


Hysterosalpingo-Foam Sonography for the Diagnosis of Tubal Occlusion

A Systematic Review and Meta-analysis

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This systematic review and meta-analysis evaluated the diagnostic accuracy of hysterosalpingo-foam sonography in suspected cases of tubal occlusion. The combined sensitivity and specificity estimates were 0.99 (95% confidence interval [CI], 0.89–0.99) and 0.91 (95% CI, 0.53–0.98), respectively, with positive and negative likelihood ratios of 11.5 (95% CI, 1.5–87.5) and 0.006 (95% CI, 0.0003–0.12), respectively. The diagnostic odds ratio was 1931.008 (95% CI, 69.7–53,460.8). These findings confirm hysterosalpingo-foam sonography as a highly accurate test for the diagnosis of tubal occlusion and show that it is on a par with standard tests.

Key Words—accuracy; fallopian tube; hysterosalpingo-foam sonography; tubal occlusion; tubal patency; ultrasound

In an evaluation of female infertility, one of the prime steps is the assessment of tubal patency.¹ The reference standard is still laparoscopy with chromopertubation.^{1,2} However, laparoscopy is both expensive and invasive and can lead to intraoperative complications.² By contrast, hysterosalpingography (HSG) is much less invasive and is considered an acceptable alternative screening method for tubal patency.^{3,4} However, HSG exposes women to ionizing radiation and contrast media, which in some cases can provoke allergic reactions.⁴ The other main drawback is the level of pain known to be caused by HSG.^{2,3}

To overcome the issues connected to the HSG procedure, contemporary ultrasound-based methods to evaluate tubal patency and the uterine cavity with contrast have attracted growing attention in infertility examinations.^{3,4} Diagnosis of the uterine cavity via saline infusion sonography is now broadly accepted in infertility workups.^{5–7} Unfortunately, saline does not provide satisfactory contrast for tubal patency, since flow within the tube is hard to detect.⁸ This is why clinicians have turned to hysterosalpingo-contrast sonography, which is noninvasive, safe, and cost-effective and can generate a rapid, reliable diagnosis for tubal patency that is easy to use.^{9–14}

Hysterosalpingo-foam sonography (HyFoSy) was first presented as an innovative approach to evaluating fallopian tube patency in 2012. The procedure consists of passing hyperechoic foam, which can be visualized as it moves from the uterine cavity to the fallopian tubes into the peritoneal cavity.¹⁵ In terms of both accuracy and effectiveness, HyFoSy has been reported to have promising features.^{16,17}

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Abbreviations

CI, confidence interval; HSG, hysterosalpingography; HyFoSy, Hysterosalpingo-foam sonography; ROC, receiver operating characteristic

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Studies that have examined the diagnostic capabilities of HyFoSy have generally only used small samples and have reported widely varying degrees of diagnostic accuracy. This poses the problem of the sensitivity and specificity and, more generally, that of reliability. The systematic meta-analysis presented below is designed to provide an up-to-date overview of the diagnostic accuracy of HyFoSy for tubal occlusion as contrasted with laparoscopy or HSG.

Methods

Search Strategies

This study was a literature review, with no funding received. The study adhered to the principles of Preferred Reporting Items for Systematic Reviews and Meta-analysis.¹⁸ The search covered PubMed, Ovid MEDLINE, and Google Scholar databases for studies published from 2012 to 2020. It included medical subject headings for “hysterosalpingo-foam sonography,” “HyFoSy,” “fallopian tube diseases,” “tubal obstruction,” “tubal patency,” and “tubal occlusion.”

Adopting guidelines in the literature,^{19–21} the search strategy consisted of terms related to the index test (HyFoSy) and the target condition (tubal occlusion) and used no filters for diagnostic studies to maximize the sensitivity of the search. This strategy was applied and reviewed by 2 authors (N.Z.S. and Y.M.). Furthermore, the search included an examination of reference lists and citations of related articles (previous reviews and studies) to identify additional eligible reports.

Inclusion and Exclusion Criteria

All studies dealing with the accuracy of HyFoSy for diagnosing tubal occlusion were included with no restrictions in terms of language. Studies whose criteria extended to women who underwent HyFoSy to confirm occlusion after tubal sterilization were also included. Articles referring to hysterosalpingo-contrast sonography and 4-dimensional sonography were excluded from analysis. Other exclusion criteria included articles without a detailed assessment of method accuracy and effectiveness, comparison of HyFoSy to other methods besides laparoscopy and HSG, and case reports. The search was restricted to

studies in which laparoscopy or HSG was the reference standard. Two authors checked the titles and abstracts independently (N.Z.S. and Y.M.). Other publications were taken from reference lists of reviews and editorials and by a manual search of key journals and websites based on predefined inclusion criteria. Two authors (N.Z.S. and Y.M.) read each full text independently for content, data extraction, and analysis. The search results were then entered into a single reference database.

