Current methods of tubal patency assessment

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Objective: To evaluate the scientific literature on current methods of uterine cavity and tubal patency assessment.
Design: Review of literature and appraisal of relevant articles using MEDLINE, OVID, EMBASE, and Cochrane on-line databases.
Result(s): Current pelvic imaging subfertility investigations are compared with the gold standard laparoscopy. The technical aspects, associated risks, potential advantages, and weighted utility of each screening study are discussed. A comprehensive analysis of the clinical evidence regarding the safety, tolerance, and accuracy of hysterosalpingo-contrast sonography compared with alternative screening studies and/or laparoscopy is reviewed.
Conclusion(s): Increasing evidence supports the more recently described hysterosalpingo-contrast sonography procedure as an acceptable screening study for the subfertile patient with the potential advantage that it is a comprehensive evaluation, methodologically simple, cost effective, and time efficient. (Fertil Steril® 2011;95: 2171–9. ©2011 by American Society for Reproductive Medicine.)

Key Words: Subfertility, sonohysterography, hysterosalpingogram, hysterosalpingo-contrast sonography

The optimal initial infertility investigation protocol is diagnostically accurate, expeditious, cost-effective, dependable, and minimally invasive. The current established diagnostic screening tests for tubal patency are regarded as accurate but have significant disadvantages. Laparoscopy with chromopertubation is viewed as the "gold standard" test for tubal assessment in many infertility centers. Adding hysteroscopy to the procedure allows for concomitant evaluation of the intrauterine cavity and may identify congenital or endometrial abnormalities. These tests, however, do not yield perfect accuracy and predictive values and are subject to provider expertise and intraoperative or technical complications. Furthermore, these procedures mandate regional or general anesthesia and incur operative costs and risks. An alternative and widely accepted procedure, hysterosalpingography (HSG), is regarded as an effective screening assessment of tubal patency and the internal uterine cavity architecture, but the HSG gives no information regarding ovarian morphology. Although the HSG is regarded as safe, the procedure exposes patients to ionizing radiation and potentially allergenic contrast media. Contrast sonohysterography, or saline-infusion sonography (SIS), accomplishes a concomitant assessment of the uterine cavity and ovarian morphology, but fails to provide reliable information regarding tubal patency. The introduction of hysterosalpingo-contrast sonography (HyCoSy) has become an increasingly popular alternative, 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. The HyCoSy is a simple, safe, and effective outpatient procedure that may add value to a streamlined initial infertility evaluation.

The intent of this article is to comprehensively review the technical aspects, associated risks, potential advantages, and, ultimately, the weighted utility of each of the following infertility screening studies: HSG, sonohysterography, HyCoSy, and laparoscopy with chromopertubation.

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SPECIFIC DIAGNOSTIC TESTS IN THE SETTING OF SUBFERTILITY

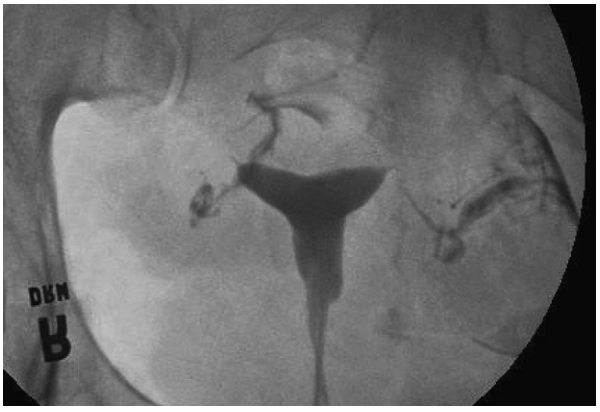
Hysterosalpingography

Hysterosalpingography is the radiographic evaluation of the uterus and fallopian tubes used predominantly in the evaluation of infertility. It is a valuable tool in the assessment and detection of congenital anomalies, leiomyomas, synechiae, polyps, tubal occlusion, salpingitis isthmica nodosum, hydrosalpinx, and peritubal adhesions (1). The procedure is performed with the patient supine on the fluoroscopy table in the lithotomy position. After cervical preparation (most commonly with povidone-iodine solution), a tenaculum may be placed with or without local anesthesia for cervical stabilization and uterine positioning. The HSG catheter (typically 5F) or Cohen's cannula is inserted through the endocervix. The catheter balloon tip may be inflated to aid in uterine traction, limit efflux of contrast, or spontaneous expulsion of the catheter. Oil or water-based contrast media is instilled through the catheter into the uterine cavity. Radiograph images are obtained intermittently to document filling of the uterine cavity and fallopian tubes (Fig. 1). Some patients may experience bleeding, usually light spotting lasting less than 24 hours, or pelvic pain during or after the procedure. Pain is most notable in the setting of obstructed fallopian tubes (1). Significant pain may also lead to premature termination of the procedure or vasovagal reaction. Patients may experience rare adverse reactions to the iodinated contrast media, ranging from urticaria to bronchospasm and laryngeal edema. The incidence of these adverse events is increased in patients with a history of prior hypersensitivity to iodinated contrast agents. The likelihood of a recurrent event is 8%–25% (2, 3).

