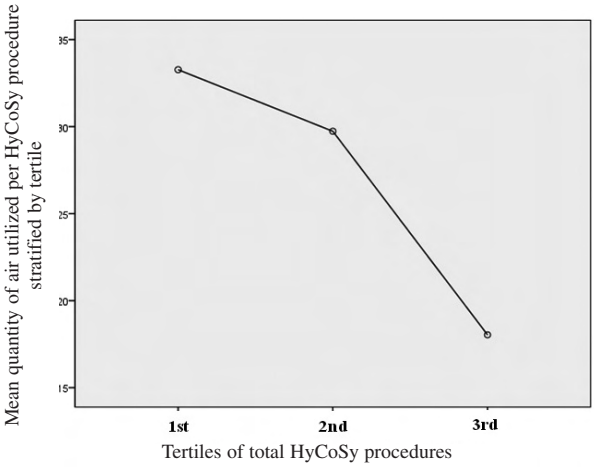

Figure 1. — HyCoSy ultrasound still image demonstrating bilateral proximal scintillations.
This still image of a HyCoSy transvaginal ultrasound procedure demonstrates the bilateral proximal scintillations as echogenic air contrast traverses the bilateral uterine cornua (indicated with arrows) with the uterine fundus imaged in a transverse plane.
Figure 2. — HyCoSy still image demonstrating unilateral ovarian distal scintillations.
This still image of a HyCoSy transvaginal ultrasound procedure demonstrates unilateral distal scintillations (indicated with the thin arrows) as echogenic air contrast traverses the left ovary (indicated with the filled arrow).
Figure 3. — Mean quantity of saline utilized per HyCoSy procedure stratified by tertile.
Linear regression graphical representation of the decline in utilized saline (ml) per HyCoSy procedure over the study interval of 94 patients.
Figure 4. — Mean quantity of air utilized per HyCoSy procedure stratified by tertile.
Linear regression graphical representation of the decline in utilized air (ml) per HyCoSy procedure over the study interval of 94 patients.

Eighteen of the 94 completed HyCoSy procedures, or 19 percent, revealed unilateral (n = 8) or bilateral (n = 10) non-patency. Of the eighteen non-patent results, nine, or 50 percent, occurred in patients with BMI greater than 30; five, or 28 percent, occurred in patients with a BMI greater than 40. Examined in another way, 15 percent of patients with a BMI < 30 yielded non-patent results, 25 percent of patients with a BMI ≥ 30 yielded non-patent results, and 38 percent of patients with a BMI ≥ 40 yielded non-patent results. Despite an apparent trend of increasing non-patent findings with increasing patient BMI (Figure 5), no statistically significant differences were noted when patency results were compared to obese and non-obese patient categories using a Mann-Whitney U test ($p = 0.214$).

Additional findings

Over the course of the study interval, the following additional pelvic findings were noted: endometrial polyps (n = 8), submucosal fibroid (n = 6), intrauterine synechiae (n = 2), and adnexal masses (n = 8). Of the eight adnexal masses, three appeared to be endometriomas and two appeared to be hydrosalpinges. Combined, a total of 24 patients, or 25 percent, were noted to have incidental pelvic pathology during HyCoSy imaging.

Abnormal findings from HyCoSy studies were further investigated by HSG as/or laparoscopy with or without hysteroscopy. As of March 2011, 19 of the HyCoSy patients have undergone laparoscopic and/or hysteroscopic procedures for further subfertility evaluation and treat-

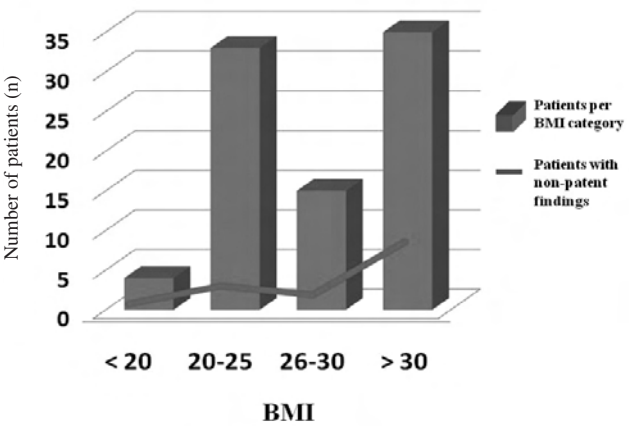

Figure 5. — Patient BMI correlated with non-patency findings. Graphical representation of the BMI distribution across the total study group correlated to non-patency results per BMI category.

ment. There were no incongruent findings between those noted at the time of surgery and the HyCoSy findings of pelvic pathology (e.g.: endometrial polyps, submucous myomas, ovarian cysts) and/or tubal patency. In fact, seven of the ten patients with bilateral, non-patent HyCoSy results were subsequently evaluated by laparoscopy. All seven laparoscopic assessments were congruent with bilateral tubal occlusion. Two of the remaining three bilateral, non-patent HyCoSy results were followed with HSG imaging, one of which was concordant with bilateral proximal tubal occlusion and the other was discordant with bilateral tubal patency. The remaining patient with a bilateral, non-patent HyCoSy result declined further investigation or treatment and was lost to follow-up.

Other notable findings were nine post-HyCoSy conceptions with documented, viable intrauterine pregnancies. All nine patients conceived within six months of their HyCoSy procedure. Three patients conceived spontaneously, two conceived with oral-agent ovarian stimulation and intrauterine insemination, and four conceived with in vitro fertilization and embryo transfer.

