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RESEARCH

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Diagnostic accuracy of hysterosalpingo-lidocaine-foam sonography combined with power Doppler (HyLiFoSy-PD) compared to laparoscopy and dye testing in tubal patency assessment in cases of infertility

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Abstract

Background: Tubal patency testing is an essential part of female subfertility evaluation. Hysterosalpingogram is less invasive and less expensive compared to laparoscopy and dye testing (LDT), i.e., laparoscopic chromopertubation. Hysterosalpingo-foam sonography (HyFoSy) uses commercial echogenic gel foam that is easily visible on ultrasound to assess the tubes. It offers a safer and less painful alternative to HSG, with no radiation exposure. Hysterosalpingo-lidocaine-foam sonography with power Doppler (HyLiFoSy-PD) uses lidocaine-made gel foam as a contrast medium. It was postulated to as to be less painful and easier to detect on ultrasound, compared with hysterosalpingo-foam sonography using other contrast media and that it can also be used whenever the commercial gel used with HyFoSy is not available or is relatively expensive.

Methodology: This prospective diagnostic accuracy study was carried out between February 2018 and 2020 at the Cairo Fetal Medicine Unit, Department of Obstetrics and Gynecology, Cairo University. One hundred twenty-two infertile patients, who were already scheduled for LDT as a part of their infertility work-up, were consecutively recruited for this study. The HyLiFoSy-PD (index test) was performed 1 week before the scheduled LDT for these patients. Using an intrauterine pediatric Folley's balloon catheter, 20 ml of lidocaine-made gel foam was slowly infused intrauterine,

Precis: HyLiFoSy-PD is an accurate, safe, and well-tolerated tool for tubal patency assessment that uses a contrast media of high availability and low cost. It can be carried out as an office procedure by a trained sonographer using conventional 2D TV- US system.

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while observing their flow in both fallopian tubes using a grayscale and power Doppler transvaginal two-dimensional ultrasound system. All patients then underwent LDT (reference test). The results of HyLiFoSy-PD were compared with those of LDT to determine the accuracy of HyLiFoSy-PD in tubal patency assessment. We also assessed the procedure duration, associated pain, and other complications.

Results: Comparing HyLiFoSy-PD with LDT in the 115 patients who completed the procedure, results showed 98.1% sensitivity, 90% specificity, 99% positive predictive value, 81.8% negative predictive value, 9.81 positive likelihood ratio, 0.02 negative likelihood ration, and 97.4% overall accuracy in the assessment of tubal patency (odds ratio = 463.5 with confidence interval = 79.39–2706; *P*-value: 0.687). The median procedure duration was 11 min. All patients experienced some degree of pain during the procedure with 91 patients (79%) reported mild pain and 24 patients (21%) reported moderate pain.

Conclusion: HyLiFoSy-PD was found to be an accurate tool in tubal patency assessment. It was also found to be safe and well-tolerated.

Keywords: Ultrasound, Infertility, Fallopian tube patency tests, Contrast radiography, Lidocaine, Laparoscopy

Introduction

Tubal disease accounts for 30–40% of female factors of infertility [1]. Therefore, accurate tubal testing is an essential part of female infertility work-up [2–4].

Laparoscopy with dye testing (LDT), also known as laparoscopic chromopertubation, has been referred to as the gold standard technique for tubal assessment [1, 5, 6]. It is the tubal patency test recommended by the National Institute for Health and Clinical Excellence (NICE) and the European Society of Human Reproduction and Embryology (ESHRE) for women suspected to have a tubal disease as it allows for direct visualization, diagnosis, and treatment of tubal and other pelvic pathologies [3, 7]. Even though LDT is a minimally invasive procedure that is associated with a low risk of bleeding and visceral injuries, it is carried out under general anesthesia, is expensive, and can be associated with false positive (tubal occlusion) results [1, 5, 6, 8].

Hysterosalpingogram (HSG) is one of the most commonly used initial tubal patency tests [4], as it offers a less-invasive and less-expensive alternative to LDT [5]. However, HSG is associated with risks of radiation exposure, pain, and potential allergic response. It cannot diagnose ovarian and some myometrial pathologies as well [1, 5, 7, 8].

Ultrasound-based tubal patency tests include hysterosalpingo-contrast sonography (HyCoSy), hysterosalpingo-foam sonography (HyFoSy), and hysterosalpingo-lidocaine-foam sonography (HyLiFoSy) [1, 5].

