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Transvaginal hydrolaparoscopy in the diagnosis of tubal pathology

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TRANSVAGINAL HYDROLAPAROSCOPY in the diagnosis of tubal pathology

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TRANSVAGINAL HYDROLAPAROSCOPY in the diagnosis of tubal pathology

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ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
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Content

Chapter 1

Introduction

General introduction

Subfertility

Every 6 out of 1000 women per year visit their general practitioner because of subfertility [1]. Subfertility is defined as the failure to achieve a successful pregnancy after 12 months or more of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with her/his partner [2]. Of these women, 10-30% are diagnosed with tubal infertility [3,4,5,6]. This is the result of damage and infection to the Fallopian tubes and is also known as tubal pathology or tubal abnormality. Tubal pathology can range from mild damage, for example filmy adhesions around the fimbria, to extensive damage as complete tubal blockage. Another entity of tubal infertility is hydrosalpinx, a condition in which fluid has accumulated in the Fallopian tube due to blockage at the distal end of this tube [7]. Infections, often sexually transmitted, and sometimes leading to pelvic inflammatory disease (PID) are one of the main causes for tubal pathology, with Chlamydia trachomatis and Neisseria gonorrhoeae being the most renowned [8]. Another cause for tubal infertility is endometriosis. This is a condition in which the endometrium (inner lining of the uterine cavity) grows outside the uterus [7,9]. Endometriosis causes fibrosis and adhesions, which can distort normal anatomy and its function. For example, fibrosis and adhesions are seen in endometriotic cysts with adherent Fallopian tubes. Previous abdominal surgery like tubotomy for ectopic pregnancy and abdominal or peritoneal infections, like perforated appendicitis, are known reasons for tubal infertility as well [7].

Subfertility workup

Guidelines have been developed focusing on the best care for couples with subfertility according to current standards [10,11,12]. These guidelines focus on diagnosis of the subfertility, prognosis for conceiving naturally as well as prepregnancy care to reduce health risks for both woman and her (unborn) child. Most Western guidelines start with a detailed history of the woman and her partner. For female subfertility at least details have to be known about the duration of the subfertility, menstrual history, previous pregnancies, sexual history, gynaecologic history including PID and sexually transmitted diseases (STD's), family history, intoxications, medication use, previous surgeries and (serious) illnesses. In the scoop of this thesis, especially women reporting a history of PID, complicated appendicitis, pelvic surgery, ectopic pregnancy and endometriosis are at increased risk of having tubal pathology [13].

The next step in the workup is physical examination, determining BMI and looking for visible and/or palpable abnormalities of external and internal genitals. Then transabdominal or preferably transvaginal ultrasound is carried out to investigate the pelvis for, uterine, ovarian or tubal abnormalities. Furthermore, ovulation detection and semen analysis is carried out. Which additional workup is offered, depends highly on the medical history and the abnormalities found during the physical examination and ultrasound as well as it depends per guideline and so per country [10,11,12].

Regarding tubal assessment, the Dutch guideline [11] and the NICE guideline [12] recommend to treat women with a high risk of tubal pathology in a different way than women with a low risk. Women with high risk of tubal pathology are those with a previous PID, ectopic pregnancy and/or endometriosis [12], a positive chlamydia antibody titer (CAT) and/or pelvic surgery [11]. The NICE

guideline offers women with high risk of tubal pathology a laparoscopy with dye to test tubal function and look for other pelvic abnormalities. Women with low risk of tubal abnormalities can be offered to undergo hysterosalpingography (HSG) or hysterosalpingo-contrast-ultrasonography (sono-HSG) when the appropriate expertise is available. The Dutch guideline, however, says to offer HSG only to women with high risk of tubal pathology and offer laparoscopy only directly to those who have a history of complicated abdominal surgeries, intra-abdominal infections or endometriosis or when clinical signs of severe endometriosis or hydrosalpinx are visible during ultrasound examination. The guideline of the ACOG [10] recommends to use an imaging modality for detection of tubal patency and/or pelvic abnormalities. Imaging modalities for tubal patency mentioned in this guideline are HSG and sono-HSG. Furthermore, this guideline remarks that at least evidence of tubal patency next to normal ovulation and a normal semen analysis should be present when the conclusion unexplained subfertility is drawn.

Although these guidelines differ in whom, when and which tubal patency test is performed, tubal patency tests are mentioned in all.

Tubal patency tests

Several tubal patency tests are developed on the way. Next to detecting tubal patency, most tests can detect other fertility declining pathology, including uterine pathology like polyps, myoma's or adenomyosis, ovarian pathology like cysts or endometrioma's and pelvic pathology like adhesions or endometrioses. It depends on the test characteristics of each tubal patency test what other pathology it can detect.

The first known tubal patency is hysterosalpingography (HSG), developed for evaluation of the uterine cavity in 1910 [14]. It is used since 1914 for tubal patency testing [15]. Nowadays, it is still the most commonly used tubal patency test in the Netherlands [16]. During injection of a radiopaque medium through the cervical canal into the uterus and subsequently the tubes, serial X-rays or fluoroscopy is performed to evaluate the shape of the uterine cavity and the patency of the Fallopian tubes. Next to the advantage of evaluating both uterine cavity and tubal patency directly, HSG has potential therapeutic effect when an oil-soluble contrast medium is used with a higher chance of clinical pregnancy and live birth [17]. Possible disadvantages are the need of a radiology department, the chance of an allergy to iodine-containing contrast media and the concerns for thyroid dysfunction due to the iodine containing contrast media [18]. Although HSG has higher pain scores in comparison to other tubal patency tests, it is in general well tolerated [19, 20].

Then, in 1947 R. Palmer first described the laparoscopy (DLS) to visualize the internal female genitals and used it to test tubal patency [21]. In late 60s and throughout the 70s Kurt Semm refined the laparoscopic technique and described chromopertubation in 1967 [22, 23]. Video-assisted laparoscopy was introduced in 1987, after which the recognition as reference standard for testing tubal patency was confirmed and this technique was widely implemented [24]. Though it has the advantage of directly visualizing the pelvis and all its organs, the need of general anaesthesia with hospitalization as well as the risk of major complications makes that most Dutch gynaecologist rather use another test as primary tubal patency test [16].

Sono-HSG, a more minimal invasive procedure compared to HSG and DLS, is the third known tubal patency test. After the introduction of transvaginal ultrasound, Deichert was the first to perform

sono-HSG in 1986 [18]. By infusing an echogenic contrast medium in the uterine cavity and simultaneously performing a transvaginal ultrasound examination, you can observe whether or not flow of the medium is seen through the tubes into the abdominal cavity. During the following years, sono-HSG has been refined by the usage of different contrast media and different ultrasound techniques. As in most gynaecologic offices an ultrasound machine is available, (almost) no barrier exist to adopt this technique and some studies propose to replace HSG for sono-HSG [18, 25].

Another in the Netherlands not frequently used tubal patency test is MRI-HSG. This technique is similar to HSG but instead of using X ray it uses MR-imaging. Possible advantages to HSG are the avoidance of exposure to radiation and iodine containing contrast media as well as it can be used to diagnose pelvic pathology as well as uterine and ovarian pathology. Next, another advantage of MR-HSG is, when compared to sono-HSG, the fact it is not operator-dependent with a better reproducibility [26, 27].

Transvaginal hydrolaparoscopy

History

Transvaginal hydrolaparoscopy (THL) was first described by S. Gordts In 1998 [28]. This procedure replaces the diagnostic laparoscopy under general anaesthesia to an outpatient procedure without compromising the visualization of the internal genitals. THL is based on culdoscopy, a technique described first in 1944 by Decker using the transvaginal approach [29]. During these first procedures the patient was placed in the knee–chest position, thereby creating a spontaneous pneumoperitoneum. Culdoscopy was mainly used in subfertility investigation as well as in diagnosing ectopic pregnancies and PID. In the same way, minor procedures such as tubal sterilization could be performed by culdoscopy. Nevertheless, the majority of the European and British gynaecologists remained sceptical in performing culdoscopy. Mainly due to the complications and the reported pain when performing the culdoscopy under local anaesthesia next to the impaired visibility compared to laparotomy. Whilst in the 70's the interest in laparoscopy grew, culdoscopy was abandoned [29].

Procedure

Gordts et al [28] however reinvented culdoscopy by adding the technique of hydroflotation. This means warm saline is infused via a Verres needle in Douglas' pouch, which allows inspection of the tubo-ovarian structures "under water" in their natural position without any manipulation. Moreover, the saline "pushes" the bowel cranial and apart from the female internal organs . This means less risk of bowel injury compared to culdoscopy. With use of a fiber optic light source and a video camera system with monitor, the problem of impaired visibility has been solved. Furthermore, Gordts et al [28] performed THL in an outpatient setting with the woman in dorsal position. In this way, the woman could watch the procedure on the monitor whilst undergoing the THL. This allows the surgeon to explain the findings at the same time.

For THL specially designed reusable and disposable instruments have been invented (Storz© re-usable system (Karl Storz SE & Co. KG, Tuttlingen, Germany), disposable Fertiloscope© (Fertility Focus, Warwick, UK) and the reusable circon-system (Circon ACMI, Stanford, CA, USA). The optic can be used for hysteroscopy in the same setting if necessary.

Implementation

In the Netherlands, Maxima Medisch Centrum in Veldhoven started with the procedure in 1999 [30]. First, gynaecologists with special interest in reproductive medicine were trained in performing THL by the inventors of this technique in Leuven, Belgium. Then they performed the first seven procedures under general anaesthesia after which all procedures were performed under local anaesthesia. From the start, women undergoing THL were asked to participate in a prospective cohort and were followed until pregnancy or at least 12 months. This resulted in a publication and a book chapter [30, 31]. After Maxima Medisch Centrum, three other hospitals started to perform THL, respectively in 2008 St. Antonius Ziekenhuis, Nieuwegein, in 2009 Medisch Spectrum Twente, Enschede and in 2010 Isala Klinieken, Zwolle. Just like in Veldhoven, first they were trained by experienced surgeons and the first procedures were performed under general anaesthesia where after all procedures were performed local anaesthesia. In one other Dutch hospital, Onze Lieve Vrouwe Gasthuis West (formerly known as St. Lucas Andreas Ziekenhuis), one gynaecologist performs THL as well, though under general anaesthesia.

Diagnostic accuracy

In studies describing diagnostic accuracy for detecting tubal patency, THL was performed under general anaesthesia by experienced minimal invasive surgeons in all. In these studies the laparoscopic surgeon was blinded for the result of the THL. Sensitivity for tubal patency ranged from 70 to 100% with a specificity of 100% when compared to laparoscopy as reference standard [32, 33, 34]. When looking at the concordance rate for tubal testing in THL and DLS, one multicenter prospective study showed concordance in 95.2% with a kappa index of 0.80 which means a strong level of agreement between the different raters [35]. In this study THL was performed in 81 women by two experienced surgeons for each center. Just like the studies above, THL was carried out under general anaesthesia, randomised prior to or directly after DLS. For endometrioses however, sensitivity and especially specificity seems lower compared to DLS, maybe due to of overlooking foci near the sacro-uterine ligaments and the inability of inspecting the bladder peritoneum [33, 36]. Though other studies state THL can visualize subtle endometriotic lesions and adhesions better than DLS [37, 38].