In addition to contrast allergy, there are two other contraindications to HSG: pregnancy and active pelvic infection. Performing the procedure between menstrual cycle days 6 and 11 will help to ensure the absence of pregnancy and facilitate maximum uterine cavity visibility with a thin proliferative phase endometrium. Decisions concerning the use of prophylactic antibiotics are left to the discretion of the physician. The American Congress of Obstetricians and

FIGURE 1

Hysterosalpingogram. Infusion of radiographic contrast into the uterus and fallopian tubes using fluoroscopic guidance. (Image provided by Steven Nakajima, M.D., University of Louisville, Louisville, Kentucky.)



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Gynecologists provides guidelines that recommend empiric treatment of patients with a history of previous pelvic infection or if hydrosalpinx is noted at the time of the study. A commonly prescribed antibiotic is doxycycline, 100 mg orally twice daily for 5 days (4). Although previous studies report a post-HSG serious infection rate of 0.3%–1.3%, a 2-year, retrospective analysis reported a post-HSG infection incidence of 14 of 464 patients (3.1%) (5). Nine of these 14 patients received periprocedure prophylactic antibiotics, usually ampicillin, 250 mg four times daily for 5 days (the timing of initiation of the antibiotic doses was unspecified). The alternative regimen for patients with penicillin allergy was doxycycline, 100 mg twice daily (4). All of the 14 patients were noted to have abnormal hysterosalpingogram findings (5). In their conclusion, the investigators in this study reviewed five major risk factors for the development of a post-HSG infection: [1] history of infertility, [2] previous pelvic inflammatory disease, [3] previous pelvic surgery for an infection, [4] adnexal tenderness at the time of the procedure, and [5] adnexal mass. Patients noted to have three or more of these risks factors were 40 more times likely to develop a procedure-related infection. The investigators suggested that patients prospectively deemed to be at high risk for a post-HSG infection or in whom laparoscopy is contemplated should avoid the HSG procedure (5).

Little has been written about the direct effect of various contrast agents used during HSG on the fallopian tube at the cellular level. A rabbit animal model was designed to observe the effects of four contrast agents: ethiodized oil (n = 5), iothalamate meglumine 30% (water-based, n = 3), iothalamate meglumine 60% (water-based, n = 3), and ioxilan (water-based, n = 4), on the fallopian tube architecture and cellular structure compared with 15 contralateral fallopian tube controls (6). The iothalamate meglumine 60% agent was reported to create mild inflammatory changes and mucosal edema with giant cell reaction and periovarian adhesions; the ethiodized oil resulted in papillary fibroid adhesions on the ovarian surface with fat granulomas on periovarian tissues. These findings raised concerns regarding the safety of oil-based contrast agents (6). No pathology was noted from the remaining agents. Further investigation in another animal model study involving 88 rabbits treated with seven different water and oil-based contrast agents was undertaken (7). All agents demonstrated local inflammation that resolved completely between 4 days and 2 weeks from the time of exposure. Due to universal disappearance of these temporary changes after the procedure, all agents were deemed suitable for human use (7).

Further studies have been conducted to determine the diagnostic quality and utility of oil versus water-based media in humans (Table 1). A randomized, prospective study in Denmark on 417 patients revealed that the visualization of the uterine cavity and fallopian tube architecture (specifically ampullary rugae) was improved in women who received water-soluble media, whereas, after the procedure, vaginal bleeding was less in women who received the oil-based media (8). There were no reported differences in patient discomfort during the actual HSG procedure. The study revealed no differences between the groups with respect to diagnosis and assessment of tubal patency. The investigators concluded that either media type yielded acceptable diagnostic accuracy with respect to fallopian tube architecture, patency, spill, and intraperitoneal distribution. Other studies, however, have reported a higher incidence of allergic reactions and anaphylaxis associated with oil-based contrast media, as well as the formation of lipogranulomas after the procedure. These

TABLE 1

Current contrast agents available for hysterosalpingography.

Generic name	Trade name	Iodine (mg/mL)	Contrast type	Vial volume	Vials per case	Estimated cost per patient ($)[e]
Ethiodized oil	Ethiodol[a]	475	Oil	Unavailable	Unavailable	Unavailable
Diatrizoate meglumine + Iodipamide meglumine	Sinografin[b]	380	Ionic	10 mL	10	50.00
Iopamidol	Isovue 300[b,d]	300	Nonionic	30 mL	10	43.00
Iothalamate meglumine 60%	Conray-60[c,d]	282	Ionic	30 mL	10	47.50
Ioxaglate meglumine 39.3% + Ioxaglate sodium 19.6%	Hexabrix[c]	320	Ionic	20 mL	10	33.00

[a] Nycomed US Inc., Melville, New York; manufacturing ceased February 2010.
[b] Bracco Diagnostics Inc., Bracco Imaging, Princeton, New Jersey.
[c] Covidien Pharmaceuticals, Mansfield, Massachussetts.
[d] Although use is reported, these products lack US Food and Drug Administration approval for use in hysterosalpingography.
[e] Assumes use of 10 mL of contrast per patient.

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findings have led to a provider-directed movement to use predominantly water-soluble contrast media (8, 9). In February 2010, the manufacture of the US Food and Drug Administration (FDA)-approved, oil-based contrast media for HSG, Ethiodol, by Savage Laboratories (a division of Nycomed US Inc., Melville, New York) was discontinued. At present, access to the Ethiodol media is limited to distribution wholesalers (Cardinal Health, Dublin, Ohio; McKesson Medical-Surgical, San Francisco, California; and Amerisource Bergen, Valley Forge, Pensylvania) with stocked inventory. This cessation of production of oil-based media may lead to the exclusive use of water-soluble contrast media. At present, Guerbet L.L.C., Bloomington, Indiana, has acquired the Ethiodol NDA from Nycomed US Inc. and is working with the FDA to resume manufacturing of Ethiodol.

