



## A comparison of hysterosalpingo-foam sonography (HyFoSy) and hysterosalpingo-contrast sonography with saline medium (HyCoSy) in the assessment of tubal patency



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### ABSTRACT

**Objective:** A randomized controlled selective cross-over trial was performed to compare the diagnostic yield and efficacy of ExEm foam (HyFoSy) with saline medium (HyCoSy) as a contrast agent for hysterosalpingo-contrast sonography in subfertile patients.

**Study design:** 40 patients were randomized into HyCoSy with saline medium and HyFoSy with ExEm foam. Tubal patency were assessed according to pre-determined objective criteria that classified tubes based on degree of certainty in tubal patency. Selective cross-over testing with the other medium was performed in patients who had at least one possibly occluded or unexaminable tube on the initial test. **Results:** 80 tubes were evaluated. On initial testing, the proportion of tubes that were classified as patent was higher with HyFoSy compared to HyCoSy (70.0% vs 40.0%,  $p = 0.01$ ). A higher proportion of patients in the HyCoSy group required crossover testing [80.0% (16/20) vs 45.0% (9/20),  $p = 0.02$ ]. On cross-over testing, 41.7% (10/24) of possibly occluded or unexaminable tubes in the HyCoSy group were re-classified as patent when examined with Ex-Em foam, compared to 8.3% (1/12) of possibly occluded or unexaminable tubes in the HyFoSy group ( $p = 0.03$ ).

**Conclusion:** ExEm foam medium (HyFoSy) might improve the diagnostic yield and efficacy over saline medium (HyCoSy) for hysterosalpingosonography.

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### Introduction

Evaluation of the fallopian tubes forms an essential part of the infertility investigation as tubal disorder accounts for 25–35% [1] of female infertility. Hysterosalpingo-contrast sonography (HyCoSy) has been validated for the first-line evaluation of tubal patency [2].

The diagnosis of occlusion in HyCoSy rests on the non-visualization of tubal patency. It is usually not possible to differentiate between true tubal occlusion and a 'false' occlusion. 'False' occlusions may be due to a mucous plug, blood clot, myometrial spasm, mucosal oedema or technical difficulty [3]. The fallopian tubes usually follow a multiplanar course. Sometimes it may only be possible to demonstrate proximal patency by visualizing paracornual flow of contrast. Tracing the flow of contrast through the entire tubal length increases confidence in

the diagnosis of proximal and distal patency but is more technically demanding [4].

Saline [5,6] or a mixture of saline and air [7,8] have traditionally been used for HyCoSy [1]. Agents such as Echovist-200<sup>®</sup> (Schering AG, Berlin, Germany), Infoson<sup>®</sup> (MBI, San Diego, USA) and SonoVue<sup>®</sup> (Bracco, Milan, Italy) which produce more intense contrast effects were subsequently introduced. More hyperechogenic media [2] may enhance contrast visualization and enable clearer delineation of tubal anatomy. This may enhance confidence in the diagnosis of tubal patency, reduce 'false' occlusion results and improve the diagnostic yield of the test.

Most hyperechogenic contrast media are now no longer commercially available or not licensed for intrafallopian use. In 2007, a non-embryo toxic gel known as ExEm-gel<sup>®</sup> (GynaecologyIQ, Delft, The Netherlands) containing hydroxyethylcellulose and glycerol was introduced [9]. The gel is mixed with water to create a hyperechogenic foam that is used as a contrast medium for hysterosalpingo-contrast sonography (HyFoSy).

We performed a randomized controlled selective cross-over trial to compare the diagnostic yield and efficacy of ExEm foam

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(HyFoSy) with saline medium (HyCoSy) as a contrast agent for hysterosalpingo-contrast sonography in subfertile patients.

