Study protocol

Project title: **Hysteroscopic evaluation of Fallopian tubal patency compared to laparoscopic chromopertubation: a prospective, randomized study on the "flow" and "Parryscope" techniques**

Brief title: **Hysteroscopic evaluation of Fallopian tubal patency**

Participants:

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Introduction and scientific background:

Hysteroscopy is an important tool in the evaluation of sterility. [1-5] It allows direct visualization of the uterine cavity and enables the diagnosis of numerous pathologies, including endometrial polyps, intracavitary myomas and also more rare diseases associated with sterility and infertility, such as Asherman-syndrome and anomalies of the uterus itself. Hysteroscopy shows high reliability and is considered the gold standard for intrauterine evaluation [1-6].

When performing hysteroscopy, experts often assess the patency of the tubes via the visibility of flow of the hysteroscopic fluid going through the ostia of the tubes. In the recently published study "Assessment of tubal patency: A prospective comparison of diagnostic hysteroscopy and laparoscopic chromopertubation" it was demonstrated that visualizing contrasting substances disperse through the ostia is a significant and meaningful metric for tubal patency (sensitivity 85.2, 95% CI: 76.1-91.9; specificity: 66.1, 95% CI: 52.2-78.2). This confirmed the value of this approach, consistent with our previous retrospective study on the same topic [7]. Nevertheless, it is important to mention that the prospective study showed both a lower specificity (66.1% vs. 77.6%) and a lower positive predictive value (79.8% vs. 91.3%).

Pre- and posthysteroscopic vaginal sonography for the evaluation of the hysteroscopic fluid in the pouch of Douglas [9,10], selective hysteroscopic pertubation of the tubes [11] and the visibility of air bubbles traversing through the Fallopian tube ostia after an air infusion into the uterine cavity [10,12] have been reported to be reliable methods for hysteroscopic tubal patency assessment. Particularly the last one, also called the "Parryscope technique", named after its inventor, seems to be highly reliable, easy to conduct and clinically relevant [8,10,12]. The "Parryscope technique" reaches a sensitivity of min. 98.3% and a specificity of 83.7% [9] and, thus, seems to perform even better than the technique evaluating the "tubal flow".

Assessing tubal patency during hysteroscopy is highly relevant, particularly when it allows for a low cost, fast, gentle, and accurate way of gathering information that may guide clinical care. Therefore, it is important to know which of the above-mentioned techniques is the best. This prospective randomized study aims to compare the hysteroscopic assessment of the tubes via "tubal flow" [7] and the "Parryscope technique" [10,12]. At our department, the Clinical Division of Gynecological Endocrinology and Reproductive Medicine of the Medical University of Vienna, a diagnostic hysteroscopy is usually performed directly before every infertility-related laparoscopy. These operations are always performed by an expert in the field of reproductive surgery, which should guarantee a good clinical quality of our data set.

Study aims:

The primary aim of this study is to evaluate the relalibilty of (1.) the hysteroscopic visualization of a "tubal flow" and (2.) the "Parryscope technique" as compared to the gold standard, namely laparoscopic chromopertubation.

Study hypothesis:

Null hypothesis: The hysteroscopically visualizable „tubal flow" and the „Parryscope technique" are similarly reliable in the evaluation of tubal patency.

Alternative hypothesis: The hysteroscopically visualizable „tubal flow" shows a lower sensitivity and specificity than the „Parryscope technique" for the evaluation of tubal patency.

Study design:
Prospective, randomized study.

Participants:
Inclusion criteria:

- The patient is subfertile, defined as being unable to become pregnant within a year despite unprotected sexual intercourse. It is also within the standard of care to be presumed subfertile if one has tried for six months and has known risk factors that would hinder conception, including but not limited to anovulation and endometriosis.
- A concurrent diagnostic hysteroscopy and laparoscopy with chromopertubation are performed at the Clinical Division of Gynecological Endocrinology and Reproductive Medicine at the Medical University of Vienna.
- The patient has given her written informed consent after detailed information on the study by medical professionals at the Department of Obstetrics and Gynecology of the Medical University of Vienna.
- The patient is ≥18 and ≤45 years old.

Exclusion criteria:

- The patient had a tubectomy on one or both sides.
- There is no "informed consent".
- The patients has active vaginal infection or other conditions that would preclude hysteroscopy.

Primary Outcome Parameters:
Hysteroscopic evaluation of tubal patency (either by a positive "tubal flow" or a visible flow of air bubbles in the "Parryscope technique") and the result of the laparoscopic chromopertubation (tubal patency existing or not existing).