Duplicates were removed by hand. To extract the study characteristics and outcomes, a predesigned protocol was applied that included the author institution, year of publication, country, dates, total number of cases, study type, type of reference test, inclusion and exclusion criteria, and completeness of verification. The primary outcome was the diagnostic accuracy of HyFoSy for tubal occlusion in reference to laparoscopy or HSG. In certain studies, a test was considered positive if an occluded tube was detected, whereas in others, the criterion was a patent tube. Here, we defined a positive test as an occluded tube to harmonize the data set.

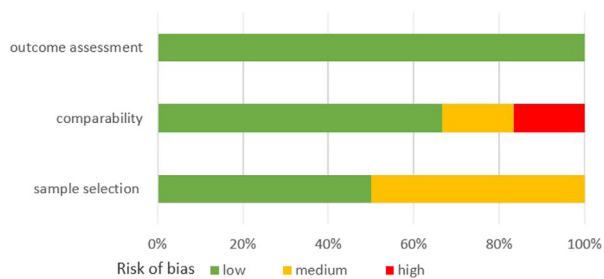
Quality Assessment

The Newcastle-Ottawa Scale for cohort studies was used to assess the qualities of the studies meeting the inclusion criteria.²² The Newcastle-Ottawa Scale rates each study on 3 criteria: choice of the sample for the study, comparability of groups, and ascertainment of the outcome. Items are rated “low,” “medium,” or “high” for the risk of bias. At least 2 of the authors scored each study independently; disagreements were resolved through discussion. Of the 6 studies included in the final review, 3 had a low risk of bias for sample selection; 4 had a low risk of bias for the outcome assessment; and all 6 had a low risk of bias for the comparability of cohorts (Figure 1). Overall, the risk of bias was low for all 6 studies.

Data Analysis

The guidelines in the Cochrane handbook for systematic reviews of diagnostic accuracy were followed.²³ A meta-analysis pooled the findings from the selected studies to evaluate variations in outcomes using the Metaprop program (StataCorp, College Station, TX). A random-effects model and exact confidence intervals (CIs) for proportions in pooling the results were used

Figure 1. Average quality assessment by the Newcastle-Ottawa scale for cohort studies.



to adjust for variation across studies. Statistical heterogeneity was assessed with the I^2 statistic, which represents the proportion of variation in study estimates ascribed to heterogeneity rather than a sampling error. We expressed the clinical effectiveness of the tests by the diagnostic odds ratio. The diagnostic odds ratio is calculated as the ratio of the odds of the test result being positive if the patient has a disease relative to the odds of the test result being positive if the patient does not have the disease. The rate of each outcome was estimated over all studies with these data.

We assumed that the outcomes were classified without error. Each study was reconfigured into a 2×2 table corresponding to the true-positive, true-negative, false-positive, and false-negative results of the diagnostic test versus the outcome. Forest plots for sensitivity and specificity of the index test were constructed from contingency tables. Then summary estimates of sensitivity and specificity and the 95% CI were calculated with the Metandi package for Stata version 16 statistical software (Stata Corp). The small sample size precluded running a regression correction for potential covariates. In this case the Metandi bivariate model and hierarchical summary receiver operating characteristic (ROC) models are equivalent; thus, only the results for the bivariate model are presented. We used the Metandiplot command to generate the ROC curve. A graph of the sensitivity-specificity pairs from each study provides a better visualization of the between-study heterogeneity than simple summary estimates.^{24,25}

Study Selection and Description

The literature search identified 375 citations. Of these, 6 were included in the final analysis (Figure 2).

All studies were prospective and were published from 2012 to 2020. Of these, 5 were from a single medical center, and 1 was a multicenter study. Half assessed tubal patency as part of a fertility workup. The others were conducted to confirm tubal occlusion after Essure (Bayer AG, Leverkusen, Germany) placement for hysteroscopic sterilization.