Several randomized studies have pursued information regarding the post-HSG procedure conception rates. In a Cochrane review meta-analysis, pregnancy rates (PR) varied from 17%–23% after using water-soluble contrast media and 24%–38% after using oil-soluble contrast media, compared with a PR of 8%–21% without the HSG procedure (10). This comprehensive evaluation demonstrated that the use of oil-soluble HSG contrast media resulted in significantly higher PRs than water-soluble media, with an odds ratio of 1.92 (95% confidence interval 1.6–2.29) (10). A theoretical mechanism for this finding includes a reduction in peritoneal macrophage function after exposure to oil-based contrast during HSG (11, 12). Specific in vitro studies, in fact, demonstrated a reduction of phagocytosed *Candida* and sperm by derived pelvic peritoneal macrophages and a decrease in macrophage adherence after exposure to the Ethiodol (oil-soluble) contrast agent. This reduction in phagocytosis and adherence was not demonstrated when the peritoneal macrophages were exposed to Singografin (water-soluble) media (11, 12). Other animal studies report evidence of improved endometrial receptivity after exposure to oil-based contrast media (10).

When addressing the risks of the HSG procedure, pelvic radiation exposure is commonly quoted as a risk. Previous studies have reported gonadal doses up to 5 mGy of radiation exposure during one completed HSG procedure. This dose was calculated by attaching lithium fluoride thermoluminescent dosimeters to anatomic landmarks on the patient's skin to detect entrance surface radiation doses (13, 14). The Committee of the National Academy of Sciences on the Biologic Effects of Ionizing Radiation in its 1990 report concluded that the genetic risks from fluoroscopy involving the pelvis was exceedingly low when radiation time was limited and the equipment was appropriately calibrated (15). One rad (10 mGy) of radiation at a dose rate of 1 rad/min limited to maximum of 10 minutes was defined as an appropriate low dose, resulting in 5–25 additional offspring with a serious genetic handicap in one million newborns. Restated, a woman exposed to 1 rad of radiation will increase her risk of delivering a child with a serious handicap by 1:50,000 (15). Thus the radiation exposure of patients during a HSG using standard techniques is broadly considered to be within the margins of safety (15).

The accuracy of the HSG procedure has been widely studied. However, it is not easy to define a standard of reference for comparative studies involving HSG, as laparoscopy with chromopertubation does not yield perfect sensitivity, specificity, positive and negative predictive values for detecting tubal pathology, or patency. Nonetheless, comparisons between HSG and laparoscopy show discrepancies up to 45% (16). A commonly referenced meta-analysis conducted in the Netherlands compared 20 related articles and involved more than 4,100 patients (17). Although recognizing that laparoscopy with chromopertubation is not an ideal standard for tubal patency, the investigators reported a comparative HSG sensitivity of 65% and specificity of 85% (17). They further concluded that the diagnosis of peritoneal adhesions based on HSG findings was unreliable and advised caution when assuming proximal tubal occlusion or "cornual block." They added that proximal occlusions may be secondary to transient tubal spasms (20% of cases) or collections of amorphous debris or minimal adhesions (40% of cases) (17, 18). Historically, providers may have chosen to use IM or parenteral glucagon or other pharmacologic agents or selective catheterization involving interventional radiology to assess and potentially treat proximal tubal blockage (19). Due to their costs and complexity, however, these methods of assessing and treating tubal spasm has seemingly fallen out of favor.