Learning curve

Different ways to evaluate the learning curve for THL have been described. The first study was a survey study [39]. In this study gynaecologists (n=44) worldwide performing THL were asked to state the number of THLs performed, to provide details on all procedures complicated by bowel injury, and to describe how much experience the operator had had at the time of the bowel injury. In this study, the number of procedures, predetermined in groups of 50, was used to classify experience. THL was performed under local anaesthesia, conscious sedation or general anaesthesia. They found that after 50 procedures the incidence of bowel injury decreased significantly from 1.35% to 0.25%. Another study stated again a learning curve of 50 procedures, although this was a single operator experience study. THL was performed under conscious sedation. His failure rate decreased from 10% to 2.6% as well as after the first 50 THL's a decrease in complications (bleeding: 10 vs 1.9% and bowel perforation: 8 vs 0.1%) was seen [40]. In a third study the operating time of a single well experienced laparoscopic surgeon was compared to that of an experienced surgeon in THL. They found a

comparable operating time after 20 diagnostic THL-procedures, all performed under general anaesthesia [41].

Tolerability

Though most of the above mentioned studies perform THL under general anaesthesia, THL is thought to be acceptable when performed under local anaesthesia. One study showed significantly less pain after THL with mini-hysteroscopy in comparison to HSG, though they did not stated which difference between the pain scores was found [20]. Another study showed a mean pain score of 2.7 (SD ± 1.5) in 60 women undergoing outpatient THL with only five (8%) patients marking a score above 5 [42]. In this group 96% would undergo the procedure again under the same conditions if necessary. In a study of Van Tetering et al. VAS pain score was rated 4.3 for outpatient THL in 159 women with a mean tolerability of 1.8 [31].

In literature however, most THL studies do not reflect daily practice in Dutch teaching hospitals. First, studies with THL procedures performed under general anaesthesia or conscious sedation are more common. As written above, Gordts et al [28] proposed to perform THL under local anaesthesia which is standard in most Dutch hospitals. Second, many learning curve studies use gynaecologist with substantial experience in minimal invasive surgery. When reporting on complications, big series of procedures performed by only one or a small number of surgeons are used. It is unclear if these figures apply to the Dutch teaching hospitals. And last, after investigating safety, efficacy and costs, these items must be reviewed in comparison to the currently used techniques and reference standard [43].

Scope of this thesis and research questions

In this thesis we aim to study the capacity of transvaginal hydrolaparoscopy for diagnosing tubal pathology as a first choice tubal patency test in an outpatient setting. Therefore, we have focused on the following questions:

- Is THL feasible as an outpatient tubal patency test in terms of performance, learning curve reflected by failures and complications, and tolerability?
- What is the diagnostic accuracy of outpatient THL compared to the current reference standard laparoscopy?
- Can THL replace HSG as a first choice tubal patency test; what is the capacity of these tests to diagnose tubal pathology and their performance in safety, pain and acceptability?
- Does a strategy with outpatient THL as first choice tubal patency test lead to as many live births when compared to a strategy with HSG?
- Can THL replace diagnostic laparoscopy as reference standard?

Outline of this thesis

First, we evaluated the performance of THL in terms of success rate, findings, complications and woman's tolerability in terms of pain scores and acceptability. For this, we used a retrospective cohort of 1127 subfertile women undergoing THL as first choice tubal patency test. The results are described in **chapter 2**. In **chapter 3** we evaluate the findings of THL and laparoscopy in 126 subfertile

women in whom, as part of their subfertility workup, THL was performed as the first choice tubal patency test in an office setting. **Chapter 4** describes the results of the randomised controlled trial (RCT) between HSG and THL, focusing on their diagnostic capacity on tubal pathology. In this trial we analysed the findings of HSG (n=150) and THL (n=144) as well as failures and complications in a group of infertile women with a low risk of tubal pathology. Alongside this RCT, VAS pain scores and acceptability scores were evaluated. In **chapter 5** we describe the same RCT, then focusing on prognostic capacity of THL versus HSG. The primary outcome in this RCT was a conception leading to live birth within 24 months after randomisation. In **chapter 6** the protocol for a Cochrane review in search for a new reference standard to replace DLS is reported. We discuss the answers of the research questions in **chapter 7** and put them aside current literature and describe future perspectives. **Chapter 8** contains a reflection on the clinical and social impact.

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Chapter 2

Performance of outpatient Transvaginal Hydrolaparoscopy

R. Coenders-Tros, M.A. van Kessel, M.M.A. Vernooij, G.J.E. Oosterhuis, W.K.H. Kuchenbecker, B.W.J. Mol, C.A.M. Koks. Human Reproduction 2016 Oct;31(10):2285-91

Abstract

Title: Performance of outpatient transvaginal hydrolaparoscopy

Study question: What is the feasibility of performing transvaginal hydrolaparoscopy (THL) in an outpatient setting?

Summary answer: It is feasible to perform THL in an outpatient setting, reflected by a low complication- and failure-rate and a high patients' satisfaction.

What is known already: THL is a safe method to investigate tubal patency and exploring the pelvis in subfertile women.

Study design, size, duration: Retrospective cohort study of 1,127 subfertile women who underwent THL as primary diagnostic method for testing tubal patency in an outpatient setting.

Participants/materials, setting, methods: We studied all THL procedures performed as a primary diagnostic tubal patency test in an outpatient setting in subfertile women starting from the initial THL in four large hospitals. Baseline characteristics were obtained, as well as the outcome of the procedures in terms of success, complications and findings by examining medical records. We used a uniform visual analogue scale (VAS) score document to collect data on pain and acceptability prospectively and compared two methods of pain relief.

Main results and the role of chance: We studied a total of 1,103 women who underwent THL. Successful access to the pouch of Douglas was achieved in 1028 women (93.2%), and 1,017 women had a complete evaluation (92.2%). Double-sided tubal patency was found in 844 women (83%), unilateral tubal patency in 127 women (12.5%) while in 46 women (4.5%) bilateral occluded tubes were diagnosed. Endometriosis alone was seen in 64 women (6.3%), adhesions alone in 87 women (8.6%) and both endometriosis and adhesions in 42 women (4.1%).

Complications occurred in 29 (2.6%) women, including 10 perforations of the rectum (0.9%), 8 perforations of the posterior uterine wall (0.7%) and 5 infections/pelvic inflammatory diseases (PIDs) (0.5%). Bleeding of the vaginal wall requiring intervention and hospital admissions due to pain was seen in 4 (0.4%) and 2 women, respectively (0.2%). The average pain score was rated 4.0 (±2.4 SD) on a VAS from 0 to 10 with 0 meaning no pain at all with no difference in different types of pain relief. Acceptability was rated 1.5 (±2.1 SD).

Limitations, reasons for caution: the main limitation of the study is its retrospective character and the fact that only a fourth of the women were asked for pain- and acceptability scores.

Wider implications of the findings: THL can be used as a primary method for tubal assessment in an outpatient setting. Further randomized studies are needed to assess whether THL is superior to other methods and strategies for tubal assessment in terms of prognostic capacity and cost-effectiveness.

Introduction

Subfertility, i.e. the failure to conceive within one year of unprotected regular sexual intercourse, occurs in approximately 10% of couples who wish to conceive. Tubal pathology is an underlying cause in 10 to 30% of the couples with subfertility [Evers, 2002]. As a consequence, a basic fertility workup includes assessment of tubal patency. The feasibility and cost-effectiveness of the different techniques to investigate tubal patency, however, is subject of debate.

Diagnostic laparoscopy is considered to be the reference standard, but poses a risk of major gastrointestinal and vascular complications next to the need for general anesthesia and hospitalization [Chapron et al. 1999; Tarik and Fehmi, 2004]. Hysterosalpingography HSG, often used as the primary method, has a limited sensitivity of 65% and a specificity of 83% [Swart et al., 1995]. In women without risk factors for tubal occlusion the sensitivity is even lower [Broeze et al., 2011]. Furthermore, HSG is known to have limitations in diagnosing peritubal adhesions and has the disadvantage of exposing the women to radiation.

An alternative for diagnostic laparoscopy and HSG, is transvaginal hydrolaparoscopy (THL), which was first described by Gordts et al in 1998. THL is a technique that uses hydroflotation as mechanism to explore the pelvic abdomen via the transvaginal route. It has been shown to be a safe procedure with a learning curve of 50 procedures [Verhoeven et al., 2004; Gordts et al., 2001]. THL can be carried out in an outpatient setting under local anesthesia [Gordts et al., 2000; Cincinelli et al., 2001; Van Tetering et al., 2007], allowing to explain the findings directly to the woman.

Over the last decade, THL has been the method of first choice for tubal testing in the fertility work up in four teaching hospitals in the Netherlands. Before this procedure is implemented in other hospitals, it is essential to know the feasibility in our daily practice as well as the drawbacks. Therefore, we report on the feasibility of THL as primary diagnostic tool for tubal testing in an outpatient setting in terms of success rate, findings, complications and woman's tolerability in terms of pain scores and acceptability.

Materials and Methods

Ethical approval

During the first attendance at the outpatient clinic, patients completed a general questionnaire in which they could consent that their findings were anonymously used for research. In accordance with the "code of conduct in health, 2004, and under Dutch law, further ethical approval was not required.

Participants and Setting

We performed a descriptive retrospective study among subfertile women who underwent THL as part of their basic fertility work-up between January 2000 and December 2011. The study was performed in four large teaching hospitals in The Netherlands (Maxima Medisch Centrum, Veldhoven; Medisch Spectrum Twente, Enschede; Isala Klinieken, Zwolle and St. Antonius Ziekenhuis, Nieuwegein). All these four hospitals use THL as the primary diagnostic procedure for tubal patency

testing in subfertile women. In Veldhoven, the gynaecologists started to perform THL in 2000, in Nieuwegein in 2008, in Enschede in 2009 and in Zwolle in 2010.

Prior to THL, women had a detailed history taken, underwent gynaecologic examination including transvaginal ultrasound, Chlamydia antibody titers (CAT) and Chlamydia PCR when CAT was positive. Chlamydia PCR positive patients were treated prior to the procedure. THL was performed irrespective of the outcome of CAT. In women with a fixed retroverted uterus, ovarian cysts or suspicion of endometriosis in the pouch of Douglas, the THL was not performed and these women were excluded, as they either underwent a HSG or conventional diagnostic laparoscopy. All women undergoing a THL at the outpatient clinic received oral and written information about the procedure.

Procedure

The THL was performed by gynaecologists with a special interest in reproductive medicine and/or minimal invasive surgery. The first procedures were carried out under general anaesthesia in order to acquire the necessary skills. In the present study, only women undergoing the THL under local anaesthesia in an outpatient setting were included, starting from the first procedure of the gynaecologist under these circumstances.

THL was performed as described by Gordts [Gordts et al., 1998]. We used the Storz re-usable system in three hospitals (Maxima Medisch Centrum, St Antonius Ziekenhuis and Isala Klinieken) while in the fourth hospital we used a specially designed fertiloscope (Medisch Spectrum Twente). In Veldhoven, for the initial 272 procedures the circon-system (Circon ACMI, Stanford, CA, USA) was used.

The procedure was scheduled in the proliferative phase of the menstrual cycle. Women were premedicated with 500 mg Naproxen, Centrafarm B.V. – the Netherlands. In Medisch Spectrum Twente, 2 ml of alfentanil, Janssen-Cilag B.V. – the Netherlands, 0,5 mg/ml was given intravenously just before the Verres needle was inserted.

Women with a positive CAT had a prophylactic dose of 1000 mg azithromycin, Pfizer B.V. - the Netherlands. In case of a positive PCR for Chlamydia, women were treated first with antibiotics and the THL was rescheduled after a negative PCR swab.