## Materials and methods

All patients referred for tubal patency assessment at the Singapore General Hospital's Centre for Assisted Reproduction were invited to participate. Inclusion criteria were subfertile women who required office tubal patency evaluation after assessment by a consultant gynaecologist. Exclusion criteria were age below the legal limit for consent (21 years old), inability to give informed consent, active pelvic infection, active uterine bleeding (including menstruation) and refusal to undergo cross-over testing. The study protocol was approved by the Institutional Review Board. Written informed consent was obtained from all patients. This included an explanation that selective cross-over would be offered if results fulfilled pre-determined criteria.

Patients were randomized using computer-generated block randomization into the two groups (HyCoSy with saline medium and HyFoSy) and were blinded to the outcome of the randomization. All tubal evaluation procedures were performed by two study investigators and a sonographer, using a GE Voluson E8 ultrasound system (GE Healthcare, Milwaukee, WI, USA) equipped with a 6–12 MHz 3D endovaginal probe.

The procedure was scheduled during the immediate post-menstrual phase (days 6–12 of the menstrual cycle). Antibiotic prophylaxis was given at the referring consultant's own discretion, if there was a history of pelvic infection, or if tubal occlusion or a hydrosalpinx was demonstrated. Analgesia was given after the procedure if required.

A routine non-contrast vaginal ultrasound assessment of the pelvic organs was performed before tubal evaluation. The procedure for HyCoSy using saline medium was as follows: The cervix was visualized with a Cusco speculum and cleaned with an antiseptic. A No. 5 paediatric Foley catheter was introduced into the cervical os, using a tenaculum if necessary. The balloon was positioned in the lower uterine cavity and inflated with 2 ml of saline to prevent backflow of contrast medium through the cervix. The speculum was removed and the vaginal transducer was reintroduced in the longitudinal plane to confirm correct placement of the catheter. Sterile normal saline (0.9% NaCl) in a 20-ml syringe was introduced into the endometrial cavity while observing the uterine cornua at the transverse plane using B-mode and colour Doppler in the 2D and 3D modes. After tubal evaluation is completed, the balloon is deflated and up to 5 ml of normal saline instilled to look for intracavitary lesions.

The procedure for HyFoSy was as follows: The cervix was visualized and cleansed in the same manner as with HyCoSy. The pre-packaged balloon-less cervical catheter was introduced into the cervical os, using a tenaculum if necessary. The speculum was removed and the vaginal transducer was reintroduced in the longitudinal plane. Up to 5 ml of sterile water was instilled to confirm correct placement of the catheter and look for intracavitary lesions then re-aspirated before proceeding to tubal evaluation. 20 ml of foam contrast was reconstituted from ExEm-gel and water according to the manufacturer's instructions and introduced into the endometrial cavity while observing the uterine cornua at the transverse plane using B-mode. 3D volume acquisition was performed during injection.

With both media, tubal patency and quality of visualization were classified according the following parameters:

- (1) Flow over the whole length of the tube, fimbrial outflow or peritoneal spillage of contrast provided definite evidence of complete (i.e. proximal and distal) tubal patency.
- (2) Paracornual flow only without visualization of fimbrial outflow or peritoneal spillage suggested at least proximal patency.
- (3) Contrast filling of the endometrial cavity without cornual flow suggested possible tubal occlusion.
- (4) Technical difficulty making tubal evaluation impossible e.g. absent filling of the endometrial cavity due to backflow of contrast, inability to introduce the catheter into the cervical os or maintain the catheter in the correct position preventing instillation of contrast into the endometrial cavity.

Selective cross-over testing was performed immediately after the initial tubal evaluation in patients who had at least one possibly occluded (parameter 3) or unexaminable tube (parameter 4). Participant blinding was maintained for the medium used for the cross-over test. A tube was considered patent when there was definite evidence of complete tubal patency (parameter 1) or suggestion of at least proximal patency (parameter 2). Cross-over testing was not performed when both tubes were patent.

Maximal pain scores assessed according to a visual analogue scale were recorded immediately after the procedure. All patients were given a 24-h contact number for emergencies and contacted by telephone two weeks later to screen for late post-procedural complications. They were also given a follow-up appointment within a month of the procedure.