HyCoSy was introduced as a safer and less-painful alternative to HSG with comparable diagnostic accuracy and superiority in diagnosing uterine, ovarian, and myometrial pathologies [1, 5, 8, 9]. HyCoSy is the recommended tubal test by NICE for women not known to have a tubal disease, as an alternative to HSG, whenever the appropriate expertise is available [3]. It was widely used in infertility clinics [5, 6, 9–11]. However, the echogenic media used with HyCoSy are currently commercially unavailable or not approved for tubal testing [1, 5, 12–15].

HyFoSy was introduced as a safe, feasible, tolerable, and accurate alternative to HyCoSy and HSG [1, 5, 6, 8, 9, 14–22]. HyFoSy uses diluted ExEm gel foam (GynaecologIQ, Delft, Netherlands) [9, 14, 23] that is an approved and commercially available medium for tubal testing [12].

In 2017, HyLiFoSy combined with power Doppler (PD) (HyLiFoSy-PD) technique was described as a possibly less painful and easier to detect on ultrasound alternative to HyFoSy and HyCoSy, which can be used whenever the contrast media used with both are either unavailable or is relatively expensive [24]. Our study's primary outcome was to assess the diagnostic accuracy of HyLiFoSy-PD by comparing it with the reference standard of LDT. The secondary outcomes included procedure duration, associated pain, and other complications.

Methodology

This prospective diagnostic accuracy study was carried out between February 2018 and February 2020 at the Cairo Fetal Medicine Unit, Department of Obstetrics and Gynecology, Cairo University. The inclusion criteria were women of reproductive age who were already scheduled for LDT as a part of their infertility work-up and whose tubal factor was not investigated before. At our center, LDT is offered pro bono for women of reproductive age who are suspected to have a tubal factor of infertility or those who have had unexplained infertility for a year or more. Since assisted reproductive techniques (ARTs) are not funded by our national (Egyptian) health insurance and most infertile couples cannot afford to proceed with ARTs right away, many infertile women undergo LDT as a diagnostic and therapeutic step before undergoing ART. During the study period, HyLiFoSy-PD was offered to those patients in the week preceding the

LDT. All patients provided written consent to participate in the study after informing them of the details of the procedure.

The following exclusion criteria were applied: patients whose LDT was scheduled for a known tubal or ovarian pathology, previously investigated tubal factor, using contraception, known allergy to lidocaine, active pelvic inflammatory disease, undiagnosed genital tract bleeding, evident tubal pathology (such as hydrosalpinx) or pregnancy diagnosed by transvaginal ultrasound (TV-US) prior to performing the HyLiFoSy-PD. This study was reported using the Standard for the Reporting of Diagnostic Accuracy Studies (STARD). Ethical approval was provided by the Institutional Review Board (code:18009) in January 2018. The study was registered with the identifier NCT05209542.

Sample size calculation was based on the sensitivity of HyFoSy-PD in diagnosing tubal patency in infertile women as it is commonly used as a screening tool. According to a study by Ludwin et al. [16], the prevalence of blocked tubes was measured at 7% (18 blocked tubes among 259 tubes examined). The recorded sensitivity and specificity for the alternative diagnostic test (2D/3D-HyFoSy) were 87% and 94%, respectively, after excluding the inconclusive cases. Therefore, we considered a total sample size of 221 tubes to achieve 95% power with a significance level of 0.05 to detect blocked tubes, which was increased to 230 tubes to compensate for any possible dropouts.

The primary outcome was to assess the accuracy of HyLiFoSy-PD in the assessment of tubal patency, by comparing it with the reference standard of LDT, using the measures of diagnostic accuracy: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ration (LR), negative LR, and overall accuracy. The secondary outcomes included procedure duration, procedure-associated pain, and any other complications or side effects occurring during or after the procedure.

Following the reference technique described by Ludwin et al. in 2017 [24], HyLiFoSy-PD procedure was performed in the proliferative phase of the cycle (days 5–10). Clinical evaluation included history taking and a baseline two-dimensional (2D) TV-US examination was carried out just prior to starting the HyLiFoSy-PD procedure. HyLiFoSy-PD was performed using a 2D endovaginal probe of frequency 4–9 MHz (Samsung WS80A with Elite ultrasound system).