The procedure was performed with the woman in the dorsal gynaecological position positioned. The women and their partners could follow the procedure on a video screen. After insertion of a trelat speculum the vagina was disinfected with aqueous chloorhexidine solution. The central part of the posterior cervix was infiltrated with 1-2 ml of ultracainD S, Sanofi Aventis B.V. – the Netherlands. A tenaculum was placed on the posterior cervix and a balloon catheter was put in the uterine cavity and the balloon inflated with 1-2 ml of air for the chromopertubation. Local anaesthesia with 2-3 ml of ultracain was performed in the vaginal vault, 1 to 2 cm below the cervix. A small incision was made at this place.

The following steps were performed depending of using the specially designed Storz re-usable system or the fertiloscope.

For the Storz reusable system at the place of the incision the trocar system is introduced. The system consists of an adapted needle, a dilatation device and a trocar 3, 9 mm in outside diameter. All three parts fit together but the needle is longer than the dilatation device. The Verreslike needle is inserted

by a special needle loading system. Progressively, the dilatators and trocar are inserted into the pouch of Douglas after which the needle and dilatators are removed and replaced by a rigid 2, 7 mm wide-angel 30 optical system. Continuous infusion with warmed saline solution is then started.

For the fertiloscope, a Veress needle was inserted at the place of the incision. After infusion of 100 to 200 ml pre-warmed saline solution the Verres needle was removed. At the same puncture site the fertiloscope was inserted. The fertiloscope is designed with a balloon to keep the trocar in place. The 30° endoscope was inserted in the trocar and after conforming correct placement the saline infusion was connected to the fertiloscope to give the opportunity to infuse more saline when necessary. Finally the balloon was inflated with 5 ml of air. After correct insertion, the speculum was removed in order to avoid discomfort for the women and allowing free movement of the scope. After infusion of saline and some orientation, the investigation started at the posterior uterine wall. Then the scope was moved laterally to identify the tubo-ovarian structures on the right and the left side consecutively. The ovarian surface was inspected, consecutively the ovarian ligament, the fossa ovarica and the dorsal part of the ovary. Subsequently, both the fimbrial part of the Fallopian tubes and the tubo-ovarian contact were inspected. Then a dye test was performed to test the patency of the tube. Throughout the whole procedure, continuous irrigation with warm saline kept the bowel and the tubo-ovarian structures afloat enabling clear vision.

After the procedure the fluid was allowed to drain from the pouch of Douglas. The puncture site in the fornix posterior was not sutured unless active bleeding was noted. An additional hysteroscopy was only performed in case of suspected uterine anomaly or intrauterine pathology.

Women were informed that some vaginal leakage or bleeding could occur, and were advised not to use tampons. The women left the outpatient clinic within one hour after the procedure, except for those whom had been given alfentanil (Janssen-Cilag B.V. – the Netherlands) iv.

Outcome measures

In this study, we studied performance of the THL in terms of four categories:

i. Complete evaluation, defined as visualisation of the entire pelvis meaning the tubo-ovarian structures, pelvic sidewalls and the pouch of Douglas together with a blue dye test.

ii. Incomplete evaluation procedure. This meant that there was an inability for complete evaluation due to pelvic abnormalities like endometriosis or adhesions.

iii. Incomplete non diagnostic procedure. The procedure was classified as incomplete non diagnostic when the pouch of Douglas was reached and seen, but complete visualisation could not be achieved due to for example technical problems, blurred vision or pain. This meant that no diagnosis could be made and that the woman had to undergo another procedure for testing tubal patency, for example a HSG or diagnostic laparoscopy with tubal testing.

iv. Failure, defined as the inability to reach the pouch of Douglas due to tenting of the peritoneum, masses in the pouch of Douglas, obesity or technical problems.

Furthermore, we recorded the findings of the THL. These were classified as normal or abnormal. Abnormal findings were defined as tubal occlusion, endometriosis and/or adhesions. Next to this complications and woman's pain scores and acceptability were analyzed.

Complications were defined as an unintended and undesirable event or condition during or following THL, with a negative effect on the patients' health with the need for an intervention, hospital admission or another medical treatment.

Pain scores and acceptability of the THL in an outpatient setting were investigated in Maxima Medisch Centrum during the period of January 2000 and December 2004, after which they stopped because of an acceptable score. Furthermore, in Medisch Spectrum Twente and Isala klinieken pain scores and acceptability were investigated during the period of March 2010 and December 2011. Hereby, women were asked to rate their pain directly after the procedure on a visual analogue scale (VAS) ruler, which were then read by trained nurses. VAS score 0 for pain meant no pain at all and 10 meant the worst pain one could imagine. For acceptability a VAS score of 0 meant total willingness to undergo the procedure again under same circumstances if necessary and 10 meant no acceptability at all.

Statistical analysis

Data were analyzed using the software package SPSS for Windows version 22 (IBM Corp. USA). Nominal variables are reported as numbers and frequencies; continuous variables as mean ± standard deviation. The Mann-Whitney U test was used for analyzing the VAS-scores. $P < 0.05$ was considered statistically significant.

Results

From January 2000 till December 2011, a total of 1,127 women were scheduled for THL in an out-patient setting. Of these women, 24 had abnormal findings during vaginal examination before starting the THL procedure, such as masses in the pouch of Douglas, a suspicion of extensive endometriosis or a fixed retroverted uterus. They were therefore rescheduled for HSG or diagnostic laparoscopy. Consequently, 1103 women underwent THL at the outpatient clinic. The characteristics of the women are shown in table I.

Table I Characteristics of the participants

Women (n)	**1103**
Mean Age (years ± SD)	31.7 ± 4.2
Primary subfertility (%)	778 (70.5)
Mean duration of subfertility (months ± SD)	22.7 ± 12.1
Ovulatory cycles (%)	926 (86.8)
Positive Chlamydia serology (%)	95 (8.6)
Normal semen analysis partner (%)	870 (81.6)

The 1103 procedures were performed by 16 different gynecologists. The number of procedures per gynecologist varied between one and 296 procedures (mean 75, table II). Four of them each carried out more than 100 procedures for a total of 695, accounting for more than 60% of the THLs performed. The average procedure time was 13.7 minutes (± 6.7 SD). All gynecologist performing up to ten THL's were supervised by an experienced gynecologist during these procedures.

Access to the pouch of Douglas was achieved in 1028 women (93%). In 1017 women (92%) a complete evaluation (n = 989) or an incomplete evaluation procedure (n=28) could be carried out (table II). There were 11 incomplete diagnostic procedures (1.0%) due to technical problems, inability to find the tubo-ovarian structures or blurred vision of unknown etiology. Consequently, in 75 women (6.8%) a THL failure occurred. In 39 of these women pre-peritoneal Verres needle- or trocar placement (3.5%) was the underlying cause. Other causes were vaginismus/pain n=12 (1.1%), rectum perforation n=8 (0.7%), perforation of the uterus n = 5 (0.5%), a retroverted uterus n=5 (0.5%), cervical stenosis (occluding adhesions of the internal cervical ostium) n = 3 (0.3%), or obesity n=3 (0.3%).

Table II Performance THL

		Performance THL				Total
		Complete evaluation	Incomplete diagnostic	Incomplete non diagnostic	Failure	
Surgeon	1	281	2	2	11	296
	2	145	1	0	10	156
	3	119	11	1	10	141
	4	81	7	1	13	102
	5	75	0	1	5	81
	6	52	3	4	9	68
	7	59	0	2	4	65
	8	50	2	0	4	56
	9	30	0	0	3	33
	10	30	0	0	2	32
	11	27	1	0	3	31
	12	18	1	0	1	20
	13	10	0	0	0	10
	14	7	0	0	0	7

15	4	0	0	0	4
16	1	0	0	0	1
Total	989 (89.7%)	28 (2.5%)	11 (1.0%)	75 (6.8%)	1103

Although a retroverted uterus is a relative exclusion criterium for performing THL, 31 women with a mobile retroverted uterus underwent a THL. Access to the pouch of Douglas was achieved in 25 women (80.6%), and in 22 (71.0%) a complete evaluation or incomplete evaluation procedure could be performed. Moreover, four complications occurred in this group (12.9%), whereas only 29 complications (2.6%) occurred in all women (table III).

Table III Complications

	Frequency	Percent
Rectumperforation	10	0.9
Uterusperforation	8	0.7
Infection/PID	5	0.5
Bleeding requiring intervention	4	0.4
Hospital admission	2	0.2
Total	29	2.6

Of all complications, rectum perforation was the most common one and occurred 10 times (0.9%) (table III). In all cases expectant management was applied with (n=4) or without (n=6) antibiotics. Eight times the rectum perforation was the cause of the THL failure, two times the procedure could be continued after replacing the trocar. One major complication occurred in this series: a case of bleeding of the vaginal wall which required suturing under general anesthesia with more than 500 ml blood loss in total. No blood transfusion was needed and the woman recovered uneventfully.

When looking at the performance of the four gynecologists exceeding 100 procedures, the THL failure rate (n=44 out of 695) was 6.3%. Gynecologists, who performed between 50-100 procedures, had a failure rate of 8.1% (n=22 out of 270) and gynecologists between 11-50 procedures of 7.8% (n=9 out of 116). Complication rate of the four gynecologists exceeding 100 procedures was 2.3% (n=16 out of 695) with 10 complications in the 50 first procedures (5%) performed, 4 between 50-100 procedures (2%) and 2 above 100 procedures performed (0.7%).

Table IV shows the findings of the THL. In the 1017 women with a complete evaluation or incomplete evaluation procedure 729 (71.7 %) showed bilateral tubal patency without other abnormalities. In the other 288 women (28.3%) tubal occlusion or abnormalities were detected. Bilateral tubal occlusion was seen in 46 (4.5%) women, while 127 women (17.0%) had unilateral tubal occlusion.

There were 115 (11.3%) women with bilateral tubal patency, who had endometriosis (n=49; 4.8%), adhesions (n=41; 4.0%) or both (n=25; 2.5%).

Table IV THL findings

Tubes \ Abnormalities	None	Endometriosis	Adhesions	Both	Total
Bilateral patency	729	49	41	25	844 (83.0%)
Unilateral patency	77	14	25	11	127 (12.5%)
Bilateral occluded	18	1	21	6	46 (4.5%)
Total	824 (81.0%)	64 (6.3%)	87 (8.6%)	42 (4.1%)	1017 (100%)

Pain scores from 356 women were obtained in three hospitals (Maxima Medisch Centrum, Isala klinieken and Medisch Spectrum Twente) with a response rate of 86%. The mean pain score was rated 4.0 (±2.4 SD) on a scale from 0 till 10 with 0 meaning no pain at all and 10 meaning the worst pain one can imagine (figure 1). It must be stated that 163 of these women (45.5%) received 2 ml of alfentanil 0.5 mg/ml intravenously prior to the procedure. No statistical significant difference in VAS scores was found between the women with and without alfentanil (VAS 4.2 (SD 2.3) and 3.8 (SD 2.5) respectively). Acceptability was valued 1.5 (±2.1 SD) by 233 women, with 0 meaning absolute acceptance, whereas 10 meant no acceptance (figure 2).

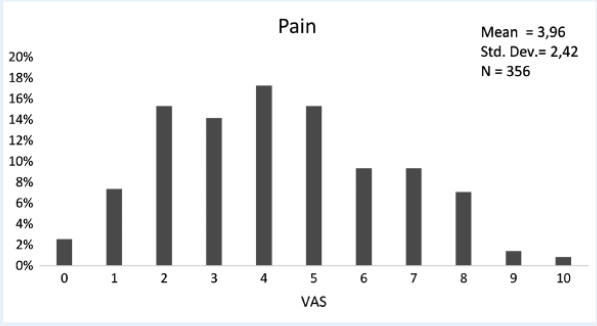

Figure 1 Visual analogue scale (VAS) score for pain; 0 meant no pain at all and 10 meant the worst pain one could imagine.