Synthesis of the Results

Table 1 lists the characteristics of the studies.^{15,16,26–29} A total of 622 fallopian tubes were used to estimate the accuracy of HyFoSy in diagnosing tubal occlusion. Hysterosalpingo-foam sonography was directly compared to the reference, which was either HSG (4 studies) or laparoscopy with chromotubation (2 studies). Figure 3 displays the individual and pooled estimates of diagnostic accuracy parameters for HyFoSy and the summary ROC curve. For HyFoSy, the pooled estimates of sensitivity and specificity were 0.99 (95% CI, 0.89–0.99) and 0.91 (95% CI, 0.53–0.98), respectively, with positive and negative likelihood ratios of 11.5 (95% CI, 1.5–87.5) and 0.006 (95% CI, 0.0003–0.12). The diagnostic odds ratio was 1931.008 (95% CI, 69.7–53,460.8).

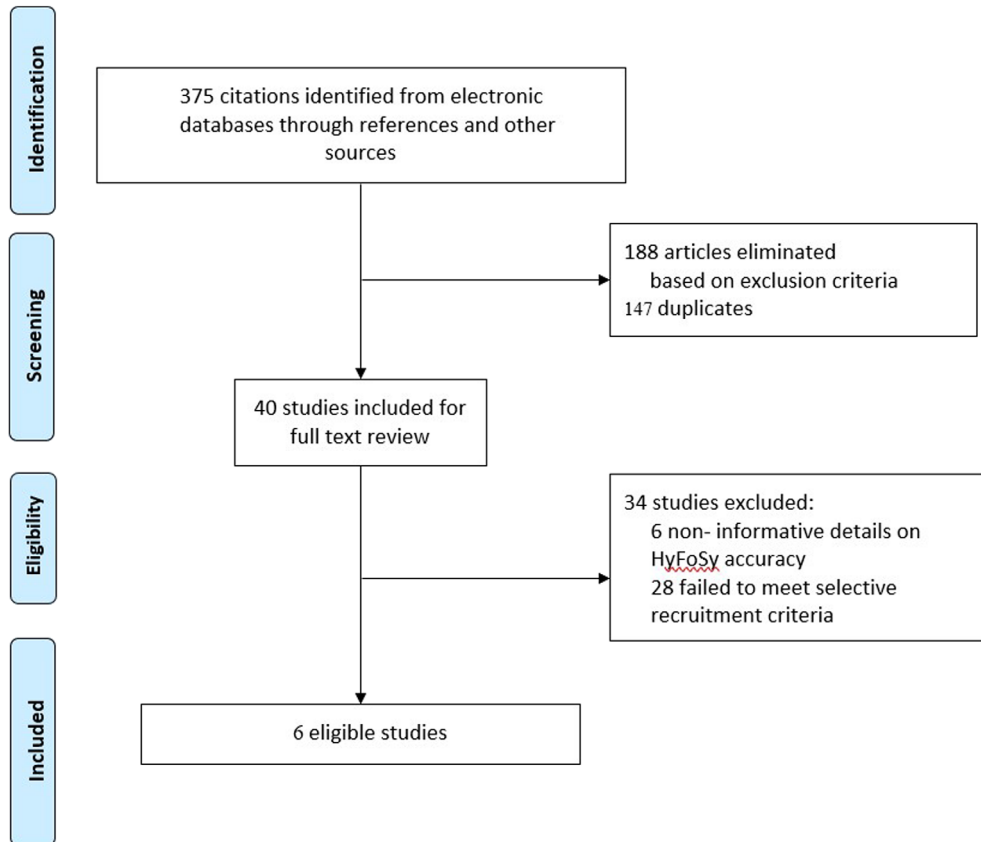
The overall heterogeneity between study estimates of sensitivity and specificity for diagnosing tubal occlusion appears in Figure 4. There was substantial heterogeneity across studies for sensitivity and specificity, with I^2 values of 53.2% (95% CI, 30.33%–69.59%; $P = .06$) and 86.55 ($P = .001$), respectively. The source of heterogeneity was the publication by Ludwin et al,¹⁶ which showed much lower sensitivity (86.7%) than all other studies (4 times, 100%; and once, 97%). After exclusion of the article by Ludwin et al,¹⁶ the heterogeneity fully disappeared ($I^2 = 1.8\%$). The summary ROC plot is presented in Figure 5, with an area under the curve of 0.95 (95% CI, 0.93–0.96).

Discussion

Main Findings

The findings point to the high diagnostic accuracy of HyFoSy in the evaluation of tubal occlusion. Both sensitivity (99%) and specificity (91%) were high,

Figure 2. Flow diagram of study selection.



thus making it a very accurate test that has high positive and low negative likelihood ratios.