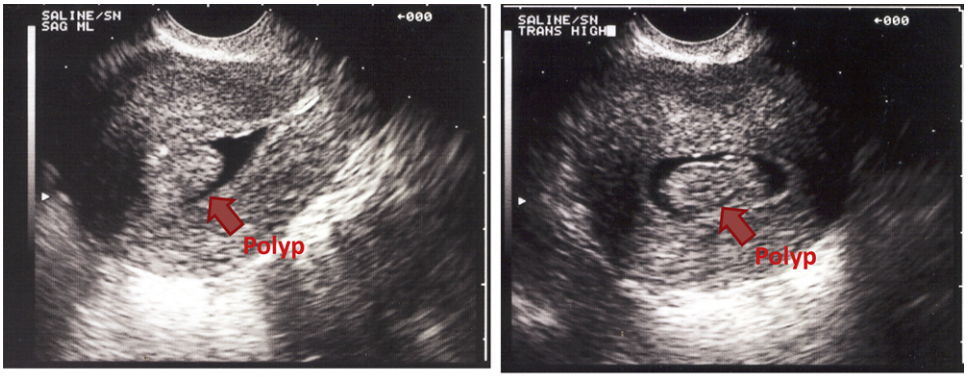
Ultrasonography and Sonohysterography

Transvaginal sonography provides excellent overall depiction of the uterus, endometrial lining, and ovarian architecture. Its first reported use to assess the ovaries in the subfertile patient was in 1972 (20). Ultrasound has been widely used in infertility investigations and procedures: follicle maturation monitoring, oocyte retrieval, endometrial lining assessment, management of ovarian cysts, and evaluation of pelvic pain (21). Improved depiction of the endometrial lining and intrauterine cavity has been achieved with the development of SIS. The concept of intrauterine saline infusion during concomitant ultrasonography was described by Nanini and co-workers in 1981 after early experiences revealed improved uterine cavity images in physiologic conditions of hematometra or serometra (22–24). The SIS requires the instillation of saline under continuous sonographic visualization of the endometrial cavity to improve detection of intrauterine cavity defects (Fig. 2). In a normal SIS study, the endometrium appears symmetric, surrounding an anechoic, saline-distended uterine cavity. This instillation of fluid allows for differentiation of intrauterine, endometrial, and submucosal abnormalities without the use of potentially harmful contrast agents or ionizing radiation. In support of its implementation as an outpatient infertility evaluation, a randomized, blinded prospective trial investigated the diagnostic accuracy of SIS compared with HSG and hysteroscopy in 46 infertile subjects (25). The investigators reported statistical equivalency among these three procedures with respect to the evaluation of intrauterine pathology (24). Extrapolating from this and other similar study findings, SIS can be incorporated into investigation protocols for evaluating complaints of abnormal uterine bleeding, postmenopausal bleeding, recurrent miscarriage, or subfertility (25–28).

In regard to tubal assessment, transvaginal ultrasound can be a useful diagnostic tool in the detection of hydrosalpinges. A European multicenter study involving nine medical centers and 1,066 women with known adnexal masses before surgical evaluation reported a sensitivity of 86% for detecting hydrosalpinx (18/21) (29). In a different prospective Italian trial, 378 premenopausal nonpregnant women were evaluated by transvaginal ultrasonography before completion of gynecologic surgery for various indications: subfertility, pelvic pain, uterine fibroids, endometrial hyperplasia, or adnexal masses (30). One aim of the study was to investigate the role of vaginal ultrasonography in screening for a hydrosalpinx. Sensitivity and specificity for the ultrasonographic images were 84.6% and 99.7%, respectively, calculated for each adnexa ($n = 756$). These values changed to 93.3% and 99.6%, respectively, when calculated for each identified mass, differentiating hydrosalpinx from other pathologic diagnoses. Interobserver and intraobserver agreements, expressed in terms of κ-values, were 0.87 and 0.93, respectively (30). In a separate prospective observational study involving women with complaints of pelvic pain, in 6 of the 120 recruited subjects ultrasonography revealed evidence of a hydrosalpinx. In five of these

FIGURE 2

Saline infusion sonogram. Images depict an endometrial polyp (*arrow*). (Images provided by Steven Nakajima, M.D., University of Louisville, Louisville, Kentucky.)



Sagittal View Transverse View

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six patients it was confirmed by laparoscopy. The remaining 114 women all underwent laparoscopy, none revealing the presence of a hydrosalpinx (31).

The diagnosis of hydrosalpinges plays an important role in prognosis and management decisions for women seeking treatment for subfertility. Many recently published comparative studies have revealed that hydrosalpinges are associated with reduced IVF success (32–34). A meta-analysis investigated IVF outcomes with tubal-related subfertility involving 5,592 patients (35). This study revealed significantly lower rates of pregnancy, implantation, live delivery, and increased rates of pregnancy loss in the presence of a hydrosalpinx as determined by HSG or laparoscopy. The investigators concluded that when a hydrosalpinx is present at the time of ET it has negative consequences on pregnancy outcomes (35). A different retrospective study investigated 550 patients, undergoing IVF, with known tubal pathology as determined by ultrasound imaging, rather than the more conventional HSG or laparoscopy. The investigators determined that the rates of implantation and ongoing pregnancy per transferred embryo were significantly lower only in the presence of an ultrasound-visible hydrosalpinx, rather than the hydrosalpinx noted during HSG or laparoscopy (36). Using a life-table approach, they confirmed that patients with a hydrosalpinx noted at either laparoscopy or HSG, but not on ultrasound, did not reveal this decreased implantation and pregnancy outcome (36).

Although ultrasonography with combined SIS provides a reliable ability to evaluate ovarian and uterine cavity architecture as well as detect other pelvic pathology (e.g., hydrosalpinges), it has some limitations. Qualitative ultrasound images and their interpretation are subject to the experience and expertise of the technician and provider. Even when combined with SIS, ultrasonography is unable to detect or assess the patency of normal or diseased fallopian tubes. Thus, although a valuable tool in the initial subfertility investigation, ultrasonography with SIS requires a supplemental study or procedure if the determination of tubal patency is desired.