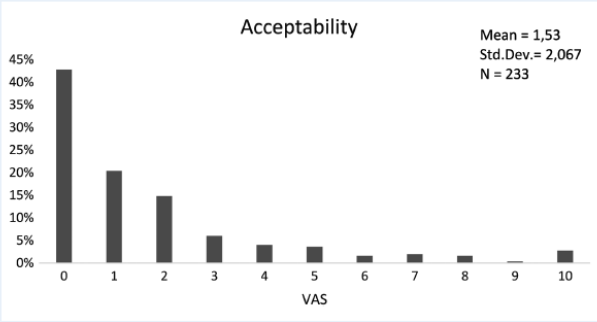

Figure 2 Visual analogue scale (VAS) score of acceptability; 0 meant total willingness to undergo the procedure again under the same circumstances if necessary and 10 meant no acceptability at all.

Discussion

This study shows that THL is a safe and reliable method for tubal patency testing as we demonstrated low complication rates (2.6%), a high acceptability and pain scores (respectively VAS 1.5 and 4.0) at acceptable performance with a complete evaluation in 92% of the women. The major drawback of the study is the retrospective study design with lack of controls and thus possible selection and information bias. Nevertheless, it gives a good overview of tubal testing in daily practice in teaching hospitals.

The overall failure rate of THL in this study is higher than reported in some studies [Verhoeven et al., 2004; Gordts et al., 2000; Van Tetering et al., 2007; Kissler et al., 2011], but comparable to others [Darai et al., 2000; Nawroth et al., 2001]. Pre-peritoneal Veress needle- or trocar placement was the main reason for failure, which is known to happen more often during the first procedures as reported by Verhoeven et al [Verhoeven et al., 2004]. In this study all first procedures in four hospitals performed by 16 gynecologists were taken into account. Only eight of them exceeded fifty procedures, proposed to be the learning curve threshold [Verhoeven et al., 2004, Gordts et al., 2001].

Another contributor to the failure rate could be the fact that 31 women with a retroverted uterus were included. The reason for these inclusions are speculative in this retrospective cohort. Many women in this cohort were selected and planned for THL not by the operators themselves but by fertility doctors. Poor selection of women for the THL procedure could therefore be an explanation for the higher failure rate. This is also reflected by the fifteen women who were planned to undergo

a THL but were excluded from the procedure after assessment by the gynecologist due to perform the THL. The women with a retroverted uterus had a higher risk for an incomplete non diagnostic evaluation or THL failure compared to the whole group, 29.1% versus 7.8% and a higher complication risk overall (12.9% vs. 2.6%). This emphasizes that a retroverted uterus can be considered as a relative contraindication for performing a THL. Nevertheless, our overall complication rate is in the same range as known in literature [Gordts et al., 2000; Gordts et al., 2001; Van Tetering et al., 2007; Kissler et al., 2011, Shibahara et al., 2007]. Our analysis also indicates that experience might lower the complication rate with a decrease in complications from 5% within the first 50 procedures to 0.7% after 100 procedures.

An advantage of THL is that it can discover subtle fertility problems at an early stage of the fertility workup contrary to the poor performance of HSG to diagnose these abnormalities. Cincinelli et al. described, among others, a concordance of 95% in tubal patency testing between THL and HSG, but HSG missed other pathology know to compromise fertility such as peritubal adhesions and endometrioses [Shibahara et al. 2001; Fujiwara et al. 2003]. In the present cohort, endometriosis and/or adhesions were diagnosed in 115 women (11.3%) with patent tubes and these subtle fertility problems would have been missed if HSG was applied as a tubal patency testing method. The clinical implications of these problems is discussed by Van Kessel et al. [unpublished data], who showed a fecundity rate ratio of 0.42, meaning less probability of spontaneous intra uterine pregnancy per time unit for women with patent tubes but with endometriosis and adhesions, compared to those without.

Another possible advantage is that less diagnostic laparoscopies are needed. Many hospitals initially use HSG as tubal patency test but plan a diagnostic laparoscopy when no spontaneous pregnancy is achieved in 6 to 12 months in case of unexplained subfertility or before treatment is started or when HSG shows abnormalities. In our four hospitals no diagnostic laparoscopy was scheduled for the 729 (71.7%) women with no abnormalities during THL. Furthermore, when abnormalities during THL were seen, the women were counselled and planned directly for fertility enhancing surgery. As an estimate, in this series over 800 women were spared undergoing diagnostic laparoscopy which gives an avoidance rate of 70%. In other studies, avoidance rates from 46.2% [Watrelot et al., 1999], 63% [Dechaud et al., 2001], 72% [Gordts et al., 1998, Campo et al., 2002] to as high as 93% [Watrelot et al., 2003] are stated. When looking at the concordance of THL with laparoscopy, several studies show that abnormal findings during THL are confirmed with laparoscopy. Sensitivity and specificity respectively ranges from 70% and 100% [Dechaud et al., 2001], 92.3% and 100% [Darai et al., 2000] to 100% and 100% [Casa et al., 2002]. In case of normal findings during THL, laparoscopy could still demonstrate endometriosis as THL cannot reach the bladder region [Nawroth et al., 2001; Darai et al., 2000; Dechaud et al., 2001]. In the case of discordant results, Wartrelot et al., 2003, showed that in only 1% it had clinical consequences.

When performing the THL, the gynecologist may also consider to do a hysteroscopy in the same session. The question is if routine hysteroscopy is necessary during basic fertility screening. Recent preliminary result of the inSIGHT-study has shown that routine hysteroscopy does not improve IVF outcome in terms of live birth rate [Smit et al.; 2015]. In the studied centers a hysteroscopy was performed only when there was a suspicion of intrauterine pathology or congenital abnormality of the uterus.

Although this study shows that THL is a well-tolerated, safe and reliable method, in these days of economic decline, cost-effectiveness is an important issue when introducing a potentially new standard reference procedure. To our knowledge only Khouri [Khouri and Magos, 2005] performed a comparative study with THL in a one-stop fertility clinic to laparoscopy as an in-patient investigation. They calculated a saving of over 380 pounds sterling in favor of the one-stop fertility clinic or 28% cost saving to the hospital.

Besides THL, other relatively new tubal patency techniques like hysterosalpingo-foam sonography (HYFOSY) are also being implemented. These ultrasound based techniques might have advantages over HSG with similar test results [Maheux-Lacroix et al., 2014]. A RCT between THL and sono-HSG has not been conducted as far as we know, although Ahinko-Hakamaa et al., 2009, verified tubal patency by THL after performing hysterosalpingo-contrast-sonography (HyCoSy) first. They showed a concordance of 77%. In our opinion, before implementation of novel techniques, these should first be compared to existing techniques. Eventually, all strategies for basic fertility workup and fertility treatment should be compared in order to know what the best practice is.

In conclusion, our study shows that THL can be implemented as a method for tubal patency testing and exploration of the female pelvis to exclude abnormalities which may compromise conception. THL enables the surgeon to schedule fertility enhancing surgery immediately if required without performing a diagnostic laparoscopy beforehand. Whether or not THL is superior to HSG in terms of prognostic capacity and cost-effectiveness should be studied before implementing THL as a primary method. This is currently evaluated in a randomized setting in various fertility clinics in The Netherlands.

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Author's roles

All authors provided a substantial contribution to the conception of the paper. CK and BM designed the study. CK, GO, MV and WK participated in the trial. RC and MK collected the data. Data was analyzed by RC. All authors participated in the interpretation of data. RC elaborated a first draft of the paper. All other authors were involved in redrafting and revising of the paper and approved the final version of the manuscript that is now being submitted for publication.

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Chapter 3

Transvaginal hydrolaparoscopy and laparoscopy

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Abstract

Research question: To evaluate the findings of outpatient transvaginal hydrolaparoscopy (THL) in comparison to diagnostic laparoscopy combined with chromo perturbation in subfertile women.

Design: In a retrospective study in four large teaching hospitals, we studied all subfertile women who underwent a THL and a conventional laparoscopy as part of their fertility work up in the period between 2000-2011. Findings at THLs were compared with findings at diagnostic and therapeutic laparoscopies. Tubal occlusion, endometriosis and adhesions were defined as abnormalities.

Results: Out of 1119 women, 1103 women underwent THL. A complete evaluation or incomplete but diagnostic procedure could be performed in 989 (89.7%) and 28 (2.5%) respectively. An incomplete non-diagnostic procedure was performed in 11 (1.0%) women. Failure of THL occurred in 75 women (6.8%) and 40 of these women (3.6%) underwent laparoscopy subsequently. Laparoscopy was performed in a total of 126 patients with a median time interval of 7 weeks (IQR 3-13 weeks). Of 64 patients who successfully underwent both THL and laparoscopy concordant findings were found in 53 women and discordant results in 11 women, 6 of which were caused by tubal spasm. Sensitivity of THL in detecting abnormalities was 100% and specificity was 22.2% with a likelihood ratio of 1.29.

Conclusion: THL in an outpatient setting can detect anatomical abnormalities comparable to the, more invasive, reference standard diagnostic laparoscopy. If THL succeeds, there is no need to add a diagnostic laparoscopy in the work-up.

Introduction

Testing for tubal function is an important part of the fertility workup. Several options are available, for example serology test for Chlamydia, hysterosalpingo-contrastsonography, hysterosalpingography, transvaginal hydrolaparoscopy (THL) and diagnostic laparoscopy with tubal testing. Diagnostic laparoscopy is considered to be the reference standard, but this procedure requires hospitalization as well as general anesthesia. Furthermore it has a complication rate of around 2% with an incidence of major gastrointestinal and vascular injuries between 0.62 and 1.60 per thousand laparoscopies (Chapron et al. 1999; Tarik and Fehmi 2004).

Therefore in many fertility protocols less invasive methods like HyCoSY or hysterosalpingography (HSG) are used as primary method. When HyCosy or HSG show signs of tubal occlusion or other pathology, usually a laparoscopy is scheduled to explore the pelvis and, if needed, to perform fertility enhancing surgery. Most fertility clinics omit the diagnostic laparoscopy when HyCosy or HSG show no abnormalities. Nevertheless, in the Netherlands 20% of the gynecologists perform a diagnostic laparoscopy despite normal outcome of the HSG, mostly when no pregnancy occurs after expectant management of 6 months (Roest et al. 2018).

The transvaginal hydrolaparoscopy (THL), an alternative for both HSG and diagnostic laparoscopy, was first described by Gordts et al in 1998. THL is a technique that uses the transvaginal route to explore the pelvis with warm saline. THL is a proven safe procedure (Verhoeven et al. 2004; Gordts et al. 2001). THL is well-tolerated in an outpatient setting under local anesthesia (Coenders-Tros et al. 2016), with the opportunity to explain the findings directly to the patient. In case of a normal THL with bilateral patent tubes and no signs of endometriosis or adhesions, a laparoscopy is usually not required. If abnormal findings are seen with THL, fertility enhancing surgery can be considered.

THL and diagnostic laparoscopy have been compared in several prospective trials showing a sensitivity of respectively 86% - 92.3% and 87% (Watrelot et al. 2003, Darai et al. 2000; Dechaud et al. 2001). In these three studies THL was performed under general anesthesia followed directly by laparoscopy. Furthermore, only a small number of highly experienced surgeons performed both procedures. It is questionable whether the performance of THL is equal to laparoscopy in the diagnosis of tubal pathology and endometriosis or adhesions where THL is performed in an outpatient setting, with more surgeons performing THL. Furthermore, the question is if THL can replace diagnostic laparoscopy combined with chromopertubation leaving laparoscopy only as a therapeutic procedure. The aim of this study was to evaluate the findings of THL and laparoscopy in subfertile women in whom THL was performed as primary tubal patency test in an outpatient setting.