All our patients were subjected to antibiotic prophylaxis using oral azithromycin 500 mg per day for 3 days, which began the day before the procedure and continued for 1 day afterwards. This was done as we do not have screening programs for chlamydia trachomatis at our local health system [1]. Administration of non-steroidal anti-inflammatory drug (NSAID) rectal suppository was also carried out 1 h before the procedure (diclofenac sodium 100 mg) [1, 24].

For the procedure, the patient was asked to lie in a dorsal lithotomy position, the cervix was visualized using a Cusco speculum, cleaned with a cotton pad that is soaked with betadine 7% antiseptic solution, then a 5- or 6-Fr pediatric Foley's balloon catheter was introduced into the cervical canal with the help of a Bozeman forceps. 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 then removed from the vagina, and the TV-US probe was reintroduced in a longitudinal plane to confirm the correct placement of the catheter.

The foam contrast agent was created by mixing 3–4 ml of 2% lidocaine gel (Xylocaine Jelly 2%, AstraZeneca, Sweden) with 16–17 ml of saline. The assistant created the foam immediately before application by shaking the mixture (approximately 10–20 times) between two connected syringes. This was done until a whitish suspension was obtained.

Twenty milliliters of the lidocaine-made foam were slowly infused into the uterine cavity while observing the flow of the contrast media in each fallopian tube using greyscale and power Doppler (PD) 2D ultrasound. Foam flow over the whole length of the tube (Figs. 1 and 2), fimbrial outflow, or peritoneal spillage of contrast provided evidence of tubal patency. Contrast filling of the uterine cavity without cornual flow or cornual flow without fimbrial outflow or peritoneal spillage was interpreted as tubal occlusion.

The results, procedure duration, associated pain, and patients' demographic data were recorded in data collection sheets by an author who immediately filled them into an Excel sheet. HyLiFoSy-PD was performed by a single experienced sonographer (MA) who has more than 20 years of experience in ultrasound.

Patients were asked about the degree of discomfort or pain they felt during the procedure. Using the 4-point categorical verbal rating scale (VRS) [25], patients were asked if the procedure was not painful at all, bearable (mild pain), a bit painful (moderate pain), or severely painful. The procedure was to be canceled if a patient experiences severe pain. Patients were observed for 15–30 min after the procedure for any complication or increase in pain, then discharged. They were contacted again in the evening through a phone call to check for any complications. Procedure duration was calculated from the introduction of the Cusco speculum to its removal from the vagina.

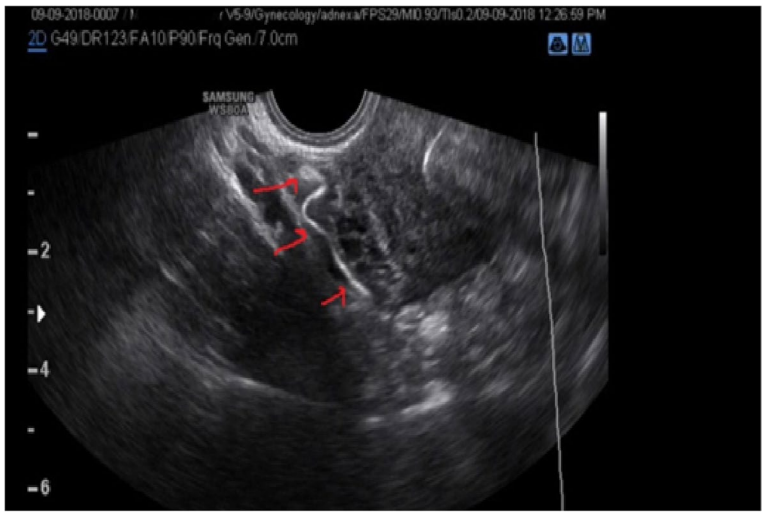

Fig. 1 Whole right tube is visualized until the fimbrial end with an evident distal spill of foam