Hysterosalpingo-foam sonography has the advantages of being an office procedure in which patients are not exposed to radiation, and the procedure itself involves less patient discomfort.¹⁷ In addition to tubal patency, data on the pelvic anatomy including the uterus and the ovaries as well as pelvic diseases such as endometriosis, adenomyosis, congenital uterine abnormalities, and ovarian findings can be obtained. The office setting may be more comfortable than a radiology department, where HSG is performed on a hard, flat x-ray table.^{17,30,31} Hysterosalpingo-foam sonography is well tolerated by most women and has few adverse effects.¹⁷ Reports indicate that it is less painful for women than HSG.³⁰

A number of publications have recommended that a complete pelvic ultrasound scan should be part of the evaluation of subfertile women, since it provides

valuable information affecting treatment decisions and the prognosis.³² Clearly, a complete assessment of the uterus, uterine cavity, endometrium, ovaries, follicles, tubes, and their patency can help identify anomalies that could result in prolonged, invasive, or unnecessary interventions.³² Although beyond the scope of this meta-analysis, the introduction of ultrasound-based contrast media for tubal patency assessments as a first line of investigation of infertile patients appears promising and should be considered as a replacement for other methods in reproductive medicine.

Strengths

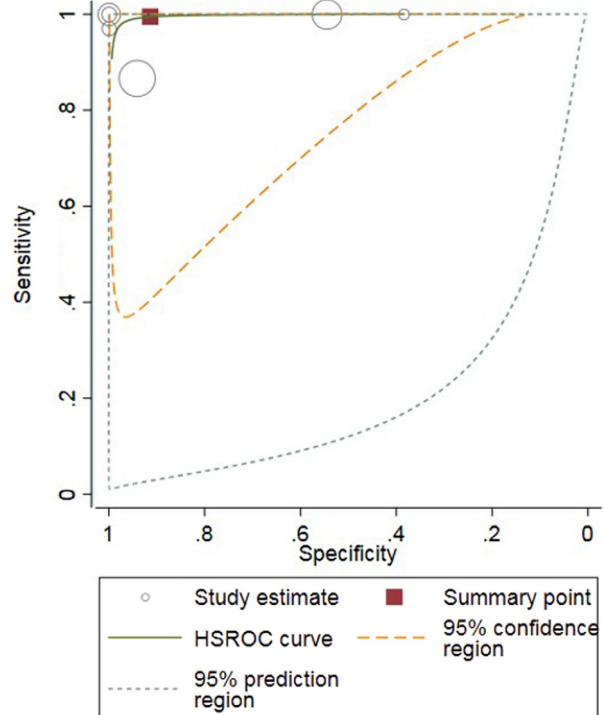
To our knowledge, this was the first meta-analysis of studies exploring the accuracy of HyFoSy in diagnosing tubal occlusion. We conducted a broad search for tubal assessment by HyFoSy to compensate for its recent availability. The start date for the search was 2012, which corresponds to the time when the first

Table 1. Characteristics of Studies in the Data Set

Author	Year	Reference Test	Tubes	PPV, %	NPV, %	Sensitivity, %	95% CI, %	Specificity, %	95% CI, %	TP	TN	FP	FN
Emanuel ¹⁵	2012	HSG	20	47	100	100	59–100	39	13.9–68.4	7	5	8	0
Van Schoubroeck ²⁶	2013	Laparoscopy with methylene blue	40	100	100	100	39.8–100	100	90.3–100	4	36	0	0
Dreyer ²⁷	2015	HSG	38	100	80	97	85–99.5	100	40–100	33	4	0	1
Ludwin ¹⁶	2017	Laparoscopy with methylene blue	259	50	99	89	65–99	93	89–96	13	225	14	2
Rosic ²⁸	2018	HSG	170	97	100	100	97–100	54.60	23–83	159	6	5	0
Zizolf ²⁹	2018	HSG	95	100	100	100	96–100	100	54–100	89	6	0	0

Only the first author's name is listed for each reference. FN indicates false-negative; FP, false-positive; NPV, negative predictive value; PPV, positive predictive value; TN, true-negative; and TP, true-positive.

Figure 3. Summary ROC plot of sensitivity and specificity for diagnosing tubal occlusions. Test sensitivity is plotted against specificity, thus enabling comparison of both parameters at the same time. The circles represent individual studies, and the size of the circles is proportional to the number of patients included in the study. The dark square is the summary estimate for sensitivity and specificity, and the yellow ellipse around the spot represents the 95% confidence region around the summary estimate. HS indicates hierarchical summary.