Materials and methods

We compared the outcome of THL and laparoscopy among subfertile women who underwent both procedures. THL was part of their basic fertility work-up in four large teaching hospitals in the Netherlands (Maxima Medisch Centrum, Veldhoven; Medisch Spectrum Twente, Enschede; Isala, Zwolle and St. Antonius Ziekenhuis, Nieuwegein). Both methods as well as the THL procedure has been described before (Coenders-Tros et al. 2016).

In short, these hospitals used THL as the primary diagnostic procedure for tubal patency testing in subfertile women. During the first attendance at the outpatient clinic, patients completed a general

questionnaire in which they could consent that their findings were anonymously used for research. In accordance with the code of conduct in health, 2004, and under Dutch law, further ethical approval was not required.

A standard protocol was followed before scheduling THL, which included a detailed history, performing gynaecological examination including transvaginal ultrasound and investigation of Chlamydia antibody titres (CAT) and/or Chlamydia PCR. Chlamydia PCR positive patients were treated prior to the procedure. Depending on the local protocol, THL was performed during initial workup, irrespective of the outcome of CAT in 3 centres.

Women were not scheduled for THL when having a suspicion of adhesions in Douglas pouch, a fixed retroverted uterus, ovarian cysts or suspicion of endometriosis in the pouch of Douglas by either vaginal examination and/or transvaginal ultrasound. This means that when Douglas pouch was empty and reachable during examination, both women with a high and low risk for tubal pathology were counselled for THL.

All women undergoing a THL at the outpatient clinic received oral and written information about the procedure. They were instructed to take 500 mg Naproxen (Centrafarm B.V., the Netherlands) two hours before the scheduled procedure, furthermore in one centre alfentanil 2 ml (Janssen-Cilag B.V., the Netherlands), 0.5 mg/ml was given intravenously. The Storz reusable system for hydrolaparoscopy was used in three hospitals as the fourth used the specially designed fertiloscope. The steps during the use of these two scopes differ slightly, as previously described (Coenders-Tros et al. 2016). Here we summarize the THL procedure with the re-usable system.

After a speculum was placed, the vagina was disinfected with aqueous chlorhexidine solution. A tenaculum was placed on the posterior side of the cervix after infiltration with 1–2 ml of ultracain D-S (Sanofi Aventis B.V., the Netherlands). The same local anaesthetic was then used for infiltration of the posterior vaginal vault, 1-2cm below the cervix, after which an incision was made. A small catheter with a balloon inflated with 2-3 ml air was placed inside the uterine cavity to use for the chromopertubation with methylene blue. The Storz reusable system was then inserted in the pouch of Douglas after which infusion of warm saline is started after replacement of the dilatators by a rigid 30 degree angle scope (fertiloscope trocar and The 30 degree angle endoscope was inserted (fertiloscope system). After removal of the speculum the inspection of the posterior side of the uterus, the tubes, fimbrial parts, ovaries as well as the pelvic side walls started and the dye test was performed. No salpingoscopy or therapeutic interventions were performed during the THL. The entire procedure could be followed by the woman and her partner on a video screen. When the procedure was finished, the saline was drained from Douglas pouch. After removal of the instruments the vaginal wall was only sutured when active blood loss was seen. The women could leave the outpatient clinic within 1 hour after the procedure, only the women given alfentanil intravenously had to be monitored for two hours afterwards.

Depending on the outcome and findings of the THL and depending on local protocol, women were either counselled for expectant management, fertility treatment (mild ovarian stimulation with or without insemination or IVF/ICSI) or fertility enhancing surgery.

We described the findings in THL and in conventional CO2 laparoscopy and analysed the results. The THL procedures were described in four groups (Coenders-Tros et al. 2016):

A. Complete evaluation, defined as visualization of the entire pelvis meaning the tubo-ovarian structures, pelvic sidewalls and the pouch of Douglas together with a blue dye test.
B. Incomplete evaluation procedure. This meant that there was an inability for complete evaluation due to pelvic abnormalities like endometriosis or adhesions. In these cases a diagnosis could be made and treatment could be planned.
C. Incomplete non-diagnostic procedure. The procedure was classified as incomplete non-diagnostic when the pouch of Douglas was reached and seen, but complete visualization could not be achieved due to, for example, technical problems, blurred vision or pain. This meant that no diagnosis could be made and that the woman had to undergo another procedure for testing tubal patency, for example, a HSG or diagnostic laparoscopy with tubal testing.
D. Failure, defined as the inability to reach the pouch of Douglas due to tenting of the peritoneum, masses in the pouch of Douglas, obesity or technical problems.

Outcome measures were tubal occlusion, endometriosis and/or adhesions. Tubal occlusion was defined as blockage of the Fallopian tubes with a negative blue dye test. Endometriosis was classified as described in the ASRM classification (ASRM 1996). The definition of adhesions are thick or filmy fibrous bands between the internal organs with the (pelvic) sidewalls, which are fertility diminishing. For example, when adhesions block a normal ovum pickup.

We included all laparoscopies that were performed in the study period in women who underwent THL as part of their fertility workup prior to the laparoscopy.

Software package SPSS for Windows version 24 (IBMCorp.,USA) was used for statistical analyses. Sensitivity, specificity and the measurement of agreement between the findings of THL and diagnostic laparoscopy (DLS) was calculated for THL using Cohen's Kappa (κ). κ was considered < 0 as 'poor' , 0 to 0.20 'slight', 0.21 to 0.4 'fair', 0.41 to 0.60 'moderate', 0.61 to 0.8 'substantial', and above 0.81 'almost perfect' (Landis and Koch 1977). Positive and negative likelihood ratios were calculated manually using the formula positive likelihood ratio = sensitivity/(1-specificity) and negative likelihood ratio = (1-sensitivity)/specificity . $P<0.05$ was considered statistically significant.

Results

Between January 2000 and December 2011 1119 subfertile women were scheduled for outpatient THL. On the day of the procedure, THL was cancelled in 16 women (1.4%) due to abnormal findings on vaginal examination. Of these 16 women, 12 were scheduled for laparoscopy. One woman became pregnant before hence the laparoscopy was cancelled. In four women, no tubal patency test was performed, in three cases because of withdrawal of the fertility investigations and in one case because IVF was started based upon the woman's history and clinical examination.

In the 11 women in whom THL was cancelled, subsequent laparoscopy showed tubal patency in all, but other abnormalities were found in all 11 women: there was endometriosis in 10 women while the other woman had adhesions. Adhesiolysis, coagulation and excision of endometriosis spots were performed in 5 women, while the other 6 women did not have additional treatment (figure 1).

Eventually, 1103 women underwent THL in an outpatient setting, performed by a total of 16 surgeons. Patients characteristics as well as the complications and patients preference is described

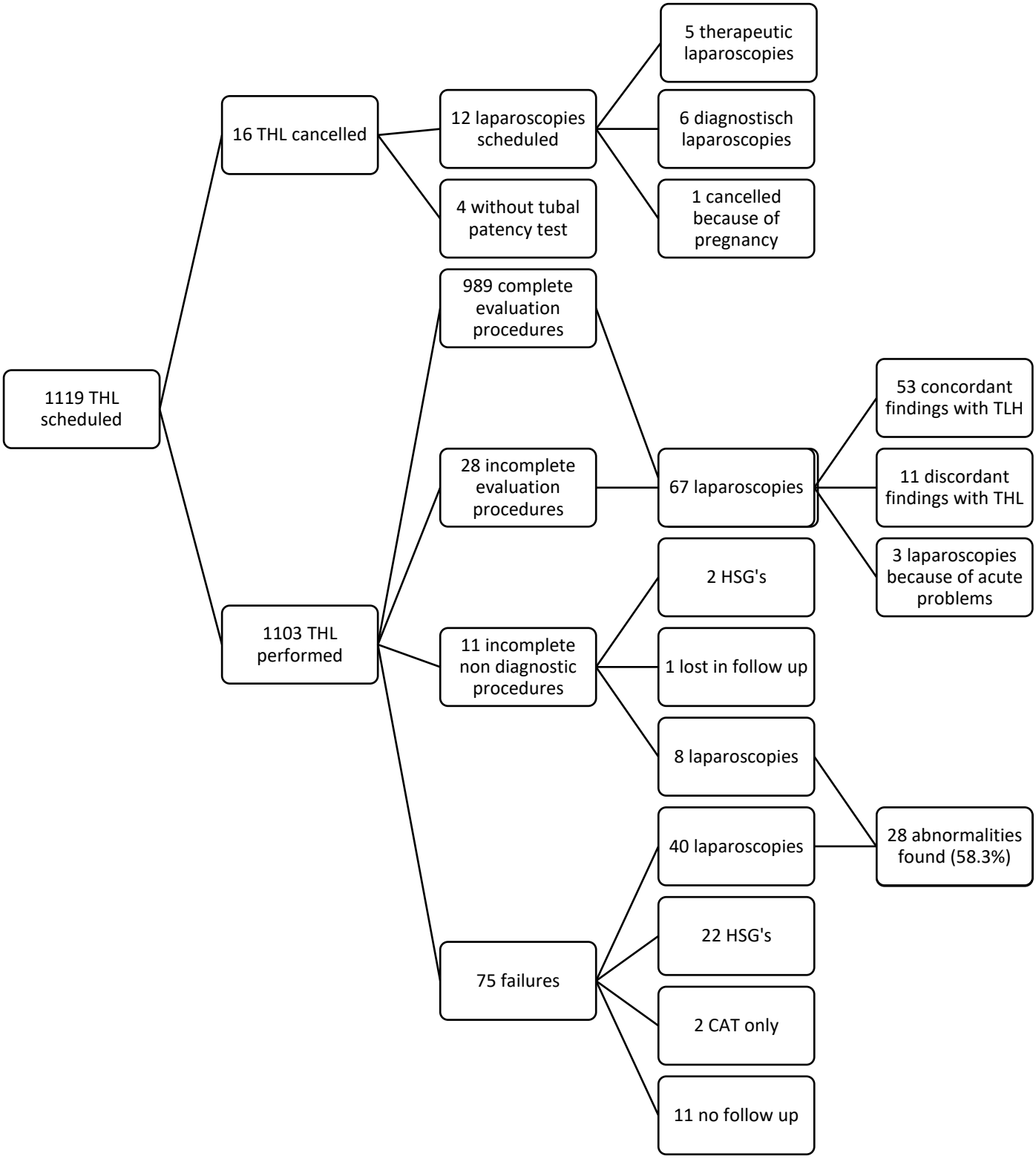
in more detail in Coenders-Tros et al (2016). In short, women had a mean age of 31.7 (+/- 4.2) years, had not be pregnant before in 70.5% and had a mean duration of 22.7 (+/-12.1) months of subfertility. CAT was positive in 8.6% of the women with a normal semen analysis in 81.6%. A complication rate of 2.6% was seen, with 10 rectum perforations (0.9%), 8 uterine perforations (0.7%), 5 infections/PID's (0.5%), 4 bleedings of the vaginal wall acquiring reintervention (0.4%) and 2 hospital admissions due to pain (0.2%). Mean pain score was rated 4.0 (SD 2.4) on a scale from 0 to 10 with 0 meaning no pain at all and 10 meaning the worst pain one could imagine. There was no statistical significant difference found between when alfentanil was or was not used (VAS 4.2 (SD2.3) and 3.8 (SD 2.5) respectively). Acceptability was scored 1.5 (SD2.1) with 0 meaning total willingness to undergo the procedure again under same circumstances if necessary and 10 meant no acceptability at all.

