Cairo University

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Title **:**

Comparison of the diagnostic accuracy of Hysterosalpingo-lidocaine-foam sonography versus hysterosalpingography in tubal patency assessment to the gold standard of laparoscopy and dye testing

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Faculty of Medicine, Cairo University Postgraduate Research Program Template

1- Study

Title **:**
Comparison of the diagnostic accuracy of Hysterosalpingo-lidocaine-foam sonography versus hysterosalpingography in tubal patency assessment to the gold standard of laparoscopy and dye testing

Degree**:**
Date of registration: May 2022

2. Investigators :

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3. Investigators:

4. Background:

Tubal disease accounts for 30-40% of female factors of infertility.(1) Therefore, tubal testing is an essential part of female infertility work-up.(2,3) Since falsely occluded tubes may lead to unnecessary interventions and falsely patent tubes may lead to unsuccessful in-vitro fertilization embryo transfer (IVF-ET) trials,(5,6) an accurate tubal test is an essential.

laparoscopy with dye testing (LDT), i.e., laparoscopic chromopertubation, is the gold standard tubal patency test.(1,6,7) It is the recommended tubal test 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 tubal disease as it allows for direct visualization, diagnosis, and treatment of tubal and other pelvic pathologies.(3,8) However,

LDT is an invasive procedure requiring general anesthesia that can be associated with bleeding and visceral injury.(1,6,7,9)

Hysterosalpingogram (HSG) has been reported to have sensitivity of 53% and specificity of 87% in the diagnosis of tubal block.(4) It has been the most commonly used initial tubal patency test as it offers a less-invasive and less-expensive alternative to LDT.(6) However, HSG is associated with radiation exposure, pain, and allergy. It cannot diagnose myometrial or ovarian pathologies as well.(1,6,7,9)

Hysterosalpingo-contrast sonography (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.(1,6,9,10-12) HyCoSy is the recommended tubal test by NICE for women not known to have tubal disease, as an alternative to HSG, whenever appropriate expertise is available.(3) Air and saline use as contrast medium with HyCoSy made the procedure highly operator dependent.(1,6,13-16) Hyperechogenic and longer-lasting echogenic media then followed but are currently commercially unavailable or not approved for tubal testing.(1,6,14–19)

In 2007, ExEm gel (GynaecologIQ, Delft, Netherlands) was introduced(20) and registered as European Confirmatory (CE) approved drug for tubal testing.(15) Hysterosalpingo-foam sonography (HyFoSy), using diluted ExEm gel foam, has been established as a safe, feasible, tolerable, and accurate alternative to HyCoSy and HSG that has been widely used in infertility clinics.(1,6,7,9,10,14,18,19,21–26)

In 2017, hysterosalpingo-lidocaine-foam sonography combined with power doppler (HyLiFoSy-PD) was introduced as a cost effective and less painful possible alternative to HyFoSy that can be used whenever the contrast media is unavailable. “Flaming tube” sign, detected using power doppler (PD), was also described as to allow easier recognition of tubal patency.(27) Our study aims to compare the diagnostic accuracy of HyLiFoSy-PD with the most commonly used tubal test; HSG, with reference to the gold standard tubal test; laparoscopy and dye testing.

5. Objective:

The aim of this study is to evaluate the difference between the diagnostic accuracy of Hysterosalpingo-lidocaine-foam sonography and hysterosalpingography, with reference to the gold standard tubal test; laparoscopy with dye testing.

6. Study Design:

This will be a cross-sectional study

7. **Scientific committee approval:**

8. **Study methodology:**

Population of study, disease condition and setting:

Women in the reproductive age group between 18- and 40-years old presenting with primary or secondary infertility who underwent HSG in the previous 5 years as a part of their infertility work-up with availability of good-quality HSG images, & did not get pregnant in this period, and gave no history of incidences that might affect their tubes, such as : abdominal surgery or laparoscopy, pelvic inflammatory disease, smoking, and intrauterine device insertion.

Women fitting these inclusion criteria and scheduled for LDT as part of their infertility work up will be considered. HyLiFoSy-PD will be carried out few days before the already scheduled LDT.

The study will be conducted in the Cairo fetal medicine unit, department of Obstetrics and gynecology, Cairo university.

Inclusion criteria:

1. Age group (18-40)
2. Informed signed Written consent.
3. Scheduled for LDT as a part of their infertility management

4. Have undergone HSG in the previous 5 years with the availability of good-quality HSG images.
5. No incident factors that might have affected the tubal status after she underwent HSG within the previous 5 years, such as ; abdominal surgery or laparoscopy, pelvic inflammatory disease, smoking, and intrauterine device insertion.

Exclusion criteria:
Women with any of these factors will be excluded:

1. LDT scheduled for a therapeutic purpose due to a known tubal or ovarian pathology
2. Lack of good-quality HSG images.
3. Withdrawal of consent.
4. Using contraception
5. Women outside reproductive age
6. Known allergy to lidocaine
7. Active pelvic inflammatory disease
8. Undiagnosed genital tract bleeding.
9. Evident tubal pathology (such as hydrosalpinx) or pregnancy diagnosed by transvaginal ultrasound (TV-US) prior to performing HyLiFoSy-PD

Methodology in details

Interpretation of HSG results:

Review of the HSG films will be done for assessment of the tubal patency; tubes will be considered patent if the dye is seen throughout their whole length and till their ends with a positive immediate spill or a spill in the delayed film. If the dye does not pass through one or both cornual ends, or if a part of the tube is seen filled with dye but not the whole length then tubal obstruction will be considered. Patients with hydrosalpinx seen by HSG are to be assessed first by US if no visible hydrosalpinx is seen by US and she has no signs of PID then she can proceed to the HyLiFoSy-PD procedure.