## Analysis

The following outcome measures were used to assess diagnostic yield:

- Proportion of patent tubes detected with the initial tubal patency test.
- Proportion of possibly occluded or unexaminable tubes that were re-classified as patent on cross-over testing.

Efficacy was defined as the proportion of patients who required cross-over testing (i.e. had at least one possibly occluded or unexaminable tube on the initial tubal patency test).

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 22 (SPSS Inc, Chicago, IL, USA). Analysis was by intention-to-treat. Differences in outcomes of quantitative data were tested for statistical significance using the Mann–Whitney *U* test. Differences in outcomes of qualitative data were tested for statistical significance using the Fisher's exact test or Chi-square test. All variables with a *p*-value of less than 0.05 were significant.

## Results

51 women were referred for sonographic tubal evaluation at the Singapore General Hospital Centre for Assisted Reproduction over a 9-month period from April 2014, of which 40 participants were recruited, giving a response rate of 78.4%. There were no significant differences in baseline characteristics between the two groups (Table 1).

80 tubes were evaluated (Table 2). A higher proportion of tubes in the HyFoSy group demonstrated complete tubal patency (60.0% vs 35.0%, *p* = 0.04). A higher proportion of tubes in the HyCoSy group demonstrated possible tubal occlusion (55.0% vs 25.0%, *p* = 0.01). Overall, the proportion of tubes that were classified as patent was higher with HyFoSy compared to HyCoSy (70.0% vs 40.0%, *p* = 0.01).

There was no significant difference in median maximal pain scores between the two groups (*p* = 0.17).

Technical difficulty was encountered in the initial evaluation of two patients with 4 tubes. There was significant backflow

**Table 1**  
Baseline characteristics of study participants.

Characteristic	No. of patients			P value
	All (n = 40)	HyCoSy (n = 20)	HyFoSy (n = 20)	
Median age, years (IQR)	31.0 (22–33.8)	32.0 (29.3–37.0)	31.0 (29–31.8)	0.17 <sup>a</sup>
Ethnicity				
- Chinese	22/40 (55.0%)	11/20 (55.0%)	11/20 (55.0%)	1.00 <sup>b</sup>
- Malay	4/40 (10.0%)	0/20 (0.0%)	4/20 (20.0%)	0.11 <sup>b</sup>
- Indian	5/40 (12.5%)	4/20 (20.0%)	1/20 (5.0%)	0.34 <sup>b</sup>
- Others	9/40 (22.5%)	5/20 (25.0%)	4/20 (20.0%)	1.00 <sup>b</sup>
Subfertility type				
- Primary	31/40 (77.5%)	15/20 (75.0%)	16/20 (80.0%)	1.00 <sup>b</sup>
- Secondary	9/40 (22.5%)	5/20 (25.0%)	4/20 (20.0%)	
Duration of subfertility, years (IQR)	1.5 (1.0–3.0)	1.0 (0.6–2.6)	2.0 (1.0–3.4)	0.09 <sup>a</sup>
Risk factors for tubal occlusion <sup>c</sup>	6/40 (15.0%)	3/20 (15.0%)	3/20 (15.0%)	1.00 <sup>b</sup>

<sup>a</sup> Mann–Whitney *U* test.<sup>b</sup> Fisher's exact test or Chi-square test.<sup>c</sup> Risk factors for tubal occlusion include past history of tubal occlusion, previous tubal surgery, previous ectopic pregnancy, previous pelvic infection, hydrosalpinx on imaging, endometriosis.**Table 2**  
Results of initial tubal patency test.

