

# 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

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## ABSTRACT

**Objectives** The aim of the present study was to examine the role of hysterosalpingocontrast sonography (HyCoSy) as a screening test for endometrial and tubal pathology at the start of the infertility investigation protocol.

**Methods** HyCoSy was compared with X-ray hysterosalpingography (HSG) for the assessment of the endometrial cavity and Fallopian tube patency. A total of 103 women with a history of at least 1 year's infertility were included. Each woman underwent both HyCoSy and HSG on the same day. Laparoscopy was performed in 43 cases. For HyCoSy examinations, saline was used for evaluation of the endometrial cavity and Echovist<sup>®</sup> contrast medium to assess Fallopian tube patency.

**Results** The concordance between HyCoSy and HSG for the presence of endometrial cavity pathology was 90%, but for tubal patency the concordance was lower (72%). HyCoSy classed more examinations of tubal patency as uncertain. HSG more frequently classified tubes as occluded. In the subset of patients in whom all three techniques were used, HSG and HyCoSy demonstrated a high concordance with laparoscopy (83% and 80%, respectively). The prevalence of occluded tubes according to laparoscopy as the reference standard was 13%. The two methods had a high negative predictive value for tubal disease (HSG, 94%; HyCoSy, 88%), and the positive predictive values were 47% and 75%, respectively. The detection rate for occluded tubes was 73% and 27%, and specificity 87% and 90%, respectively.

**Conclusions** Our data demonstrate that HyCoSy obtains similar information about the status of the endometrial cavity and Fallopian tube patency to that of HSG. It is possible that in some cases HyCoSy may replace HSG in order to select women with patent tubes who may be suitable for further infertility treatment without more invasive investigation.

## INTRODUCTION

Infertility investigation protocols often include the use of both X-ray hysterosalpingography (HSG) and laparoscopy with dye intubation for the assessment of Fallopian tube patency, as well as for the detection of pathology within the endometrial cavity. However, HSG has limitations and disadvantages, as the patient is subjected to radiation and potentially allergenic agents. Recently, the use of transvaginal ultrasonography has become routine practice in both general gynecology and reproductive medicine. The introduction of ultrasound contrast agents has introduced the possibility of assessing tubal patency at the time of the pelvic scan, a technique known as hysterosalpingocontrast sonography (HyCoSy). The use of an ultrasound contrast agent to assess the endometrial cavity was first reported in 1981 by Nanini and co-workers<sup>1</sup>, who described the injection of saline as a negative contrast agent to enhance its visualization. Deichert and associates<sup>2</sup> later showed how, in a naturally fluid-filled uterus, intrauterine structures were highlighted by the surrounding fluid. Since these early

publications, several studies have reported the use of contrast agents for the evaluation of Fallopian tube patency and the endometrial cavity<sup>3-9</sup>.

The aim of the present study was to assess patients presenting with subfertility, in order to compare HyCoSy with HSG for the evaluation of tubal patency and the endometrial cavity. In a subset of patients, we compared the performance of these two techniques with laparoscopy and dye intubation as the reference procedure.

## METHODS

To evaluate the agreement between the results obtained by HSG and HyCoSy, a prospective clinical trial was initiated in which the patients acted as their own controls. Between November 1995 and October 1996, a total of 103 consecutive patients attending the fertility clinic were recruited to the study (mean age 31.5 years, range 18-41 years; mean duration of infertility 2.5 years, range 1-7 years).

As HyCoSy was already established as a technique in our hospital, approval from our hospital ethics committee was not required. Both procedures were undertaken on the same day during the preovulatory phase of the menstrual cycle. HyCoSy was performed first, followed by HSG usually 1-2 h later. A single 200-mg dose of doxycycline (Doxyferm<sup>®</sup>, Nordic Drugs AB, Sweden) was given orally immediately after the procedures as prophylaxis against infection. No analgesia was given. Separate reports were produced for the two procedures. The clinicians performing the HSG were blind to the results of the ultrasound contrast studies (HyCoSy). Data collected included demographic information, the contrast agents used and the presence or absence of pathology in the uterus and Fallopian tubes.

Each HyCoSy examination was performed by one of four gynecologists. The experience of the operators ranged from five to over 100 previous HyCoSy procedures. The less experienced operators were supervised by the most experienced gynecologist, who made the final evaluation. All patients had empty bladders and were scanned in the lithotomy position with a slight reverse Trendelenburg tilt to localize free fluid in the pouch of Douglas. A transvaginal B-mode scan was performed prior to the use of the contrast agent (HyCoSy). The presence of a hydrosalpinx was considered a contraindication to the installation of ultrasound contrast media. Transvaginal ultrasound was performed using a 6.5-MHz transducer with a 90° sector (Aloka SSD 2000, Aloka Co Ltd, Tokyo, Japan). A 1.2-mm balloon catheter (Schering) was inserted to the level of the internal os of the cervix and the cuff was slowly inflated with 0.5-2 ml air. An average of 6 ml of sterile saline (range 2-15 ml) was injected into the endometrial cavity in order to achieve distension of the cavity walls. The presence or absence of polyps, submucous fibroids and synechiae was noted.