Secondary Outcome Parameters:
For the descriptive analysis, several hysteroscopically visualizable additional parameters will be evaluated: (i) existence of any hysteroscopic abnormalities (including endometrial polyps, myomas, adhesions, anomalies or cervical stenosis). (ii) characteristics of the tubal "flow" – clearly visualizable or questionable, visualization of air bubbles and/or floating structures in the cavity. (iii) clarity of the hysteroscopic view (clear versus hazy).

Recruitment:

Women will be invited to participate by medical professionals at the Department of Obstetrics and Gynecology of the Medical University of Vienna using the above-mentioned criteria in the course of their admission to the ward one day before surgery. Potential participants are informed about the procedure, clinical relevance and the balance of risk and benefits incurred through study participation. Patients willing to participate will express this through written affirmation (a "consent form").

Parameters obtained:

The following parameters will be collected and included in the database. They do not require additional effort on behalf of the patients. All data will be obtained using the study-specific case report form and will be entered into a SPSS database in a semi-anonymized manner.

- Patient's age
- Body mass index
- Primary/secondary subfertility
- Obstetrical history (gravidity, parity)
- History of risk factors relating to tubal disease (chlamydia infection, endometriosis, etc.)
- Detailed information about the indication for surgery
- *Main outcome parameter 1*: Hysteroscopic findings: tubal patency assumed or not assumed in right/left tubal ostium (information provided separately for each side)
- *Additional findings*: any hysteroscopic abnormalities (including endometrium polyps, myomas, adhesions, anomalies or cervical stenosis). In the "tubal flow" group an additional finding would also be the presence of air bubbles. Moreover, the clarity of the hysteroscopic view will be evaluated (clear versus hazy).
- Duration of the hysteroscopic evaluation of tubal patency (in minutes).
- Additional interventions: Curettage and operative hysteroscopy.
- Uterine length.
- *Main outcome parameter 2*: Laparoscopic findings: tubal patency as assessed by chromopertubation (information provided separately for each side)
- Amount of blue dye used in chromopertubation
- Performance of any additional laparoscopic interventions during the operation
- A subjective assessment of pressure used in demonstrating patency with chromopertubation (low vs high, which affects accuracy and prognosis)

The additional data acquisition will be conducted to give an exact characterization of the patient population to allow a comparison with the published literature.

Techniques of hysteroscopic evaluation of tubal patency:

"Tubal flow"-group: a positive "flow" is defined as the observation of saline directly traversing the ostia, endometrial structures floating toward the ostia, or air bubbles traversing the ostia.

"Parryscope"-group: A small amount of air is introduced into the iv tubing by inverting the drip chamber to create air bubbles. When air enters the uterine cavity, a single large air bubble or stream of air bubbles traversing the ostia is considered indicative of tubal patency. At least 10 seconds of intracavitary evaluation is typically performed before air bubble entry to allow pressure equilibration if a hydrosalpinx is present [10]. At least 30 seconds of observation per ostia is performed if patency is not observed.

Additional considerations:

1. Since in the "flow"-group air bubbles might develop spontaneously and, thus, should be assessed, conducting the "Parryscope"-technique is only possible after the evaluation of the tubal flow.
2. Reactive tubal spasms could occur especially during a prolonged hysteroscopy.
3. This is why in one particular patient only one technique should be performed.

Sample size calculation:

The calculation is based upon the following considerations:

1. Direct comparison of the two groups is not possible. Hence, separate evaluation of the two methods will be performed. Evaluating both methods in one particular patient in the course of a single intervention is impossible without a mutual interference (see: "Additional considerations" above).
2. The "flow effect" is considered the less reliable method and thus, the sample size was aligned to this method. An odds ratio of approximately 10, an alpha of 5%, a power of 80%, a general disease likelihood of 39% and a sensitivity of 66% for occluded tubes result in a total amount of 59 tubes and, accordingly, 30 patients.
3. Thus, the group for the "Parryscope"-technique should also contain 59 tubes (= 30 patients).
4. The randomization of the total 60 patients is performed as block randomization in 4 blocks via the software "R".