Hysterosalpingo-lidocaine-foam sonography procedure:

1. HyLiFoSy-PD procedure will be performed in proliferative phase of the cycle (Days 5 – 12).
2. Clinical evaluation including history taking and a baseline two-dimensional (2D) TV-US examination will be carried out prior to starting the HyLiFoSy-PD procedure.
3. TV-US will be performed using a probe of frequency 4-9 MHz (Voluson E10 ® GE Healthcare).
4. Administration of a non-Steroidal anti-inflammatory drug (NSAID) rectal suppository will be carried out one hour before the procedure (diclofenac sodium 100 mg), in addition to antibiotic prophylaxis using

oral azithromycin for 3 days, starting the day before the procedure and continued for one day afterwards

5. In the dorsal lithotomy position, the cervix will be visualized with a Cusco speculum, cleaned with an antiseptic, then a 5- or 6- Fr pediatric Foley's balloon catheter will be introduced into the cervical canal with the help of a Bozeman forceps and a tenaculum if necessary.
6. The balloon will be positioned in the lower uterine cavity and inflated with 2 ml of saline to prevent backflow of contrast medium through the cervix, then the speculum will be removed. The TV-US probe will be reintroduced in a longitudinal plane to confirm correct placement of the catheter.
7. The foam contrast agent will be created by mixing 3–4mL of 2% lidocaine gel (Xylocaine Jelly 2%, Atrazeneca, Sweden) with 16–17mL of saline. The assistant will create the foam immediately before application by shaking the mixture (approximately 10–20 times) between two connected syringes. This will be done until a whitish suspension is obtained.
8. Repeated small doses (3-5 ml) of the lidocaine-made foam will be infused slowly into the uterine cavity while observing the flow of the contrast medium in each fallopian tube.
9. Using greyscale US, flow over the whole length of the tube, fimbrial outflow, or peritoneal spillage of contrast will provide definite evidence

of tubal patency. Contrast filling of the uterine cavity without cornual flow will suggest tubal occlusion.

10. PD will then be added to re-assess tubal patency and assess the "flaming tube" sign. Flaming sign interpretation will be classified as: strong, weak, or absent.
11. Images will be stored as 2D and PD still images and video clips. HyLiFoSy-PD will be performed by experienced sonographers at our unit, who will be blinded to the results of LDT.
12. Patients will be asked about the degree of discomfort or pain they felt during and immediately after the procedure. Using categorical verbal rating scale (VRS),(28) Procedure will be stopped if a patient experiences severe pain.
13. Patients will be followed up overnight and monitored for any other procedure-related side effects or complications.
14. Within a week following the HyLiFoSy-PD procedure, standard LDT will be carried out by experienced endoscopists who will be blinded to the results of HyLiFoSy-PD. During LDT, tubal patency will be tested using methylene blue dye. Tubal evaluation during LDT will be classified as: patent with immediate spill, patent with delayed spill, or blocked.

Possible Risk (mention if there is any risk or not)

Side effects such as vasovagal reactions, allergic reaction, and venous intravasation have been reported in literature in hysterosalpingo-foam studies. However, in our previous hysterosalpingo-lidocaine-foam sonography study, none of these side effects were encountered. For the possible risk of infection, all patients will be given prophylactic antibiotics. In addition, any case with visible hydrosalpinx or signs or symptoms of PID on US prior to performing HyLiFoSy-PD will not perform the procedure.

9. Study outcomes:

Primary outcomes

1. Diagnostic accuracy of HyLiFoSy and HSG with reference to LDT, in terms of sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy.

Secondary outcome parameters

1 -Diagnostic accuracy of adding power doppler to the HyLiFoSy.

2-Evaluate the procedure associated pain

3-Evaluate the procedure duration

4-Percentage of failed or inconclusive attempts and possible reasons for that

5-Incidence and rate of potential complications for example: vasovagal and allergic reactions, venous intravasation.

10. Sample size:

Using the following equation:(29)

$$N_{\text{Disease}} = \frac{\left\{z_{1-\alpha/2}\Lambda + z_{1-\beta}\sqrt{\Lambda^2 - \zeta^2(3+\Lambda)/4}\right\}^2}{\Lambda\zeta^2},$$

where $\Lambda = (1 - Se_1)Se_2 + (1 - Se_2)Se_1$ and $\zeta = (1 - Se_1)Se_2 - (1 - Se_2)Se_1$.

With power of the study 90%, CI 95%, average sensitivity of HSG is 0.55,(4) and sensitivity of HyLiFoSy-PD is 90%,(30), prevalence of tubal pathology is 30%,(1); 100 patients are required to fulfill the sample size. To compensate for any possible dropouts (5%), 5 more patients will be recruited. So, the total sample size will be 105.

11. Statistical analysis:

After recording and collecting the data, statistical analysis will be performed using the Statistical Package for the Social Sciences (SPSS, version 16.0, SPSS Inc, Chicago, Illinois, USA). Data will be statistically described in terms of mean and standard deviation if they were of normal distribution, and in terms of median and range if they were not normally distributed. Frequencies (number of cases) and percentages will be used when appropriate. Accuracy will be represented using the terms sensitivity, specificity, PPV, NPV, and overall accuracy. Testing the difference in the results of tests was done using

one-way analysis of variance (ANOVA) test. P-values less than 0.05 will be considered statistically significant.

12. Source of funding:

Self-funding

13. Time plan

From 1/6/2022 – 1/6/2024 (2 years)

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