The distribution among the above mentioned groups was as follows: a complete evaluation procedure (group A) was performed in 989 women (89.7%), while in (group B) 28 women (2.5%) the evaluation was incomplete. There were 11 incomplete non-diagnostic procedures (1.0%) (group C) due to technical problems, inability to find the tubo-ovarian structures or blurred vision of unknown aetiology. THL failure (group D) occurred in 75 women (6.8%).

A total of 126 women underwent laparoscopy. The median time interval between (attempted) THL and laparoscopy was 7 weeks (IQR 3-13). The time interval depended on the findings during THL, timing in menstrual cycle (preferable in follicular phase), surgical waiting list and preference of the women. After an incomplete non diagnostic procedure or THL-failure (group C and D), 48 women underwent a laparoscopic procedure (4.4%), finding tubal pathology and/or abnormalities in 28 women (2.5%).

In the group of women with a complete evaluation and an incomplete evaluation procedure, a total of 67 laparoscopies (group A n = 64 and group B n = 3) were performed (6.6%) (figure 1). In 3 women (all group A) the laparoscopy was performed for acute gynaecologic problems instead of fertility reasons (two women with an ectopic pregnancy respectively one and two years after the THL procedure and one woman with a dermoid cyst and complaints 2 years later). Other reasons for laparoscopy were diagnostic in 21 women (2.1%) - to confirm THL results in 2.0% (n = 20; group A n=19 and group B n=1) and to rule out a complication of the THL in 0.1% (n = 1 of group A) – and therapeutic in 43 women (4.2%) (group A n = 41 and group B n = 2).

Figure 1. Flow chart of patients undergoing transvaginal hydrolaparoscopy (THL) and/or laparoscopy.



Consecutively, concordance of findings could be studied in 64 completed THL and laparoscopic procedures (group A n = 61, group B n = 3). Concordant results were found in 53 women. One woman (group A) with normal findings at THL underwent diagnostic laparoscopy because of the suspicion of having an infection after the THL procedure. No abnormalities were detected and the tubal patency test results were concordant. In the other 52 laparoscopies; one sided (n= 17) or bilateral occlusion (n=23) was seen in THL as well as in laparoscopy. Furthermore in this group endometrioses (n=3), adhesions (n=25) or both endometrioses and adhesions (n= 16) were discovered in the THL-procedure as well as in laparoscopy (table 1).

Table 1 Findings of women with concordant results in THL and laparoscopy

			Abnormalities				Total
			No abnormalities	Endo-metriosis	Adhesions	Both	
Tubes	Bilatateral occlusion	N	5	0	14	3	22
		%	9.4%	0%	26.4%	5.7%	41.5%
	Unilateral patency	N	3	5	6	6	20
		%	5.7%	9.4%	11.3%	11.3%	37.7%
	Bilateral patency	N	1	0	4	6	11
		%	1.9%	0%	7.5%	11.3%	20.8%
Total		N	9	5	24	15	53
		%	17.0%	9.4%	45.3%	28.3%	100%

Nine of these 52 women (group A n = 8, group B n = 1) with abnormalities during THL underwent a diagnostic laparoscopic procedure only to confirm the findings of the THL, after which, fertility treatment was started. In the other 43 women (group A n = 41, group B n = 2) fertility enhancing surgery, including adhesiolysis (n=33), neostomy (n = 12), coagulation or removal of endometriosis (n=8), tubectomy (n=6), cystectomy (n=3) or tubal recanalization (n=3), solely or a combination of 2 or more procedures was carried out.

Discordant findings were seen in 11 women (all group A) (table 2). These 11 laparoscopies were only diagnostic procedures. In six women tubal occlusion alone, one-sided (n=2) or bilateral (n=4), was seen during THL. Tubal spasm was stated as cause of these occlusions. To confirm this finding, laparoscopy was performed and showed indeed bilateral tubal patency in all six women. THL showed bilateral occlusion in one woman in whom the procedure had to be stopped due to pain when applying higher pressure in order to demonstrate patency of the Fallopian tubes. During laparoscopy high perfusion pressure could be given after which unilateral patency could be demonstrated. Another discordant case was left-sided occlusion during THL, whereas laparoscopy showed right-

sided occlusion. Adhesions and bilateral tubal occlusion was seen in one woman during THL, which could not be confirmed by laparoscopy and only minimal endometrioses was seen. Furthermore, one woman was suspected of tubal torsion and subsequently occlusion, which was not seen during laparoscopy. The last discordant case was of mild phimosis of the left patent tube seen during THL, not confirmed by laparoscopy.

Table 2. Discordant findings of THL and laparoscopy

Discordant cases	**THL (tubal patency; endometriosis/adhesions)**	**Laparoscopy (tubal patency; endometriosis/adhesions)**
1	Bilateral tubal occlusion; no endometriosis/adhesions	Bilateral patency; no endometriosis/adhesions
2	Bilateral tubal occlusion; no endometriosis/adhesions	Bilateral patency; no endometriosis/adhesions
3	Right tubal torsion and occlusion; no endometriosis/adhesions	Bilateral patency; no endometriosis/adhesions
4	Right sided tubal occlusion; no endometriosis/adhesions	Bilateral patency; no endometriosis/adhesions
5	One sided occlusion; no endometriosis/adhesions	Bilateral patency; no endometriosis/adhesions
6	Left tube with phimosis but patent; no endometriosis/adhesions	Bilateral patency; no endometriosis/adhesions
7	Bilateral occlusion; no endometriosis/adhesions	Bilateral patency; no endometriosis/adhesions
8	Bilateral occlusion; no endometriosis/adhesions	Bilateral patency; no endometriosis/adhesions
9	Bilateral occlusion; adhesions	Bilateral patency; endometriosis without adhesions
10	Left sided occlusion; no endometriosis/adhesions	Right sided occlusion; no endometriosis/adhesions
11	Bilateral occlusion; no endometriosis/adhesions	Left sided occlusion*; no endometriosis/adhesions

*only after applying high pressure with methylene blue

When all abnormalities were combined (tubal pathology, endometriosis, adhesions or a combination of these findings) in the 64 women who had undergone both THL and laparoscopy, the sensitivity for THL was 100% and the specificity 22.2% (TABLE 3). Kappa was 0.329 ($P < 0.001$), indicating it is a fair agreement. The positive likelihood ratio was 1.29 and the negative likelihood ratio was 0.

Table 3 Outcome of THL versus laparoscopy

			Laparoscopy		
			abnormalities	no abnormalities	Total
THL	abnormalities	N	55	7	62
		% within DLS	100%	77.8%	96.2%
	no abnormalities	N	0	2	2
		% within DLS	0%	22.2%	3.1%
Total		N	55	9	64
		% within THL	85.9%	14.1%	100%

Discussion

This retrospective cohort shows comparable outcomes of THL compared with the outcomes of laparoscopy combined with tubal testing. This corresponds to the results of previous studies (Darai et al., 2000; Dechaud et al., 2001; Nawroth et al., 2001; Watrelot et al., 2003). In these studies women underwent THL under general anaesthesia immediately prior to their scheduled laparoscopy by the same (Nawroth et al., 2001) or different surgeons (Darai et al., 2000; Dechaud et al., 2001; Watrelot et al., 2003). The procedures were performed independently of the findings during THL, whereas in this study laparoscopies were only performed in cases of abnormal findings during THL, which reflects daily practice. The fact that women with normal findings during THL were spared undergoing DLS with tubal testing is in our opinion one of the two major advantages of this technique. The other advantage of THL is that in this outpatient setting, any detected abnormalities can be shown directly to the patient and explained, followed by counselling on the treatment options (surgically or with advanced reproductive techniques), without the need to undergo a DLS under general anaesthesia before the therapeutic step. Moreover, this study shows a high sensitivity of THL of 100% in detection of abnormalities. On the contrary, the specificity of THL of 22.2% in this study was rather low. This can be explained by the fact that just a few women underwent laparoscopy when their THL showed no abnormalities, which was not the case in the above-mentioned studies, where sensitivity and specificity were 88% and 100%, respectively (Watrelot et al., 2003), 92% and 100% (Darai et al., 2000), and 70% and 100% (Dechaud et al., 2001), although the study by Nawroth et al. (2001) showed the same sensitivity of 100% with the same low specificity of 20%. Six women with tubal

spasm during THL still underwent laparoscopy. The conclusion of these THL – no abnormalities, occlusion due to tubal spasm – was similar to the conclusion of the laparoscopies. If these women could be placed in the true-negative group the specificity would be 88.9% (8 out of 9). One can argue that salpingitis isthmica nodosa can also cause proximal tubal occlusion, but with an incidence of 0.6 to 11%, of which only 4% is bilateral (Bolaji et al., 2015), there is a greater chance of occlusion due to tubal spasm. To differentiate between these two conditions, one could administer an intravenous spasmolytic, more commonly given during HSG, but not common practice in the participating hospitals during THL.

Eleven discordant cases were detected. If the above-described cases of tubal spasm are left out, only five discordant cases are left. The findings in these cases were all minor problems without the need for therapeutic laparoscopy or assisted reproductive technology. We think that if THL succeeds there is no place for DLS and that a laparoscopy should only be used for fertility-enhancing procedures. Nevertheless, in some cases only a diagnostic laparoscopic procedure was performed instead of fertility-enhancing surgery. One explanation for these differences is the retrospective design of this study and the fact that gynaecologists followed their local protocol. One hospital performs more fertility-enhancing laparoscopic procedures, whereas another advises undergoing IVF earlier on.

Although this study lacks novelty because there are other prospective studies (Darai et al., 2000; Dechaud et al., 2001; Nawroth et al., 2001; Watrelot et al., 2003), it does reflect daily practice in an outpatient setting in large teaching hospitals. This is pointed out because 16 THL were cancelled just prior to the procedure due to abnormalities during vaginal examination. These were planned by registrars or fertility doctors, who do not perform THL procedures. This stresses the need for good clinical examination and (transvaginal) ultrasound before scheduling a tubal patency test. Furthermore, the procedures of 16 gynaecologists or registrars under strict supervision of a gynaecologist in four teaching hospitals were taken into account as well as all the procedures they performed during their learning curve. Although performance bias cannot be ruled out, our data on failures, complications and findings are true to daily practice. In fact the failure rate is rather high (6.8%) in this study, probably explained by the inclusion of procedures during the learning curve (Coenders-Tros et al., 2016). A striking finding is that if THL failed or was incomplete non-diagnostic, abnormalities during laparoscopy were seen in 28 out of 86 women (32.6%), compared with 55 out of 1017 women with a complete or incomplete evaluation procedure (5.4%). This could indicate that failure of THL is a sign of abnormalities and thus an indication for therapeutic laparoscopy.