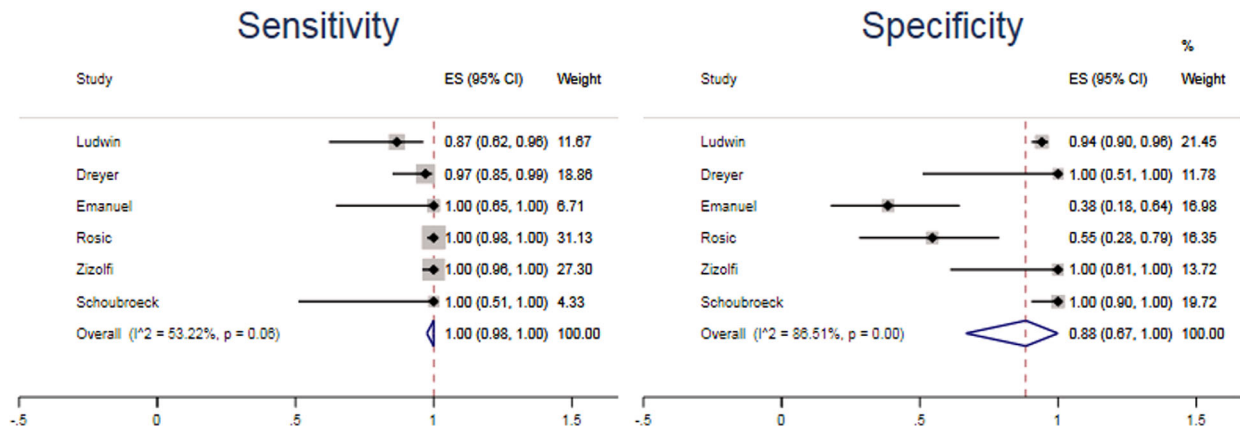


detailed HyFoSy test was conducted and reviewed by Emanuel et al¹⁵ This was done to increase the likelihood of an accurate use of the diagnostic procedure. We reassessed all previously reported calculations of sensitivity, specificity, and positive and negative predictive values to eliminate rounding off and imprecisions. This analysis was also deliberately limited to prospective studies alone, which had the advantage of eliminating recall and reporting biases. The method adhered to recent guidelines detailed in the Cochrane handbook for systematic reviews of diagnostic test accuracy.²³

Limitations

The main limitation of this study was its possible selection bias, due to the inclusion of studies involving Essure placement for hysteroscopic sterilization.

Figure 4. Forest plots showing the levels of overall heterogeneity between studies' estimates of sensitivity and specificity for diagnosing tubal occlusion. Only the first author's name is given for each reference. ES indicates effect size.



The literature search did not identify a large-enough number of studies of fertility assessments to conduct a separate meta-analysis or include a subanalysis. We also acknowledge the small number of studies included in the review, which may have resulted in a publication bias. Finally, this study did not address the aspect of the cost of HyFoSy versus saline and air agitated together, nor did it address whether the use of HyFoSy would be superior to air and saline agitated together, especially in light of the additional cost.

Conclusions

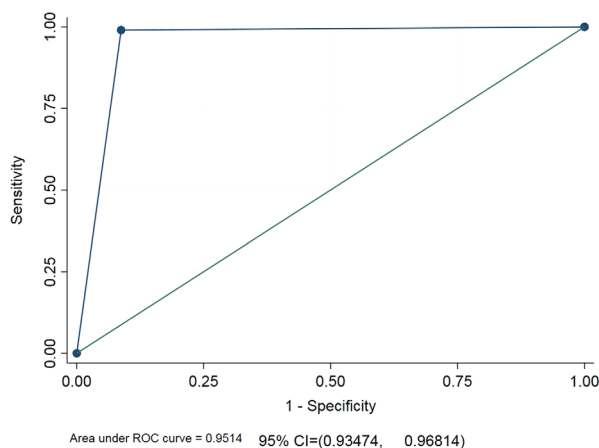
This meta-analysis confirms that HyFoSy is an accurate for diagnosing tubal occlusion and performs

similarly to standard tests. In light of the advantages of HyFoSy, this test may be included in the initial workup for subfertile couples. Note that a separate meta-analysis comparing the diagnostic accuracy of HyFoSy to reference tests in patients with infertility would provide an alternative viewpoint of interest to clinicians.

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Figure 5. Summary ROC plot.



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