Discussion

The implementation of the HyCoSy procedure at the University of Louisville has dramatically streamlined the office evaluation of the uterine cavity and the assessment of tubal patency. Combining the principles of SIS and HSG, the HyCoSy accomplishes a comprehensive assessment of the uterine myometrium, cavity contour, adnexal pathology, antral follicle count, ovarian morphology, and tubal patency. Several studies have proven this method to be time-efficient and safe with comparable patient-perceived discomfort compared to HSG [28, 32, 36]. The present report examined a single individual provider's experience with the HyCoSy procedure in a North American population with an average BMI of 29.2. This was not meant to be a definitive study in comparing the accuracy of this procedure with other modalities of tubal patency assessment. The findings are an estimate of the relative ease in implementing a new technique in the office setting with no prior experience in performing the procedure. The data provides insight into the anticipated clinical limitations and patient tolerability in an overweight or obese sample of patients.

Examination of the quantities of air and saline utilized per HyCoSy procedure demonstrates the relative ease at which methodological certainty and efficiency was achieved. In this review, a nadir mean of 26 ml of saline utilized per HyCoSy procedure occurred in the third tertile of total HyCoSy procedures. Extrapolated from the linear regression analysis, the data suggests that approximately 48 consecutive studies were required for the provider to reach a consistent use of less than 30 ml of saline per HyCoSy procedure. Meanwhile, a nadir mean of 18 ml of air per HyCoSy procedure occurred in the third tertile of patients. When extrapolated, the data reveals that approximately 54 studies were required for the provider to reach a consistent use of less than 20 ml of air per HyCoSy procedure. Thus, after approximately fifty studies, the provider was able to reach an objective plateau of mechanical ease and efficiency that accompanied subjective feelings of procedural expertise. The authors acknowledge that this analysis only demonstrated the learning curve on a single provider to reach individual technical efficiency. A much larger study evaluating the performance of several providers would be required to make broad assumptions on the number of consecutive HyCoSy procedures required before mastery of its technical skills.

With regard to patient complaints of procedure-related discomfort and other adverse effects, the results of this study are consistent with the findings in the literature [28, 32, 38]. Adverse events like referred shoulder pain and/or vasovagal symptoms occurred with a frequency that is similarly seen during hysterosalpingogram and sonohysterography procedures [28, 32]. Examination of patient-reported, HyCoSy-related pelvic pain did not yield a significant difference across the tertiles despite improved provider performance. Certainly, this analysis is limited as it did not address the patient's reported baseline pain, history of previous pelvic surgery, sexual assault, anxiety or difficult pelvic exams. The infrequent use of a cervical tenaculum (estimated at less than 5%) and/or balloon inflation (estimated at less than 25%) was not consistently documented. The retrospective nature of the study did not allow for critical assessment of the effect of tenaculum and/or balloon inflation on patient reported pain. Such confounders may have influenced trends in patient-reported pelvic pain but no trend was seen in procedure tolerability over the course of the study. Other considerations might include the possibility that any small amount of saline and/or air might incite a pain response and that perhaps no correlation exists between the amount of utilized media and perceived pain.

Although comparisons of patency results across BMI categories were not statistically significant, an apparent

trend was noted of increased non-patent findings in patients with a BMI greater than 30, a discovery that was even more pronounced in patients with a BMI greater than 40. This trend of increased non-patent HyCoSy results in heavier patients likely represents a higher proportion of non-diagnostic studies rather than true tubal occlusions. Poor ultrasound penetration and image resolution, and thus possible non-diagnostic HyCoSy findings, are logically more likely to occur in the obese patient secondary to body habitus limitations. A perceived obesity-related hindrance on image visibility and technical performance is consistent with the observations made by Hamilton and colleagues [28]. Other ultrasound image limitations might occur in women with large uterine leiomyomas or severely retroflexed uterine positions.

The ability of the HyCoSy procedure to accurately and reliably assess tubal patency has been well established in the literature [8]. The diagnostic outcomes with the HyCoSy procedure are comparable to those of traditional HSG and laparoscopy, with tubal assessment concordance rates ranging from 80 to 93 percent [8, 12-13, 21-22, 24-27, 34, 39-45]. With several randomized and controlled trials comparing the HyCoSy procedure to the alternative HSG procedure and to the gold-standard laparoscopy, this paper did not aim to investigate the sensitivity, specificity, or predictive values of the HyCoSy results in our patient population. However, it is interesting to note, that seven of the ten bilateral, non-patent HyCoSy results were confirmed as such with subsequent laparoscopy. Furthermore, there were no other discrepant findings of pelvic pathology when HyCoSy was followed by laparoscopy or hysteroscopy (n = 19). As a direct result of the HyCoSy procedure, 24 patients had newly diagnosed abnormal pelvic pathology that may have altered their subfertility treatment strategies. These incidental findings may not have been otherwise detected using an alternative diagnostic method to assess tubal patency.

In the present study, nine patients conceived following their HyCoSy procedure suggesting a fertility-enhancing effect. However, the sample size is small and findings await confirmation from a larger prospective study.

Conclusion

This paper has reviewed the initial experience of a single investigator implementing the HyCoSy procedure at the University of Louisville over a 16-month interval. The HyCoSy procedure is well-suited to the outpatient office setting. Implementation of the HyCoSy procedure afforded minimal technical challenges, satisfactory patient tolerability, and swift attainment of provider-perceived ease and efficiency.

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