Ultrasound contrast medium (Echovist<sup>®</sup>) was then injected to evaluate tubal patency. A mean volume of 9 ml of contrast was used for each examination (range 2.5-25 ml). The results were recorded for each tube sepa-

rately, including the presence or absence of contrast flow in three different segments of the tube (isthmic, ampullary and fimbrial) and over the ovary. Fallopian tube patency was defined as being the visualization of a steady flow of contrast agent within the Fallopian tube lasting at least 5 s in one imaged tubal section or the visible contrast spill from the fimbrial end over the ovary. A categorical statement was then made for each tube in relation to patency (patent, occluded or uncertain). It was noted whether contrast became visible in the pouch of Douglas. A representative photographic record of all findings was made. After the procedure was completed, the patient scored the pain she had experienced during the examination on a four-grade scale (none, mild, moderate or severe).

HSG was performed according to the established standard procedures at the Department of Radiology by a radiologist. A suction cup was used to instil contrast medium through the cervix. The contrast agent (Isopaque<sup>®</sup> 200 mg/ml, Nycomed, Norway) was injected under low pressure during fluoroscopy with intermittent film exposure. Pain during the HSG procedure was not recorded.

In 43 of the 103 cases, laparoscopy was performed to complete infertility investigations. These were carried out in a subsequent menstrual cycle within 3 months of the primary procedures, by experienced gynecologists. The surgeon was not aware of the results of the previously performed patency testing. Hysteroscopy was simultaneously performed if the pathology detected by one of the previous examinations was larger than 10 mm. The findings of the laparoscopic examination were regarded as the reference technique for tubal patency in the study.

## Statistics

For comparison between HSG, HyCoSy and laparoscopy, the sign test and McNemar's test were used. Since the three classifications (patent, occluded and uncertain) are not ordered, a pre-analysis reclassification into binary variables (uncertain vs. certain, occluded vs. non-occluded) was undertaken. A *p* value of < 0.05 was considered significant. Sensitivity, specificity and positive and negative predictive values were calculated for the subgroup for which laparoscopy could be used as a reference standard. For the purposes of this study a positive result related to a finding of tubal occlusion. Therefore, the sensitivity of each technique related to the number of correctly identified occluded tubes. In the same group, positive and negative likelihood ratios for both HSG and HyCoSy were calculated by dividing the likelihood of a positive or negative test among occluded tubes by the likelihood of a positive or negative test among healthy tubes. The probability of disease was calculated with the use of a nomogram adapted from Fagan<sup>10</sup> in order to illustrate the usefulness of likelihood ratios.

## RESULTS

A mean time of 13 min (median 15) was required for the practical aspects of each HyCoSy examination (range

5–40 min). Out of 103 patients, 21% did not experience any pain during HyCoSy, while 26% scored mild, 40% moderate and 9% severe pain. The only adverse events recorded during the HyCoSy were dizziness, bradycardia and nausea (12% of patients). One HSG examination, in a patient with a previous unilateral salpingectomy, was not completed, owing to severe pain. Therefore, only 102 patients underwent both procedures.

### Uterine pathology

Ten cases of endometrial cavity pathology were detected by HyCoSy compared to six cases by HSG, of which three cases were detected by both methods. The difference was not statistically significant ( $p = 0.34$ ). Concordance was present in 90% (92/102) (Table 1).

### Tubal patency

A total of 204 Fallopian tubes were examined. Concordance in relation to a diagnosis of tubal patency between the two diagnostic methods was present in 72% (146/204). Using HyCoSy, 8.8% (18/204) of the tubes could be classified neither as patent nor as occluded and were thus classified as 'uncertain'. The corresponding figure for HSG was 0.5% (1/204) ( $p = 0.0015$ ). HSG categorized significantly more tubes as occluded (23% (48/204) vs. 4% (9/204);  $p = 0.0002$ ) These data are shown in Table 2. In 43 cases laparoscopy was performed. Table 3 shows the findings

**Table 1** Detection of uterine pathology according to hysterosalpingography (HSG) and hysterosalpingocontrast sonography (HyCoSy) in 102 women undergoing both procedures

HyCoSy	HSG		Total
	Normal	Pathology	
Normal	89	3*	92
Pathology	7 <sup>†</sup>	3 <sup>‡</sup>	10
Total	96	6	102