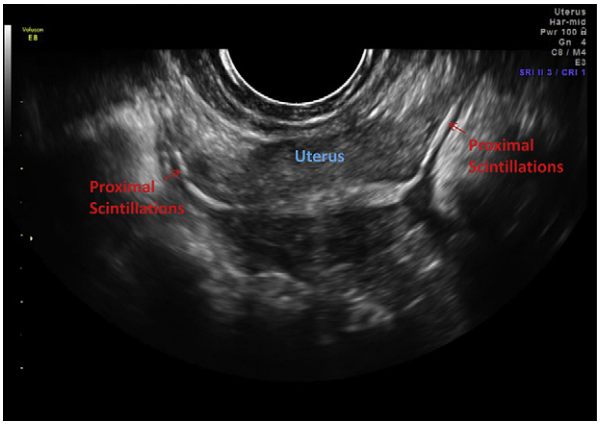
Hysterosalpingo-Contrast Sonography

Although SIS has enhanced visualization of the endometrial lining, its use in evaluating tubal patency has been limited. The investigation of tubal patency is difficult to achieve as the normal fallopian tube is a poor sonic reflector, devoid of the defined interfaces that produce clear organ outlines (37). In 1984, a technique, termed sonosalpingography, was described using Hyskon (Pharmacia Laboratories, Piscataway, New Jersey) hypertonic fluid as the intrauterine distension media (38). Adding to the concept of SIS, sonosalpingography was performed using concomitant transabdominal ultrasound imaging to identify subsequent fluid in the pelvic cul-de-sac implying patency of at least one fallopian tube. Hyskon was chosen for its presumed potential to dislodge mucus plugs or other debris from within the fallopian tubes. A minimum infusion of 20 mL of Hyskon was required in this study to visualize spilled fluid into the cul-de-sac. The investigators noted that saline could be considered in lieu of the viscous Hyskon, although saline may have a diminished potential for mechanical lavage of the fallopian tubes. Thus, a protocol was proposed to first determine patency using saline followed by a 5-mL flush of Hyskon for therapeutic purposes (38).

Rather than relying on the presence of post-procedure cul-de-sac fluid, subsequent investigations used hyperechoic contrast agents (rather than Hyskon or saline) to obtain visualization of actual contrast flow through each fallopian tube. In 1986, a model of HyCoSy was developed (39). Expanding the sonosalpingography procedure, researchers in Europe used a contrast agent, Echovist-200, commonly used during cardiac catheterization procedures, to obtain real-time images of hyperechoic flow through the fallopian tubes. Echovist-200 is a milky suspension of two components: *d*-galactose microparticles and 20% *d*-galactose carrier solution (23). One of its limitations is the rapid degradation requiring the solution to be mixed immediately before infusion, as its ultrasonic hyperechoic characteristics are usually lost within 5 minutes. Given that Echovist-200 is not FDA approved in the United States, other providers have substituted a mixture of saline and air for the distending media (16, 40–42). Some studies reported vigorously shaking a syringe of saline and air immediately before infusion. Alternatively, a syringe filled with both air and saline can be tilted such that an intermittent infusion of air is followed by saline in increments of 1–3 mL at a time (16, 40–43). More recently, Femasys has achieved US FDA approval for the Femvue Sono Tubal Evaluation System, designed to simultaneously introduce air and saline in a controlled fashion. Whether using Echovist-200

FIGURE 3

Echogenic contrast identified in bilateral proximal tubal segments during hysterosalpingo-contrast sonography. (Image provided by Steven Nakajima, M.D., University of Louisville, Louisville, Kentucky.)



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or a mixture of saline and air, "scintillations" are made possible by the positive pressure flow of echogenic contrast through the path of least resistance, from the uterine cavity and into the pelvis through patent fallopian tubes (Figs. 3 and 4). Tubal patency is then distinguished by visual intratubal flow of echogenic contrast using b-mode (real-time) ultrasound scanning for at least 5–10 seconds duration or flow extending from the distal end of a tube and over the adjacent ovary (23, 41, 44–46). When performed subsequent to SIS, HyCoSy is capable of expanding the utility of pelvic ultrasonography to include a comprehensive evaluation of adnexal architecture, uterine cavity and myometrial assessment, and tubal patency.

At present there are no large studies that address the occurrence of post-HyCoSy pelvic infection. Most providers assume a rate of post-procedure infection equivalent to that which occurs after HSG. However, a review of the literature revealed an inconsistency in the use of prophylactic antibiotics when performing the HyCoSy procedure. In more than 20 different studies, there was no defined or standard algorithm that addressed the use antibiotics. Studies varied from no antibiotic use, to single dose after procedure antibiotic administration, to 2–5 days of antibiotic coverage with differing medications (i.e., amoxicillin, doxycycline, azithromycin) (21, 39, 43, 45–50). With no consensus opinion regarding the prevention of a HyCoSy procedure-related infection, the decision to prophylactically treat the evaluated patients is left to the discretion of each provider (47).

As with HSG, HyCoSy is considered a relatively quick and non-invasive procedure amendable to the outpatient setting. Some of the associated side effects are procedural discomfort, post-procedure vaginal bleeding, vasovagal reaction, and referred shoulder pain (40, 47, 51). One study that evaluated patient tolerance of the HyCoSy procedure compared with conventional HSG was completed in the United Kingdom (47). Sixty-six subfertile women were randomized to complete one of the two screening procedures, all performed by the same operator. Data were collected to evaluate the mean procedure time, quantity of required contrast, patient-reported tolerance, use of pain relief medications (i.e., nonsteroidal antiinflammatory drugs), and other reported side effects. Information was segmented into the following categories: "during", "2 hours after completion," "24 hours after completion," and "28 days after completion" (Table 2). There was no significant difference in reported procedure time, quantity of contrast used, patient tolerability, or other reported adverse effects (i.e., vaginal bleeding, presyncope symptoms, presumed infection) (47).