Statistical analysis:

Numerical data (age, body mass index) will be reported as mean and standard deviations, nominal variables (primary/secondary sterility, indication for the reproductive medical intervention, visibility of the "flow" in the left and right tubal ostium, pathologies in the uterine cavity in the hysteroscopy, patency of the tubes via chromopertubation, information about further laparoscopic interventions during the operation) as number and frequency. The McNemar Test will be used for the calculation of the reliability of the hysteroscopic assessment of the tubes. The sensitivity, specificity, positive and negative predictive values will be provided including the according 95% confidence intervals (95% CI) for both study groups (evaluated technique versus gold standard laparoscopic chromopertubation). The according odds ratio is over 10 will be evaluated by the use of a binary logistic regression model. Statistical analyses were performed with the software "R". Differences were considered significant if $p<0.05$.

Data quality evaluation:

Extreme values will be double-checked. In addition, random checks by two independent investigators will be conducted to ensure the accuracy of our data.

Risk-benefit-analysis:

In this prospective study, no further data acquisitions, follow-up examinations or surveys will be necessary. Except from the above-mentioned additional findings during the interventions, the only additional data to be collected would already be inherently obtained as part of procreative evaluation. Accordingly, if patients would be undergoing the described interventions (hysteroscopy, laparoscopy) independent of their choice to participate, this should not shift cost or risk for them. Additionally, since the study evaluations are minimal risk (visual observation of natural intracavitary flow patterns and deliberate addition of 0.5 mL of air in to saline during hysteroscopy (where greater amounts routinely enter the uterus accidentally through how lines are primed), safety should remain high. The analysis and publication of the data will be done with patient deidentification.

Agreement on the access of the principle investigator:

The principle investigator will have access to all study documents and statistics at all times.

References:

1. CHOLKERI-SINGH, A. & SASAKI, K. J. 2015. Hysteroscopy for infertile women: a review. J Minim Invasive Gynecol, 22, 353-62.

2. GODINJAK, Z. & IDRIZBEGOVIC, E. 2008. Should diagnostic hysteroscopy be a routine procedure during diagnostic laparoscopy in infertile women? Bosn J Basic Med Sci, 8, 44-7.

3. INDRACCOLO, U., GRECO, P., SCUTIERO, G., MARROCCHELLA, S., SORRENTINO, F., MASTRICCI, L. & MATTEO, M. 2014. The role of hysteroscopy in the diagnostic work-up of infertile asymptomatic patients. Clin Exp Obstet Gynecol, 41, 124-7.

4. NEERJA & JAIN, K. 2014. Role of laparoscopy-hysteroscopy in cases of infertility with pregnancy outcome. J Indian Med Assoc, 112, 85-6, 88.

5. ZHANG, E., ZHANG, Y., FANG, L., LI, Q. & GU, J. 2014. Combined hysterolaparoscopy for the diagnosis of female infertility: a retrospective study of 132 patients in china. Mater Sociomed, 26, 156-7.

6. PARRY, J.P., Isaacson, K.B. 2019 Hysteroscopy and why macroscopic uterine factors matter for fertility. Fertil Steril 112, 203-210.

7. PROMBERGER R., SIMEK I.M., NOURI K., OBERMAIER K., KURZ C., OTT J 2018. Accuracy of tubal patency assessment in diagnostic hysteroscopy compared to laparoscopy in infertile women: a retrospective cohort study. J Minim Invasive Gynecol 25, 794-799.

8. HAGER M., SIMEK. I.M., PROMBERGER R., OTT J. The role of diagnostic hysteroscopy in the evaluation of Fallopian tube patency: a short review. Geburtshilfe und Frauenheilkunde, zur Publikation angenommen, Dez 2018

9. HABIBAJ J, KOSOVA H, BILALI S, et al. Comparison between transvaginal sonography after diagnostic hysteroscopy and laparoscopic chromopertubation for the assessment of tubal patency in infertile women. J Clin Ultrasound 2012; 40: 68 – 73

10. PARRY JP, RICHE D, ALDRED J, et al. Proximal tubal patency demonstrated through air infusion during flexible office hysteroscopy is predictive of whole tubal patency. J Minim Invasive Gynecol 2017; 24: 646 - 652

11. TOROK P., MAJOR T. Accuracy of assessment of tubal patency with selective pertubation at office hysteroscopy compared with laparoscopy in infertile women. J Minim Invasive Gynecol 2012, 19, 627-30.

12. PARRY JP, RICHE D, RUSHING J, et al. Performing the Parryscope technique gently for office tubal patency assessment. Fertil Steril 2017; 108: 718

13. HAJIAN-TILAKI K. Sample size estimation in diagnostic test studies of biomedical informatics. J Biomed Inform. 2014;48:193-204.