No significant difference between HSG and HyCoSy in detecting uterine abnormalities;  $p = 0.34$  (sign test). \*In two cases, the findings of a fibroid and synechiae could not be verified at hysteroscopy. The third case with a 6-mm polyp was not further investigated. <sup>†</sup>Six cases of polyps, size 4–14 mm. One case of synechiae, in which hysteroscopy showed atrophy. <sup>‡</sup>Two cases of fibroids, size 8–20 mm; both verified by hysteroscopy. One case with a bicornate uterus and a septum

**Table 2** Classification of tubal patency by hysterosalpingography (HSG) and hysterosalpingocontrast sonography (HyCoSy) in 204 tubes

HyCoSy	HSG			Total
	Patency	Occlusion	Uncertain	
Patency	139	37	1	177
Occlusion	2	7		9*
Uncertain	14	4		18**
Total	155	48*	1**	204

\*Significant difference between methods in classifying as occlusion,  $p = 0.0015$  (sign test); \*\*significant difference between methods in uncertain classification,  $p = 0.0002$  (sign test)

**Table 3** Classification of tubal patency in 85 tubes, comparing laparoscopy with hysterosalpingography (HSG) and with hysterosalpingocontrast sonography (HyCoSy). An 'uncertain' diagnosis in laparoscopy was given when no dye passed the tubes despite a totally normal tubal appearance

	Laparoscopy			Total
	Patency	Occlusion	Uncertain	
<i>HSG</i>				
Patency	62	3	1	66
Occlusion	8	8	1	17
Uncertain	1			1
Total	71	11	2	84*
<i>HyCoSy</i>				
Patency	65	7	2	74
Occlusion	1	3		4
Uncertain	6	1		7
Total	72	11	2	85

For laparoscopy and HSG, sensitivity 73% (8/11); specificity 87% (62/71); positive predictive value 47% (8/17); negative predictive value 94% (62/66). For laparoscopy and HyCoSy, sensitivity 27% (3/11); specificity 90% (65/72); positive predictive value 75% (3/4); negative predictive value 88% (65/74).

\*One tube missing, owing to incomplete HSG in a patient with a previous unilateral salpingectomy

from the examination of 85 tubes (one patient had undergone a unilateral salpingectomy). Both HSG and HyCoSy showed a relatively high concordance with laparoscopy, 83% (70/84) and 80% (68/85).

The likelihood ratio for a positive test result with HSG was calculated as  $(8/11)/(8/71) = 6.5$  and with HyCoSy as  $(3/11)/(1/72) = 19.6$ . The corresponding likelihood ratios for a negative test result were  $(3/11)/(62/71) = 0.3$  for HSG and  $(7/11)/(65/72) = 0.7$  for HyCoSy.

### Prevalence of occlusion

The prevalence of occluded tubes in the laparoscopy group was only 13% (11/85) when the data were analyzed on the basis of individual tubes. If tubal occlusion was assessed on a per patient basis, the prevalence of at least one occluded tube was 23% (10/43). Two patients had bilateral occlusions, and HSG and HyCoSy identified both. Of eight patients with unilateral occlusion, including one who had previously undergone a unilateral salpingectomy, four were recognized by HSG and three by HyCoSy. Thus, the sensitivity of detecting tubal occlusion in each patient for the two methods was 60% (6/10) for HSG and 50% (5/10) for HyCoSy with a specificity of 77% (24/31) and 84% (26/31), respectively.

### DISCUSSION

Our data support the view that there is a significant agreement between results obtained by HSG and HyCoSy (90% for endometrial cavity pathology and 72% for tubal patency). Parsons and Lense<sup>11</sup> compared endometrial abnormalities diagnosed by sonohysterography with findings at surgery and found concordance in 100%, although negative findings with sonohysterography were not further

evaluated. Another study<sup>12</sup> compared sonohysterography with hysteroscopy and revealed concordant findings in 90%. The same comparison was made when only patients with suspected pathology were included and concordance was then 65%<sup>13</sup>. Our series carried a similar design, performing hysteroscopy in cases where lesions were larger than 10 mm. As shown in Table 1, all cases with endometrial pathology detected by both methods were also verified with hysteroscopy.

In relation to Fallopian tube patency, Deichert and co-workers<sup>3</sup> reported a concordance of 87.5% between HyCoSy and either HSG or laparoscopy. However, in that study many of the HyCoSy examinations were performed under general anesthesia. Whilst studying HyCoSy others have shown a concordance of 72–90% with HSG<sup>4,5</sup> and 82–92% with laparoscopy and dye intubation<sup>4,14</sup>. Our slightly lower concordance figures for patency could also be explained by the fact that both HSG and HyCoSy were performed on the same day and always with the HyCoSy being carried out first. It could be argued that tubal spasm might also be more common when two procedures are combined in this way, leading to a high level of false-positive test results. However, it is not likely that a tubal spasm would last as long as 1–2 h, which was the interval between examinations. Our data may also be criticized, as the experience of the examiners with HyCoSy was variable. The constant supervision of less experienced operators counteracts this criticism and we believe that the results were not influenced by the variation in experience.