When comparing THL to other visual tubal patency tests, HSG has a lower sensitivity of 65% and a higher specificity of 83% (Swart et al., 1995). In subfertile women with a low risk history of tubal pathology the sensitivity is only 13% (Broeze et al., 2011). For hysterosalpingo contrast sonography (HyCoSy) or hysterosalpingo foam sonography (HyFoSy), pooled estimates of sensitivity and specificity are 92% (95% CI 0.82–0.96) and 95% (95% CI 0.90–0.97), respectively (Maheux-Lacroix, 2014). When using a 3D technique (3D-HyFoSy), with or without contrast, pooled estimated sensitivity is 93% (95% CI 87–97) and 100% (95% CI 84–100), respectively, and pooled estimated specificity is 92% (95% CI 84–96) and 89% (95% CI 75–96), respectively (Alcázar et al., 2016). Adding a high-definition flow technique (HDF-HyFoSy), the sensitivity might even be as high as 95.8% with a specificity of 97% (Ludwin et al., 2017). Looking at failure and complication rate, HSG and HyCoSy or HyFoSy have a better performance compared with THL. In our recently published randomized trial comparing THL and HSG (Tros et al., 2019), the failure rate was 5.4% in the THL group compared with

only 0.7% in the HSG group, with a complication rate of 2.7% and 0.7%, respectively. Failure rate for sono-hysterosalpingography (sono-HSG includes all types of HyCoSy and HyFoSy combined) is 1.3–1.5% (Ludwin et al., 2017; Savelli et al., 2009). Complications described in sono-HSG are (severe) vasovagal reaction or severe pain in 0.8–2.0% (Savelli et al., 2009). The disadvantage of these techniques is the high percentage of inconclusive test results. Dependent on the type of sono-HSG performed, inconclusive test results are seen in 6.1–21.9% of women (Dreyer et al., 2014; Emanuel et al., 2012; Ludwin et al., 2017). Another disadvantage is the interobserver variability, together with the fact that accuracy depends on the experience of the investigators (Exacoustos et al., 2009; Maheux-Lacroix et al., 2014). Pain scores for THL and HSG are comparable (Tros et al., 2019) but HyFoSy is significantly less painful (VAS median 1.7 cm, IQR 2.1) compared with HSG (median 3.7 cm, IQR 4.2) ($P < 0.01$) (Dreyer et al., 2014).

A tubal patency test is expected to be able to differentiate between subfertile women who may benefit from early (laparoscopic/fertility) treatment compared with those women not requiring any surgery. Van Kessel et al. (2018) showed that in the group of women with patent tubes, those with endometriosis and/or adhesions diagnosed at THL had a significantly lower chance of conceiving a non-IVF pregnancy compared with those with no abnormalities, which emphasizes the need for early detection of these abnormalities. Thus women who undergo fertility investigation according to a protocol that recommends HSG as tubal patency testing followed by laparoscopy if required, exposes women who require laparoscopy to a delay before accurate diagnosis and definitive treatment. This is reflected by the difference in sensitivity of THL versus HSG. The question is whether and when women with low risk of tubal pathology (e.g. negative CAT and no history of gynaecological disorders or abdominal surgery) should undergo tubal testing and if so, which tubal test. This also depends on the treatment options given afterwards (fertility-enhancing surgery, intrauterine insemination or IVF) and the wishes of the woman. The answer to this is still open to debate. We are aware that the retrospective character of this study, with a small number of women undergoing both procedures, as well as not following the same protocol, weakens our results. Furthermore, one must keep in mind that selection bias cannot be avoided, which might overestimate the performance of THL. Nonetheless, based on our findings THL can be considered as one of the options for tubal patency testing.

This study shows that THL can detect abnormalities in high concordance with the current, more invasive, reference standard laparoscopy. Furthermore, failure of THL in experienced hands is mostly related to abnormalities. When THL succeeds, there is no need to perform DLS.

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Chapter 4

The capacity of transvaginal hydrolaparoscopy versus hysterosalpingography to diagnose tubal pathology in the work-up of subfertile women, a randomised clinical trial.

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Abstract

Objective: To assess the capacity of transvaginal hydrolaparoscopy (THL) versus hysterosalpingography (HSG) as a primary tool to diagnose tubal pathology.

Study Design: We performed a multicenter RCT (NTR3462) in 4 teaching hospitals in the Netherlands, comparing THL and HSG as first line tubal test in subfertile women. The primary outcome of the trial was cumulative live birth rate at 24 months. Here, we present the secondary outcomes, the diagnostic findings of both THL and HSG as well as performance defined as failures, complications and pain- and acceptability scores.

Results: Between May 2013 and October 2016, we allocated 149 women to THL and 151 to HSG, of which 17 women in the THL group (11.4%) and 12 in the HSG group (7.9%) conceived naturally before the scheduled procedure, while 13 HSGs and 5 THLs were not performed for other reasons (withdrawal of informed consent, not willing to undergo tubal testing and protocol violations). A total of 119 THLs and 134 HSGs were carried out. Failures were seen more in the THL group (n=8, 5.6%) than in the HSG group (n=1, 0.7%) (p=0.014). Complications did not differ significantly between the groups (THL n=4; 2.8% vs HSG n = 1; 0.7%) (p = 0.20). Bilateral tubal occlusion was detected in one versus three women (0.9% versus 2.2%) of the THL group and HSG group, while unilateral tubal occlusion was detected in seven (6.2%) versus eight (5.9%) women, respectively. Normal findings were seen in 96 (79.3%) women randomised to THL and in 119 (87.5%) in women randomised for HSG (RR 0.91 95%CI 0.81 to 1.01, p = 0.08). The pain score was significantly less for THL (VAS 4.7 (SD: 2.5)) than for HSG (VAS 5.4 (SD:2.5)) (p 0.038). The acceptability rate of THL and was high and comparable.

Conclusion: THL and HSG have a comparable capacity in diagnosing tubal pathology with comparable performance in safety, pain and acceptability.

Introduction

Tuboperitoneal pathology is found in around 15–25% of subfertile women [1–4]. To assess tubal function in these women, various diagnostic tests are available, of which hysterosalpingography (HSG) and transvaginal hydrolaparoscopy (THL) are both used. HSG was first described in 1914 by Carey [5]. HSG has a sensitivity of 65% and a specificity of 83% for diagnosing tubal pathology [6] and is in the Netherlands traditionally followed by diagnostic laparoscopy (DLS) if the HSG is abnormal or if a couple fails to conceive naturally after expectative management of 6–12 months. THL on the other hand, was first described in 1998 by Gordts [7]. THL uses the transvaginal route and allows direct visualization of the pelvic cavity and tubes. Just like HSG, it can be carried out in an outpatient setting as a primary tool to assess tubal patency as well as to rule out other tuboperitoneal pathology such as endometriosis and adhesions. Sensitivity of THL is assessed as 70–100% and specificity as 100% [8–10].

Currently, HSG and THL have never been compared directly in RCTs. While THL seems promising, it is unclear what its effectiveness and costs are relative to the current first line diagnostic strategy, HSG. In view of this knowledge gap, we conducted a randomised trial on the subject.

Methods and materials

Trial oversight

The study was approved was by the institutional review board of the Amsterdam UMC location AMC Amsterdam, case number NL41088.018.12 and study number 2012_174, and by the board of directors of each of the participating hospitals. The Trial was registered in the Dutch trial register (NTR3462). All women provided written informed consent. Data collection and monitoring was performed according to Good Clinical Practice guidelines.

Trial participants

We included women trying to conceive for more than 12 months, who were over 18 years of age, in whom a transvaginal ultrasound performed in the follicular phase of the menstrual cycle showed no abnormalities and who had both ovaries present [11]. Women with positive Chlamydia status at PCR, prior tubal testing, women with a fixed retroverted uterus, masses in the pouch of Douglas or ovarian cysts (possibly interfering with THL), prior tubal surgery or a iodine or methylene blue allergy, were not eligible.

Trial randomization and intervention

Potential participants were recruited in four Dutch teaching hospitals (Amsterdam, Nieuwegein, Zwolle and Veldhoven). Women were informed about the trial by their doctors or dedicated research nurses. After providing written informed consent, eligible women were randomly allocated to a strategy starting with THL (experimental arm) or a strategy starting with HSG (control arm). An online and secured randomization program (Alea, FormsVision) with a permuted-block design, stratified for recruiting centre, was used for randomization. THL and HSG were scheduled in the follicular phase of the menstrual cycle. From the first day of the menstruation until the appointment of the tubal test,

the women were told to abstain from unprotected sexual intercourse. Furthermore, they were instructed to take paracetamol and a non-steroidal anti-inflammatory drug two hours beforehand.

THL

THL was performed as described previously [12] in an outpatient setting. If a THL failed or was inconclusive an additional DLS had to be performed.

HSG

HSG was performed in the radiology department according to hospital specific protocols, by either gynaecologist, residents or fertility doctor. Laparoscopy after THL or HSG If a THL failed or was inconclusive an additional DLS had to be performed. When abnormalities were seen at HSG or when the initial test failed or failed to show a reliable result, a DLS had to be scheduled. Subsequently, in women with a normal HSG, a DLS had to be planned if a pregnancy did not occur after 6–12 months.

Management after THL or HSG

Subsequent management was comparable, with obviously management in the HSG-arm based on the HSG result and in the THL-arm on the THL result. Women were treated according to the Dutch national guidelines for subfertility [13].

Outcome measures

The primary outcome of this RCT was conception leading to a live born child within 24 months. As the follow-up of our trial for the primary endpoint was still ongoing at the time of writing, we here focused on secondary outcomes. These were diagnostic findings and performance of both procedures in terms of failures and complications. Failure of THL was defined as the inability to reach the pouch of Douglas. Failure of HSG was defined as the inability to infuse contrast into the uterus. Other secondary outcome measures were pain scores on a visual analogue scale (VAS) from zero (no pain) to ten (unbearable pain) and acceptability for patients. The latter was defined as the willingness to undergo the same procedure under the same circumstances again and as the willingness to recommend the procedure to friends or family on a VAS from zero (total willingness, total recommendation) to ten (no willingness nor recommendation at all).

Statistical methods

Baseline patient characteristics were reported as absolute number and percentage for categorical variables, and mean and standard deviation (SD) and median and interquartile range for normally and non-normally distributed continuous variables. Descriptives of outcome variables within both groups were reported as absolute number and percentage, and mean and standard deviation. The independent t-test was used to compare continuous outcomes (VAS, time between randomisation and procedure) between groups. Fisher's exact test was performed to compare the proportion of women experiencing complications (bowel perforation, bladder perforation, bleeding, anaphylactic shock), because of the small cell expected counts. The same applied to the assessment of differences of failures, to the assessment of the number of laparoscopies (DLS) and to the assessment of concordance of the findings with DLS. In addition, the difference DLS between groups and the difference in the number of abnormal findings between water- and oil-based contrast within the HSG

groups were quantified as relative risk including 95% confidence interval (CI). All analyses were performed according to the intention to treat principle. Statistical analysis were performed using SPPS for Windows version 24.0 (IBMCorp., USA) and R version 3.3.3. P-values below 0.05 were considered to indicate statistical significance.

Sample size

The sample size calculation was performed for the primary outcome of the main paper on this RCT: the percentage of women with a live born child within 24 months after randomization. We assumed a live birth rate of 70% in both groups. The initially planned 1330 women (665 per arm) would have allowed us to exclude a difference larger than 6%, which was considered to be clinically meaningful by the clinical investigators in favor of the HSG strategy (alpha 0.05, beta .80).