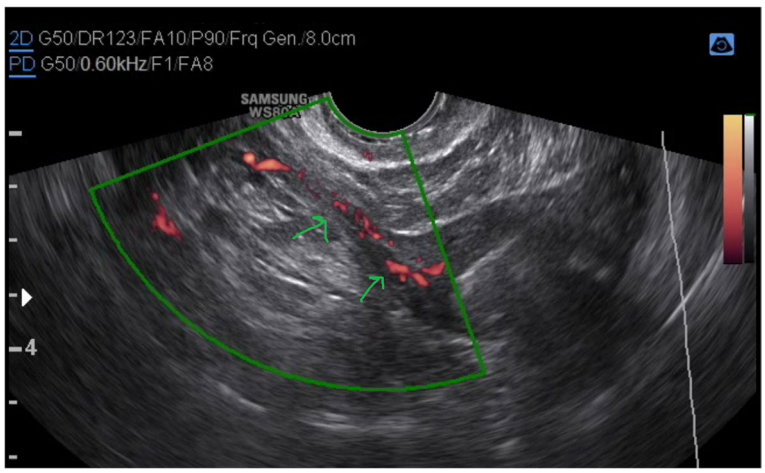

Fig. 2 Power Doppler showing the patent left fallopian tube with foam flow

One week following the HyLiFoSy-PD procedure, a standard LDT day-case procedure was carried out by experienced endoscopists at our university hospital gynecology department who were blinded to the results of HyLiFoSy-PD. During LDT, tubal patency was tested using methylene blue dye. Tubal evaluation during LDT was classified as patent or blocked. LDT results were recorded and saved into the Excel sheet as well.

Demographic data and relevant history were statistically described in terms of median, lower (Q1), and upper quartile (Q3) values, as some data were not normally distributed. Frequencies (number of cases) and percentages were used when appropriate. Accuracy was represented using the terms sensitivity, specificity, positive LR, negative LR, PPV, NPV, and overall accuracy. Testing the difference in the results of both tests was done using McNemar's test for non-parametric paired numerical data. *P*-values less than 0.05 were considered statistically significant. All statistical calculations were done using the computer program SPSS (Statistical Package for the Social Science, SPSS Inc., Chicago, IL) 16 software for Microsoft Windows.

Results

Overall, 115 patients completed the HyLiFoSy-PD procedure. Patients' demographic data, relevant history, and clinical findings are summarized in Table 1. The patient

Table 1 Demographic criteria, relevant history, and clinical findings of patients

Data (unit)			Median [lower quartile–upper quartile] or *N* (%)	
Age (years)			28 [23–30]	
BMI (kg/m^2)			30 [28–30]	
Gravidity			0 [0–1]	
Parity			0 [0–1]	
Infertility duration (years)			3 [2–4]	
Infertility type		Primary	*N* = 66 (57.4%)	
		Secondary	*N* = 49 (42.6%)	
Laparotomies	No	*N* = 81 (70.5%)		
	Yes	*N* = 34 (29.5%) Surgeries: 40	Cesarean section	*N* = 26
			Appendectomy	*N* = 8
			Myomectomy	*N* = 2
			Ovarian cystectomy	*N* = 4
Position of the uterus by ultrasound			Retroverted	*N* = 17 (15%)
			Anteverted	*N* = 98 (85%)
Duration of procedure (min)			11 [10–11]	
Total			*N* = 115	

N number, *%* percentage, *kg* kilogram, *m* meter

selection process is outlined in the STARD flowchart (http://www.stard-statement.org/) (Fig. 3).

Finally, the data of 115 patients with 230 tubes were used for assessing the diagnostic accuracy of HyLiFoSy-PD compared with LDT.

A comparison between the results of HyLiFoSy-PD and the results of LDT is illustrated in Table 2. In the assessment of tubal patency, with reference to LDT, HiLiFoSy-PD showed a sensitivity of 98.1%, specificity of 90%, PPV of 99%, NPV of 81.8%, positive LR of 9.81, negative LR of 0.02, and overall accuracy of 97.4. Our results were concordant with the final results of LDT in 109/115 (94.8%) patients and in 224/230 (97.4%) tubes. The McNemar test for the difference in accuracy between HyLiFoSy-PD and LDT gave a *P*-value of 0.687. The odds ratio (OR) was measured at 463.5, and the confidence interval (CI) was measured at 79.39–2706.

All patients experienced some degree of pain with 91 (79%) patients reported mild pain and 24 (21%) patients reported moderate pain. The median procedure duration was 11 [10–11] min.

Seven patients in our study experienced severe pain during the introduction of the speculum or the catheter, and the procedure was canceled. In three of them, the cervix was difficult to expose, being pulled-up due to a previous history of abdominal myomectomy. Two patients had retroverted uterus in addition to marked obesity with body mass index (BMI) of 35 and 40. The remaining two cases were markedly obese as well with a BMI of 34 and 35 and difficult access to the cervix. No other procedure-related side effects or complications such as vasovagal attacks, infection, allergic reactions, or venous intravasation were encountered in any patient during or following the procedure.