A more extensive retrospective review was completed in London involving 500 subfertile women at one center who underwent the HyCoSy procedure using Echovist-200 as the contrast media (40). Study end points included patient side effects, procedure logistics, and provider perceptions. Participants reported mild, moderate, or severe pain at a rate of 51%, 33.5%, and 15.6%, respectively. Severe discomfort was defined as requiring some form of analgesia or lasting up to 24 hours after the procedure. Vasovagal reactions were experienced in 2.2% of participants. All participants were contacted within 24–48 hours after the procedure and no post-procedure complications or infections were noted. The described median time for the procedure was 12 minutes, the median amount of contrast used was 15 mL. Operators noted difficulty in completing the HyCoSy procedure in obese participants, when the uterus was acutely

FIGURE 4

Echogenic contrast identified as scintillations (*arrow*) flowing over right and left ovaries during hysterosalpingo-contrast sonography. (Images provided by Steven Nakajima, M.D., University of Louisville, Louisville, Kentucky.)

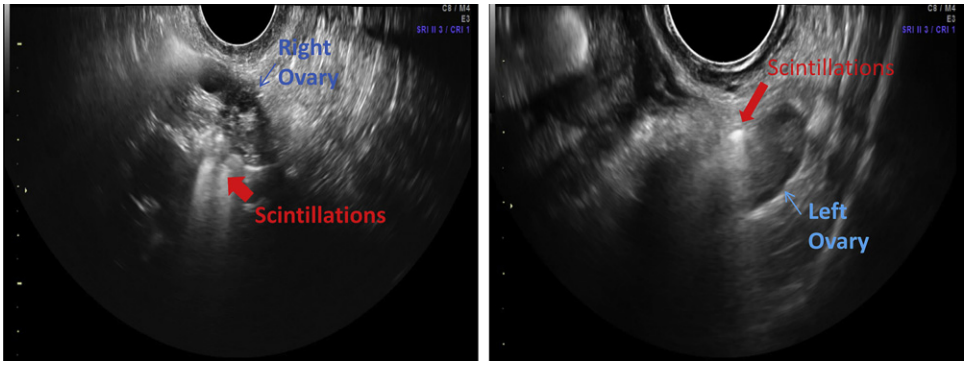

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TABLE 2

Study logistics and patient tolerance of HyCoSy compared with HSG (47).

Study	Mean procedure time (min)	Mean required contrast (mL)	Reported pain during procedure (%)	Reported pain 24 hours after procedure (%)	Pain ≤ usual menses (%)
HyCoSy	12.1	9.4	56	41	100
HSG	9.5	11.5	72	47	85

Note: HyCoSy = hysterosalpingo-contrast sonography; HSG = hysterosalpingography.

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retroverted or oblique, when multiple loops of active bowel were present, or the ovaries were located beyond the penetration of the ultrasound signal (40). Finally, a learning curve of 50–100 performed HyCoSy procedures was observed to improve fallopian tube visualization from 92.6% to 95.2%.

The HyCoSy procedure may also prove to be the most cost-effective procedure when compared to HSG due to the latter's intrinsic requirement for radiocontrast dye, roentgenogram filmography equipment, and available technicians. Most infertility centers have an ultrasound unit capable to complete the HyCoSy procedure within their own practice setting, without the need for contractual obligations to local radiography centers (16, 23, 41, 45).

Comparative studies In support of the HyCoSy procedure's applicability to clinical practice, a comprehensive meta-analysis has been published involving 1,007 women who underwent diagnostic imaging for tubal-related subfertility (Table 3, study 1) (52). In this investigation, the involved studies examined diagnostic outcomes of HyCoSy, using Echovist-200 contrast media, compared with traditional HSG or laparoscopy with chromopertubation. The meta-analysis revealed a concordance of 83% between HyCoSy and HSG when detecting tubal pathology. The same concordance was observed for women who underwent HyCoSy and laparoscopy with chromopertubation. One drawback of the HyCoSy procedure was an observed 10% false occlusion rate and 7% false patency rate when compared with laparoscopy (52).

Another extensive review was completed in 1993 involving six European countries (Austria, Belgium, Germany, Italy, Sweden, and the United Kingdom) (23). This study evaluated 600 subfertile women who completed the HyCoSy procedure using Echovist-200 as contrast media followed by a comparison study: HSG or laparoscopy with chromopertubation. The concordance values between HyCoSy and HSG, and HyCoSy and laparoscopy, were consistent with the results derived from the meta-analysis above (Table 3, study 2). The overall HyCoSy detection of occlusion and patency was reported to be 100% and 86%, respectively.

Similar results were achieved in a prospective series by Deichert and colleagues (53) who studied 425 women from 10 different medical centers (Table 3, study 10). Participants completed the HyCoSy with Echovist-200 followed by HSG or laparoscopy (23, 53). Concordance for patency between the HyCoSy and comparative "standards" was 86.3% for laparoscopy and 83.8% for HSG (23). The overall reported adverse events attributed to the HyCoSy procedure from both retrospective reviews was 5%, including symptoms of nausea, sweating, hyperventilation, or vasovagal syncope.

An analogous prospective clinical trial was performed involving 103 subfertile women who completed the HyCoSy using Echovist-200 as the contrast media followed by traditional HSG within 1–2 hours by blinded providers (Table 3, study 4) (46). The observed concordance between HyCoSy and HSG procedures for the endometrial cavity was 90%, and for fallopian tube patency 72% (46). Of the 103 participants, 43 also completed laparoscopy with chromopertubation within 3 months of the HyCoSy and HSG procedures. Both HSG and HyCoSy showed a relatively high concordance with laparoscopy, 83% (70/84) and 80% (68/85), respectively (46). Although the observed concordance between HSG and laparoscopy compared with HyCoSy and laparoscopy was not statistically significant, the investigators gave some insight into the clinical applicability of the HyCoSy procedure. While there were more "uncertain" findings on HyCoSy than HSG (8.8% vs. 0.5%), a positive or "occluded" HyCoSy result yielded a higher probability of a tubal occlusion at 75% compared to a corresponding probability of 50% for HSG (46). However, when analyzing likelihood ratios for a negative or "patent" result, the HSG performed somewhat better (L.R. HSG = 0.3 vs. L.R. HyCoSy = 0.7) (48). The high negative predictive values for both procedures speak to their usefulness in first-line subfertility screening.