	Proportion of fallopian tubes			P value
	All (n = 80)	HyCoSy (n = 40)	HyFoSy (n = 40)	
(1) Complete patency	38/80 (47.5%)	14/40 (35.0%)	24/40 (60.0%)	0.04 <sup>b</sup>
(2) At least proximal patency	6/80 (7.5%)	2/40 (5.0%)	4/40 (10.0%)	0.68 <sup>b</sup>
(3) Possible tubal occlusion	32/80 (40.0%)	22/40 (55.0%)	10/40 (25.0%)	0.01 <sup>b</sup>
(4) Technical difficulty	4/80 (5.0%)	2/40 (5.0%)	2/40 (5.0%)	1.00 <sup>b</sup>
Patent [(1) or (2)]	44/80 (55.0%)	16/40 (40.0%)	28/40 (70.0%)	0.01 <sup>b</sup>
Possible occlusion (3) or technical difficulty (4)	36/80 (45.0%)	24/40 (60.0%)	12/40 (30.0%)	
Median maximal pain score (IQR)	5.5 (3.3–7.8)	6.0 (4.0–8.0)	5.0 (2.3–7.0)	0.17 <sup>a</sup>

IQR: interquartile range.

<sup>a</sup> Mann–Whitney *U* test.<sup>b</sup> Chi-square test.**Table 3**  
Results of crossover tubal patency test.

	Proportion of fallopian tubes			P value
	All (n = 36)	HyCoSy (n = 24)	HyFoSy (n = 12)	
(1) Complete patency	8/36 (22.2%)	7/24 (29.2%)	1/12 (8.3%)	0.22 <sup>a</sup>
(2) At least proximal patency	3/36 (8.3%)	3/24 (12.5%)	0/12 (0.0%)	0.54 <sup>a</sup>
(3) Possible tubal occlusion	25/36 (69.4%)	14/24 (58.3%)	11/12 (91.7%)	0.03 <sup>a</sup>

<sup>a</sup> Fisher's exact test or Chi-square test

causing failure to fill the endometrial cavity in one patient from the HyFoSy group. Another patient from the HyCoSy group experienced multiple extrusions of the intracervical Foley's catheter.

Crossover testing with the other medium was performed when there was possible tubal occlusion or technical difficulty with the initial tubal patency test. A higher proportion of patients in the HyCoSy group required crossover testing [80.0% (16/20) vs 45.0% (9/20),  $p = 0.02$ ]. All patients who met the criteria for crossover testing consented to the procedure.

41.7% (10/24) of possibly occluded or unexaminable tubes in the HyCoSy group were re-classified as patent (i.e. complete or at least proximal patency) when examined with Ex-Em foam, compared to 8.3% (1/12) of possibly occluded or unexaminable tubes in the HyFoSy group ( $p = 0.03$ ) (Table 3).

Taking into account results of both the initial and crossover tests, there was no significant difference between both groups in

the proportion of tubes classified as patent [65.0% (26/40) of tubes in the HyCoSy group vs 72.5% (29/40) of tubes in the HyCoSy group,  $p = 0.47$ ].

No major post-procedural complications were encountered in either group.

### Comments

Compared to X-ray hysterosalpingography (HSG) and laparoscopic chromopertubation, HyCoSy is relatively inexpensive and can be done outpatient, without the need for surgery or ionizing radiation. Results of HyCoSy have been found to correlate well with those of HSG and laparoscopic chromotubation [10]. While it is generally easy to diagnose tubal patency with HyCoSy, true tubal occlusion is difficult to ascertain and usually impossible to differentiate from 'false' occlusions based on the results of a

single test. However 'false' results also occur with HSG and even laparoscopic chromopertubation, which is regarded as the gold standard for assessing tubal patency [2].

It is uncertain if the type of contrast medium affects the diagnostic accuracy of HyCoSy. Few studies have directly compared the use of commercially available hyperechogenic contrast agents with saline solution. One study [10] reported that SonoVue<sup>®</sup> was more accurate than saline and air medium, especially in the reduction of false occlusion results. Another study which compared Infuson<sup>®</sup> with saline found that Infuson<sup>®</sup>-enhanced HyCoSy provided a significantly larger number of correct diagnoses than saline HyCoSy with an accuracy comparable to that of HSG [11]. However a recent systematic review [12] found no benefit of commercially available hyperechogenic contrast agents over saline solution in diagnosing tubal patency.