Discussion

The results of our study showed that HyLiFoSy-PD had high diagnostic accuracy for tubal patency assessment, with reference to LDT. The results reported by our study are comparable to those reported in a recent systematic review and meta-analysis that summarized the results of some HyFoSy studies. In this analysis, the included studies reported sensitivity between 89 and 100%, specificity (39–100%), PPV (47–100%), NPV (80–100%), positive LR 11.5 (95% CI, 1.5–87.5), negative LR 0.006 (95% CI, 0.0003–0.12), and overall accuracy (60–100%) [6].

The accuracy of HyFoSy, using ExEm gel foam, and its comparability to HSG and LDT in tubal patency assessment were reported before by multiple studies [3, 5, 6, 8, 9, 15–17, 19–22]. However, ExEm gel is not available in Egypt and other developing countries. It is also relatively expensive to lidocaine in countries where it is available. On the other hand, the high availability, low cost, and proven safety of lidocaine gel use intrauterine [26] inspired us to test the technique described by Ludwin et al. in 2017, which describes the use of lidocaine-made gel foam as a contrast medium for HyFoSy procedures [24]. The equipment needed for this procedure were very few, affordable, and easily

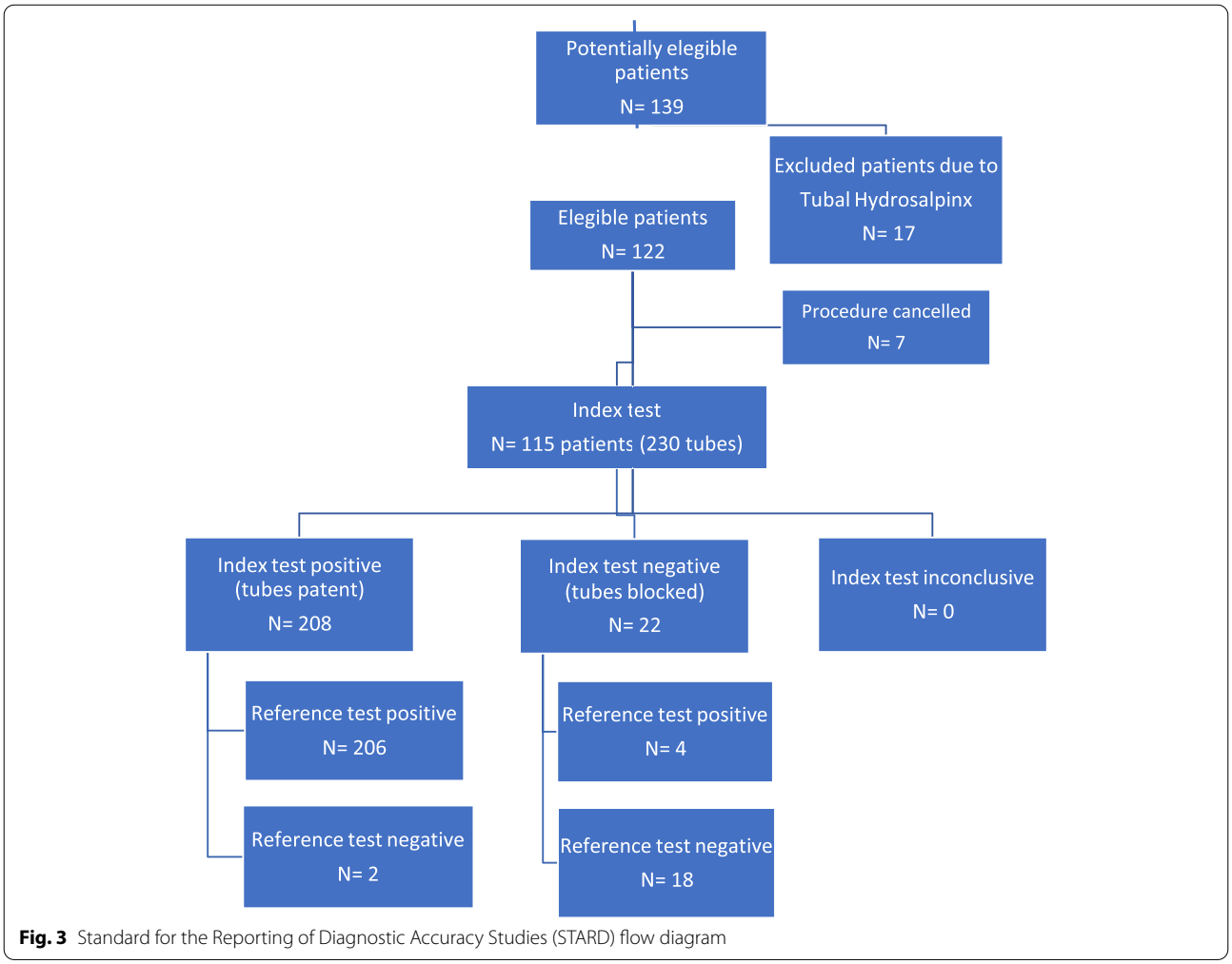

Fig. 3 Standard for the Reporting of Diagnostic Accuracy Studies (STARD) flow diagram

Table 2 Correlation between the results of HiLiFoSy with the results of LDT

Data		LDT		
		Patent	**Blocked**	**Total**
HyLiFoSy-PD	Patent	206	2	208
	Blocked	4	18	22
	Total	210	10	230

HyLiFoSy-PD hysterosalpingo-lidocaine-foam sonography combined with power Doppler, *LDT* laparoscopy with dye testing

available. These included 2 syringes, a pediatric Foley's catheter, saline, and xylocaine gel.

We did not add three-dimensional (3D) ultrasound to our examination as the assessment of tubal patency using 3D-HyLiFoSy-PD versus 2D-HyLiFoSy-PD by the same sonographer carries the risk of bias. However, we believe that standardized automated pelvic scanning and offline reconstruction of images using 3D-HiLiFoSy, if the facilities and experience are available, can help make the procedure quicker, less painful, more reproducible, and less operator-dependent [1, 5, 8, 16, 20, 27].