Several smaller studies, both prospective and retrospective, from various countries support findings from the studies reviewed previously (Table 3, studies 5–18). Although diminished in participant numbers, these studies bring forth a consistency that supports HyCoSy as a reliable and reproducible screening procedure for subfertility (16, 37, 41, 43, 45, 49–50, 53–58).

Outcome studies A retrospective study was completed in Finland to evaluate the validity of HyCoSy for tubal assessment before IUI (59). In this study, 261 women were evaluated by laparoscopy with chromopertubation, 217 with HyCoSy (using air and saline as contrast media), and 81 with HSG. All participants were noted thereafter to have at least one patent tube. The participants and partners then underwent one to five cycles of monitored superovulation (34% with clomiphene citrate, 56% with human menopausal gonadotropins, and 10% with both) with timed intrauterine insemination. Semen analysis for each participating partner was normal (male factor infertility defined as total motile sperm count less than five million). No significant differences in ovulatory disorders or patient demographics were noted among the groups. A total of 1,240 inseminations were performed. No statistical difference was revealed in the clinical implantation or pregnancy rate (PR) in all three groups (59). Ongoing PRs were 14%, 18%, and 18% for the laparoscopy, HyCoSy, and HSG groups, respectively. The investigators remarked that HyCoSy was a cost-effective method of tubal investigation for their infertile population without impairment in insemination selection or PRs (59).

At present the only double blind prospective published study assessing post-HyCoSy PRs was a clinical trial randomizing 334 initial subfertility patients into two groups: those who received

TABLE 3

HyCoSy studies compared with reference study for the detection of tubal occlusion by study design.

	Study	Study design	Sample size	Study type	Reference standard	Sensitivity (%)	Specificity (%)	PPN (%)	NPV (%)	C (%)
1	Holz et al. (1997)	MA	1,007	HyCoSy	HSG	—	—	87.2	96.1	83.1
				HyCoSy	LSC	—	—	89.7	92.3	83.3
2	Campbell et al. (1994)	R	600	HyCoSy	HSG	—	—	—	—	84–91
				HyCoSy	LSC	—	—	—	—	80–93
3	Hamilton et al. (1998)	R	185	HyCoSy	LSC	90.4	70.3	91.2	68.2	85.8
4	Strandell et al. (1999)	P, B	103	HyCoSy	HSG	—	—	—	—	72.0
			43	HyCoSy	LSC	27.0	90.0	75.0	88.0	80.0
			43	HSG	LSC	73.0	87.0	47.0	94.0	83.0
5	Chenia et al. (1997)	P, B	50	HyCoSy	HSG	—	—	—	—	85.0
6	Radic et al. (2005)	P, B	68	HyCoSy	LSC	100.0	77.0	70.0	100.0	—
7	Mitri et al. (1991)	P, B	60	HyCoSy	HSG	—	—	—	—	72.0
8	Hamed et al. (2009)	P, B	57	HyCoSy	LSC	76.1	79.4	71.4	83.1	78.1
			57	HSG	LSC	81.8	77.1	69.2	87.1	79.9
9	Kiyokawa et al. (2000)[b]	P, B	25	HyCoSy	HSG	84.4[a]	100.0[a]	100.0[a]	33.0[a]	84.0
10	Deichert et al. (1989)	P	219	HyCoSy	LSC	83.7	87	63.2	87.0	86.3
			68	HyCoSy	HSG	80.6	85	65.9	92.4	83.8
			23	HSG	LSC	71.4	84.4	—	—	80.4
11	Deichert et al. (1987)	P	76	HyCoSy	HSG or LSC	100.0	90	—	—	87.5
12	Degenhardt et al. (1996)	P	57	HyCoSy	LSC	—	—	—	—	90.9
			20	HyCoSy	HSG	—	—	—	—	89.2
13	Tanawattanacharoen et al. (2000)	P	60	HyCoSy	LSC	—	—	—	—	80.0
14	Reis et al. (1988)	P	44	HyCoSy	LSC	85.2	85.2	71.9	92.9	85.2
			44	HSG	LSC	85.2	83.6	69.7	92.7	84.1
15	Inki et al. (1998)	P	32	HyCoSy	LSC	90.2[a]	83.3[a]	94.9[a]	71.4[a]	88.7
16	Exacoustos et al. (1996)	P	38	HyCoSy	HSG	80.0	94.0	84.0	92.0	89.6
			15	HyCoSy	LSC	75	91	75	91	86.7
			15	HSG	LSC	88	86	70	95	86.7
17	Volpi et al. (2003)	P	29	HyCoSy	LSC	80.0	85.0	85.0	80.0	82.7
			10	HyCoSy	HSG	—	—	—	—	100.0
18	Dietrich et al. (1996)	P	20	HyCoSy	LSC	—	—	—	—	82.5

Note: P = prospective; R = retrospective; MA = meta-analysis; B = blinded; PPN = positive predictive value; NPV = negative predictive value; C = concordance; HyCoSy = hysterosalpingo-contrast sonography; HSG = hysterosalpingography.