The data comparing HyCoSy with HSG do not provide any information about sensitivity and specificity, as HSG has been described as having a concordance with laparoscopy of 57%<sup>15</sup>. We used laparoscopy and dye intubation as a reference standard in a subset of patients which limited the number of patients available for further analysis to 43 and the number of tubes to 85 (one patient had undergone a unilateral salpingectomy). The prevalence of tubal occlusion was only 13%, yielding relatively little pathology from which to draw conclusions. There is a possibility of a therapeutic role of HSG and HyCoSy, which could partly explain the low prevalence. However, only oil-soluble contrast media have been shown to improve fertility prospects after HSG, compared with water-soluble contrast media<sup>16</sup> which were used in the present study for both HSG and HyCoSy. Laparoscopy was not performed in the remaining cases, because a diagnosis had already been made of male factor infertility, an ovulatory disorder or recurrent miscarriage. In these cases further investigation of the tubes would have given no additional information of importance to the subsequent infertility treatment: *in vitro* fertilization including intracytoplasmic sperm injection for male infertility and ovulation stimulation for ovulation disorders. The concordance for HSG with laparoscopy was 83% and for HyCoSy with laparoscopy 80%. Both methods performed well when detecting tubal patency. Our HSG results, with a high rate of false-positive findings, contrast with a meta-analysis comparing HSG with laparoscopy<sup>17</sup> that reported that tubal obstruction on HSG was a reliable test result. Our rate of false-negative HyCoSy results

demonstrates the importance of considering all aspects of the patient's history and examination. Laparoscopy should be recommended whenever a tubal factor is suspected, despite a negative HyCoSy result.

Another way to compare the methods is to calculate the different likelihood ratios, which consider both sensitivity and specificity. The likelihood ratio for a positive test result with HyCoSy was as high as 19.6, indicating a high accuracy of the test and clinical usefulness. The likelihood ratio for HSG was also relatively high (6.5), demonstrating its clinical value. Given the low prevalence of tubal occlusion (13%), the likelihood ratio would suggest that HyCoSy performs better than HSG. A positive HyCoSy yields a probability of the tube being occluded of 75%, whilst a positive HSG yields a corresponding probability of 50%. However, when analyzing likelihood ratios for a negative test result (HSG 0.3 and HyCoSy 0.7), HSG performed somewhat better. With a negative HSG the probability of an occluded tube was 4% and, with a negative HyCoSy, it was 9%. To evaluate the methods it was necessary to compare left and right tubes separately. In clinical practice it is of course more interesting to know whether the patient suffers from tubal infertility or not. Both HyCoSy and HSG are suitable for investigating patency but all other tube-related pathology is better investigated by laparoscopy. However, HSG has the ability of detecting mucosal folds and salpingitis isthmica nodosa, and HyCoSy may be developed to diagnose tube-related pathology other than occlusion<sup>8</sup>. In this series of laparoscopies the prevalence of patients with at least one occluded tube was 23%, two patients had bilateral occlusions and eight had unilateral occlusions. The ability to identify these cases was similar for the two methods. Although patient numbers were small, the results indicate that, with experience, HyCoSy works well compared with HSG as a first-line investigation. The method was well tolerated by the patients, although half of them experienced moderate to severe pain. This finding can be compared with another study in which the tolerance of HyCoSy was investigated<sup>18</sup> and 56% of the patients were found to have pain. In our opinion, an analgesic premedication should be recommended. Other aspects such as cost, environmental factors and patient communication must be considered when evaluating HyCoSy against existing methods of assessing tubal patency and endometrial pathology. Ovarian irradiation is avoided with HyCoSy. Furthermore, its costs, including those of the catheter and contrast agent, are lower than those of existing techniques.

We conclude that HyCoSy compares well with HSG both for the evaluation of tubal patency and to assess the presence or absence of pathology in the endometrial cavity. However, neither HSG nor HyCoSy can completely replace laparoscopy. The fact that HyCoSy has a high negative predictive value for pathology means that it could have a role as a first-line screening test for pelvic pathology, including patency. Patients could therefore be selected at an earlier stage for laparoscopy or treated for ovulatory disorders in the knowledge that their Fallopian tubes are likely to be patent. In the future a transvaginal ultrasound

scan with HyCoSy may form the basis of investigations carried out at the first visit to the infertility clinic.

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