Doppler imaging can increase the diagnostic accuracy of HyFoSy [16], it also facilitates the identification of tubal occlusion [24]. In our experience, PD was found to be helpful in the confirmation of the direction of foam flow as well as the acceleration during the injection. However, we believe that greyscale 2D-HyFoSy, alone, can be of good accuracy as well if performed by an experienced sonographer [1, 8].

A possible limitation to our study was using VRS for pain assessment instead of the more accurate visual analog scale (VAS) and numeric rating scale (NRS) [25]. However, we believe that VRS was practical, easier to understand, and more convenient to use with our patients than VAS or NRS. Moreover, we assessed pain in our study at one point of time, while VAS and NRS are more powerful in the detection of change in pain [25]. This may not be the case in developed countries, where

the facilities (paper, pen, assistant) and patients' literacy help make VAS and NRS more applicable to use for pain assessment.

Using VRS, 91 (79%) patients in our study reported mild pain, 24 (21%) reported moderate pain, and seven patients experienced severe pain, which correspond to scores 1–3, 4–6, and 7–10 of the VAS and NRS, respectively [25]. This lies in line with the pain score results reported by HyFoSy studies that used VAS and NRS to assess pain [10, 16, 21, 28–30]. This suggests that HyLiFoSy-PD is a well-tolerated procedure, like HyFoSy, that can be carried out without pre-procedural analgesia [1, 5, 6].

The pre-procedural use of NSAIDs, intrauterine infusion of local anesthetic (lidocaine), procedure duration (11 min), and 2 ml filling of balloon catheter were sources of potential bias and might have affected the pain results in our study. However, the use of pre- procedural analgesia was described in multiple HyFoSy studies, with some of them also assessed (pain) as an outcome [1, 10, 15, 16, 24]. Furthermore, in spite of the intrauterine use of lidocaine, all patients experienced some degree of pain. This confirms the findings of most previous studies done on the pre-procedural use of lidocaine, which reported that it was not effective in reducing pain [1, 18, 23].

Since the procedure duration was only reported in two previous HyFoSy studies done by the same author with medians of 5 and 5.5 min, we are not sure that a longer procedure duration (median: 11 min) in our study could have raised the pain scores, as the author did not note how the procedure duration was calculated [21, 30]. The definition and calculation of the procedure duration may be considered in future HyFoSy studies to enable comparability.