[a] Positive test represented tubal patency.

[b] HyCoSy performed using CO_2 gas with saline as distension and filling media.

Saunders. Tubal patency assessment. Fertil Steril 2011.

HyCoSy with Echovist and those who proceeded with infertility treatment without any procedure-related tubal flushing (60). The PR and time to pregnancy in each group was not statistically different, leaving a clinical impression that the potential to enhance pregnancy after a HyCoSy could not be confirmed (60, 61). The investigators did not offer a power analysis to determine the presence of a type II error.

Limitations of the procedure Collectively, in the studies reviewed previously, researchers identified potential causes for false interpretation of HyCoSy findings: [1] observed echogenic flow in one segment of the tube without confirmation of distal flow over the adjacent ovary (distal occlusion overlooked); [2] presence of a tubal fistula where free tubal passage may mimic flow from the fimbria; and [3] conversely, false occluded findings may be secondary to tubal spasm. Despite these limitations, researchers have arrived at a similar conclusion that the HyCoSy procedure is comparable with traditional HSG for tubal investigation and can be used as a time-efficient, methodologically simple, well-tolerated, screening tool in the initial subfertility evaluation (Table 3).

Laparoscopy

Laparoscopy with chromopertubation is widely accepted as the "gold standard" method for evaluating tubal patency. At present, it is considered the most accurate diagnostic test available for evaluating tubal-related subfertility. Its advantages include an ability to simultaneously evaluate the abdominal cavity and other pelvic structures for an enhanced diagnostic evaluation of other etiologies of subfertility. The procedure also allows for therapeutic excision of endometriotic lesions and, usually, restoration of abnormal pelvic findings. Laparoscopy incurs, however, operative risks, costs, and a period of postoperative recovery.

A prospective, 12-month, Netherlands nationwide study was designed to discern the rate and characteristics of surgical complications in gynecologic laparoscopy. A total of 25,764 laparoscopic surgeries were performed in 72 Dutch hospitals with a reported

TABLE 4

Advantages and disadvantages of hysterosalpingogram (HSG), hysterosalpingo-contrast sonography (HyCoSy), and laparoscopy with chromopertubation (LSC).

Study	Advantages	Disadvantages
HSG	Potential visualization of entire length of fallopian tube Ability to diagnose various tubal pathologies (i.e., SIN, hydrosalpinx) Therapeutic lavage with documented improvement in pregnancy rates (10)	Exposure to radiation Potential severe adverse contrast reaction (1, 2, 8, 9) Requires trained staff with appropriate equipment & facilities Visualization of pelvic adhesions and ovaries not possible
HyCoSy	Visualization of ovaries, uterus, and fallopian tubes in a single study	Requires trained staff with appropriate equipment & facilities Therapeutic lavage or improved pregnancy rates not proven (60)
LSC	Visualization of pelvic pathology (i.e., adhesions, endometriosis) Possible concomitant therapeutic surgical correction or removal of pelvic pathology	Invasive procedure with increased morbidity and mortality (62, 63) Requires general anesthesia Longer post-procedure pain and recovery Higher medical costs

Note: SIN = salpingitis ithmical nodosa.

Saunders. Tubal patency assessment. Fertil Steril 2011.

complication rate of about 5.7 per every 1,000 laparoscopies (62). The most common of these observed complications were hemorrhage from epigastric vessels and intestinal injury. Intuitively, the diagnostic procedures yielded less frequent complications (2.7/1,000) than the more involved operative laparoscopies (17.9/1,000) (62). Similarly, a retrospective review of worldwide gynecologic laparoscopic studies performed in more than 1.5 million women revealed an overall procedure-related complication rate of 0.2%–10.3%; of which 20%–25% were unrecognized at the time of surgery (63). Cardiac abnormalities, most commonly arrhythmias, were reported in 27% of all laparoscopies. These arrhythmias included sinus tachycardia, ventricular tachycardia, and asystole. Brachial plexus injury was reported to occur in 0.16% of cases due to improper patient positioning. The overall hospital readmission rate was 0.5% and conversion to laparotomy 2.1% (63).

When there are no significant operative findings, laparoscopy may lead to an unnecessary delay in initiation of fertility therapy. Historically, laparoscopy may have been more readily performed as a first-line screening evaluation for subfertility. As an invasive and expensive procedure, however, it is not an ideal first-line, screening test for subfertility when suitable alternative office procedures (HSG or HyCoSy) are available (Table 4). When clinical history, laboratory, or these office procedures suggests tubal-related pathology, laparoscopy may disclose a definitive diagnosis and offer a treatment option.

In conclusion, the most advantageous screening infertility protocol would necessitate methods that are diagnostically accurate, timely, cost-effective, reliable, and minimally invasive. This article has explored the various tubal and uterine screening modalities (e.g., HSG, sonohysterography, HyCoSy, laparoscopy) and reviewed applicable clinical scenarios, procedure advantages, and inherent flaws. The HyCoSy procedure appears to be the most comprehensive study, while maintaining competitive diagnostic accuracy. It enables providers to simultaneously evaluate ovarian reserve and structure, uterine cavity contour and myometrial structure, and tubal architecture and patency.

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