The accuracy of HyFoSy is supported by other studies. Schoubroeck et al. [13] found a 100% agreement between tubal patency data according to HyFoSy testing and laparoscopic chromopertubation. Emanuel et al. [14] reported that HyFoSy was a successful first-line procedure to demonstrate tubal patency and could avoid a HSG in 78% of cases.

Our study has demonstrated that tubal patency assessment with HyFoSy produced a higher diagnostic yield compared to HyCoSy. Initial testing with HyFoSy was associated with higher detection of patent tubes and better demonstration of complete patency compared with HyCoSy. Crossover testing with HyFoSy increased the detection of patency in tubes that were initially classified as possibly occluded or unexaminable by HyCoSy. 41.7% of possibly occluded or unexaminable tubes in the HyCoSy group were found to be patent when examined with Ex-Em foam. On the other hand, most (91.7%) of the tubes that were possibly occluded or unexaminable on initial testing with Ex-Em foam were also occluded when examined with saline medium. As both groups were appropriately randomized and found to be homogenous in terms of baseline characteristics and risk factors for tubal occlusion, it was assumed that there should be no significant difference in the proportion of truly occluded tubes between the two groups. Therefore it is reasonable to assume that any differences in detection of patent tubes can be attributed to the performance of the test medium rather than differences in the proportion of patent tubes between the two groups.

Overall, there were no significant differences in diagnostic yield between the two test strategies – HyCoSy or HyFoSy with crossover to the other test medium if appropriate. The detection of tubal patency was 65.0% with HyCoSy followed by selective HyFoSy, compared to 72.5% with HyFoSy followed by selective HyCoSy ( $p = 0.66$ ). However the proportion of patients who required cross-over testing was higher in the HyCoSy group (64.0% vs 36.0%,  $p = 0.02$ ), suggesting that HyFoSy was more efficacious for first-line tubal evaluation compared to HyCoSy.

Our study had several limitations. We performed cross-over testing only on tubes that were possibly occluded or unexaminable on initial evaluation to avoid subjecting patients with patent tubes to the risks of an additional test which was likely unnecessary. The probability that a tube which was initially found to be patent but demonstrated blockage on cross-over testing was likely to be small. Lack of a washout period could result in bias when evaluating the effect sizes of each study arm on results, but is more convenient to the patient, minimizes delay in starting fertility treatment and more closely replicates the real-world situation. The small sample size of the study was also another limitation.

To ensure validity, all tubal patency tests were performed by the same pair of study investigators. Although the participants were blinded to their group allocation, it was not possible to blind the study investigators due to the preparation of contrast

media. To reduce observer bias, tubal patency was assessed according to pre-determined objective criteria that classified tubes based on degree of certainty in tubal patency. There were no significant differences between the results of the two procedurists.

One of the practical issues encountered was that the echogenicity of the ExEm foam could mask intracavitary abnormalities. Thus we opted to perform uterine cavity assessment by instilling up to 5 ml of saline to visualize the uterine cavity in the longitudinal plane, then aspirating the saline before initiating tubal evaluation. We found that this practice also allowed the examiner to confirm correct placement of the cervical catheter and test for leakage before instilling ExEm foam. This was useful because the catheter being balloonless could be easily dislodged during removal of the Cussco speculum and might not provide a good seal if the os is too patulous.

## Conclusion

ExEm foam medium (HyFoSy) might improve the diagnostic yield and efficacy over saline medium (HyCoSy) for hysterosalpingosonography. Additional large prospective studies are needed to prove the role and value of ExEm foam medium for first-line sonographic tubal evaluation. Given that the overall detection of tubal patency is similar with the two test strategies, it may be worthwhile to perform a cost-benefit evaluation of sequential HyFoSy followed by selective HyCoSy versus HyCoSy followed by selective HyFoSy testing.

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