In attempts to reduce pain, balloon-less intrauterine catheters were used in multiple HyFoSy studies using ExEm gel foam [5, 8, 9, 18–21, 30], while other studies used balloon catheters and inflated them with 0.5–1.5 ml of saline [10, 15, 16, 24, 28, 29]. However, an earlier study found no difference in pain scores between different size balloon catheters and balloon-less others [31]. Therefore, we rule out the possibility that our 2-ml saline filling of the balloon catheter could have raised the pain scores.

In our study, seven patients experienced severe pain, and the procedure was canceled. Marked obesity was a criterion in four of them (BMI: 40, 35, 35, 34), retroverted uterus in two, and pulled-up cervix with a history of myomectomy in three. In our experience, difficult access to the cervix was associated with severe pain. This was related to obesity, retroverted uterus, and adhesions due to previous surgeries. On the other hand, it was reassuring to find that no other side effects or complications were encountered in any of the patients during and after the procedure. Also, the echogenicity resulting from lidocaine-made gel foam was visible on ultrasound for the whole HyLiFoSy-PD procedure, with an estimated average of 11 min in all patients.

Another potential source of bias in our study was the sample consisting of unselected infertile patients with a low prevalence of tubal occlusion. However, this was suitable for estimating the diagnostic accuracy of a HyLiFoSy-PD as a screening tool for tubal patency. Finally, doing HyLiFoSy-PD before LDT might have affected LDT results, as proximal tubal ostium spasm [1, 5] or tubal unlocking might had happened during HyLiFoSy-PD. For this, we carried out HyLiFoSy-PD 1 week before the scheduled LDT. Also, successive tubal testing with the index and reference tests was done in other HyFoSy studies [1, 6, 15, 16, 20]. Finally, tubal spasm and false tubal occlusion results can occur with LDT alone as well [1, 5, 16].

To the best of our knowledge, this is the first study to investigate the diagnostic accuracy of HiLiFoSy-PD in tubal patency assessment. Blinding of sonographers, endoscopists, and statisticians was a point of strength to our study. Given the high sensitivity (98.1%) of HyLiFoSy-PD measured in our study, we suggest that it can be a good screening tool for tubal patency that can be carried out as an office procedure using conventional 2D TV-US system, minimal equipment, and some ultrasound training on the technique. Negative results (occluded tubes), however, may warrant further tubal testing with LDT or other tubal tests, especially in the absence of risk factors or a history highly suspicious of tubal occlusion [2].

In conclusion, HyLiFoSy-PD using lidocaine-made gel foam was found to be an accurate, safe, and feasible tool for tubal patency assessment. It can be carried out as an office procedure by an experienced sonographer using a 2D TV-US system. Our opinion is that it can be a possible substitute for HyFoSy that uses ExEm gel foam whenever the gel is not available or is relatively expensive compared to lidocaine. Further research should be carried out to validate our results.

Abbreviations

LDT: Laparoscopy and dye testing; HyLiFoSy-PD: Hysterosalpingo-lidocaine-foam sonography with power Doppler; NICE: National Institute for Health and Clinical Excellence; HSG: Hysterosalpingogram; HyLiFoSy-PD: Hysterosalpingo-lidocaine-foam sonography combined with power Doppler; ARTs: Artificial reproductive techniques; TV-US: Transvaginal ultrasound; STARD: Standard for the Reporting of Diagnostic Accuracy Studies; PPV: Positive predictive value; NPV: Negative predictive value; LR: Positive likelihood ration; NSAID: Non-steroidal anti-inflammatory drug; PD: Power Doppler; VRS: Verbal rating scale; CI: Confidence interval; BMI: Body mass index; VAS: Visual analog scale; NRS: Numeric rating scale.

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Authors' contributions
Conception and design of the study: MFS and OI. Data collection: IF. Data analysis and interpretation: ITE and MA. Sonographer: MA. Statistical analysis: ITE. Manuscript preparation: ITE and YE. Recruitment of patients: IF. The authors read and approved the final manuscript.

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
Ethical approval is attached as a supplementary material document. Ethical approval was provided by the Institutional Review Board (code: 18009) in January 2018. All patients provided informed written consents to participate in this diagnostic accuracy study.

Consent for publication
All patients provided informed written consents that the study results will be published.

Competing interests
The authors declare that they have no competing interests.

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