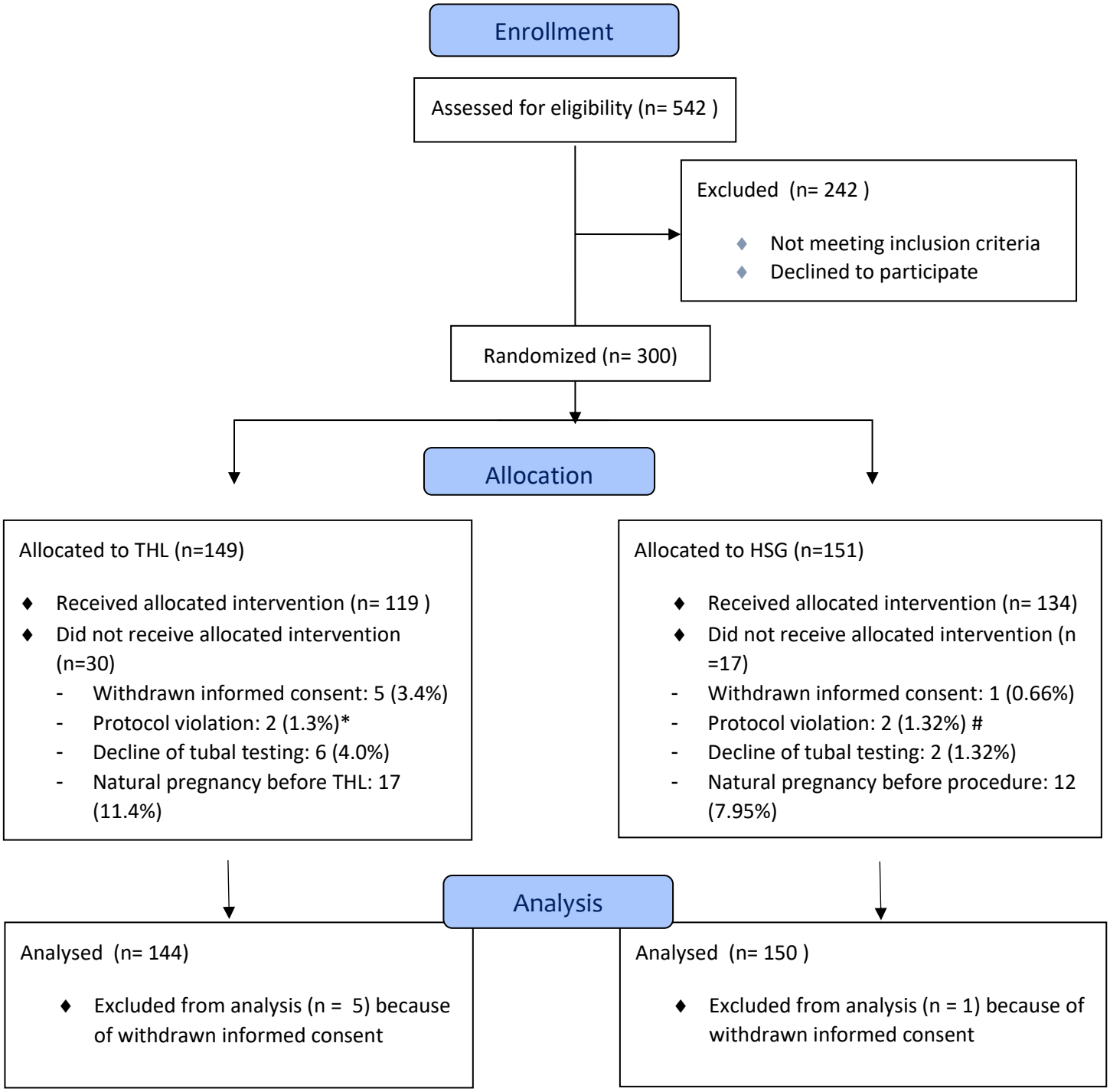
Results

From May 2013 to November 2016, 542 women were approached, of whom 242 were not eligible or declined to participate. A total of 300 women were randomised to a strategy starting with THL (n = 149) or a strategy starting with HSG (n = 151). Because the inclusion rate was slower than anticipated, and because external funding could not be obtained, the study was halted after inclusion of 300 women, despite that the calculated sample size was not met. Five women in the THL group and one in the HSG group withdrew their informed consent. Thus leaving 144 women in the THL group and 150 women in the HSG group (Fig. 1). Baseline characteristics of the two groups were comparable (Table 1).

Performance

In the THL group 119 out of 149 women (79.9%) randomized to THL underwent the allocated procedure whereas 134 out of 151 women (88.75%) randomised to HSG underwent the allocated procedure (Fig. 1). The women who underwent the other procedure than randomised for (n = 2 in THL group and n = 2 in HSG group) were analysed according to randomization result. The mean time between randomisation and THL was 42.7 days (SD: 59.0 days) and for HSG 24.9 days (SD: 23.8 days). The mean time difference between randomisation and HSG compared to THL was 17.9 days (95% CI 6.6–29.1; p = 0.002). Other procedure characteristics are shown in Table 2. THL could not be completed or failed in eight women (5.4%), while failure happened once in the HSG group (0.7%). The number of failed procedures was significantly higher in the THL group (n = 8; 5.4%) than in the HSG group (n = 1; 0.7%) (p = 0.014) (Table 2). Four (2.7%) women suffered complications after THL versus one (0.7%) after HSG (Table 3). This difference in complications was not statistically significant (p = 0.20). The mean VAS score for pain during the THL procedure was 4.7 (SD: 2.5) and during HSG the VAS score for pain was 5.4 on average (SD: 2.5) (mean difference of -0.71 (95% CI -1.38 to -0.041; p = 0.038)). The acceptability, defined as the willingness to undergo the same procedure under the same circumstances again and as the willingness to recommend the procedure to friends or family, was high for both procedures and did not differ. For both scores, a score of zero meant total willingness or recommendation respectively, whereas a score of ten meant no willingness nor recommendation at all. The willingness to undergo the procedure again was rated 2.6 (SD: 3.1) in the THL group versus 2.0 (SD: 2.6) in the HSG-group (difference: 0.6, 95% CI -0.204-1.353, p = 0.395). The average recommendation score was 2.1 (SD: 2.6) for the THL-group versus 2.2 (SD: 2.7) for the HSG-group (difference: -0.1, 95%CI -0.820-0.575, p = 0.729).

Figure 1 Follow-up per randomization



*two women underwent HSG because of a longer waiting period for the THL, but were analysed in the THL group according to the intention to treat principle.

one woman (0.66%) opted to undergo THL and one women (0.66%) underwent THL as the gynaecologist advised against HSG because of a recent chlamydia infection. These two women were analysed in the HSG group according to the intention to treat principle.

Table 1 Baseline characteristics

Women n = 294	**THL (n= 144)**	**HSG (n=150)**
Mean age (years; ± SD)	31.6 (±3.9)	31.9 (±4.0)
Median BMI (kg/m²; IQR)	23.4 (21.0-26.9)	23.3 (21.2-26.2)
Intoxications: Smoking (%) Use of alcohol (%) Use of drugs (%)	• 18.8% • 25.7% • 0.7%	• 16.7% • 29.3% • 0.7%
Median duration of subfertility (months; IQR)	19 (16-26)	22 (17-30)
Primairy subfertile (%)	71.0%	82.7%
Positive Chlamydia serology (%)	11.1%	10.7%
Ovulatory cycles (%)	75.0%	86.0%
Median VCM semenanalysis (x 10^6; IQR)	47.5 (17.3-98.5)	51.0 (22-118.0)

Table 2 Procedure characteristics

	THL n = 121 (%)	**HSG n = 134 (%)**
Procedure performed by: I. Gynaecologists II. Residents III. Fertility doctors	I. 120 (99.2%) II. 1 (0.8%) III. 0 (0%)	I. 48 (35.8%) II. 17 (12.7%) III. 69 (51.5%)
Antibiotic prophylaxis	1 (0.8%)	4 (3.0%)

Contrast medium: I. Water II. Oil	n.a.	 I. 88 (65.2%) II. 47 (34.8%)

Table 3 Failures and complications

	THL n = 144 (%)	**HSG n = 150 (%)**
Failure due to: I. peritoneal tenting II. poor visualization of fornix posterior and cervix III. pain of speculum	Total n = 8 (5.6%)* I. 5 (3.5%) II. 2 (1.4%) III. 1 (0.7%)	Total n = 1 (0.7%)# I. 0 (0%) II. 0 (0%) III. 1 (0.7%)
Complication: I. Bleeding of vaginal wall that needed suturing II. Rectal perforation III. Prolonged period of pain requiring painkillers IV. Overnight hospital admission due to cervical bleeding	Total n = 4 (2.8%) I. 2 (1.4%) II. 1 (0.7%) III. 1 (0.7%) IV. 0 (0%)	Total n = 1 (0.7%) I. 0 (0%) II. 0 (0%) III. 0 (0%) IV. 1 (0.7%)

*Four of these women underwent HSG subsequently, one underwent a DLS with chromopertubation. The other three women did not undergo further tubal testing.

This woman did not undergo further tubal testing.

Findings

THL was completely normal with bilateral tubal patency in 96 of 121 women (79.3%) undergoing THL. Abnormalities were seen in 17 women (14.0%) (Table 4). Out of 136 HSG-procedures, 119 women (87.5%) had bilateral tubal patency without other abnormalities (Table 4). Of women in whom oil-based contrast was used, we observed 2 abnormalities (4.3%) compared to 14 (15.9%) in women in whom water-based contrast was used. Nine women of the THL group with bilateral tubal patency were detected with abnormalities (endometrioses n = 5, adhesions n = 3, cyst n = 1. In the HSG group in 5 women with bilateral patent tubes abnormalities were found (intrauterine abnormalities n = 3, hydro- salpinx n = 2). A total of eight laparoscopies were carried out (6.6%) in the 121 women of the THL group with a therapeutic laparoscopy in six of them (5.0%) (Table 5). Laparoscopic tubal findings were concordant with THL tubal findings in 5 out of 7 women (71.4%) in whom THL succeed. DLS was performed in 22 (16.2%) of the 136 women who successfully underwent HSG, twelve of which were therapeutic laparoscopies (8.8%) (Table5). Concordant results in detection of tubal pathology was seen in 61.9% (n = 13) of the laparoscopies after HSG. In the HSG group significantly more often DLS

were performed (16.2% versus 6.6%, RR = 2.9, 95% CI: 1.32–6.23; p = 0.007). The concordance in findings during the initial tubal test and DLS later on did not differ significantly between the THL and HSG group (p = 1.00). With 79.3% normal findings in the THL group versus 87.5% in the HSG group, there might be a trend towards finding more abnormalities with THL although not significantly (RR 0.91; 95%CI 0.81–1.01, p = 0.08).

Table 4 Findings of THL and HSG

Findings	THL (n= 121)	HSG (n=136)	p-value
Bilateral tubal patency and no abnormalities	79.3% (n = 96)	87.5% (n = 119)	0.08
Unilateral tubal patency	5.8% (n = 7) Of which with adhesions 1.7% (n = 2)	5.9% (n = 8) Of which with intra uterine abnormality 0.7% (n = 1)	
Bilateral tubal occlusion	0.8% (n = 1) Of which with adhesions 0.8% (n =1)	2.2% (n = 3) Of which with bilateral hydrosalpinx 0.7% (n = 1)	
Bilateral tubal patency with other abnormalities: • Adhesions • Endometriosis • Intrauterine abnormalities • Hydrosalpinx • Cyst	7.4% (n = 9) 2.5% (n = 3) 4.1% (n = 5) n.a. n.a. 0.8% (n = 1)	3.7% (n = 5) n.a. n.a. 2.2% (n = 3) 1.5% (n = 2) n.a.	
Unknown due to failure	6.6% (n = 8)	0.7% (n = 1)	0.014

Table 5 Findings laparoscopy

Findings in initial test	**THL (n = 8) or HSG (n = 22)**	**Reason for DLS**	**Findings DLS**	**Laparoscopic procedure**
Bilateral tubal patency and no abnormalities	THL (n = 1)	Abdominal pain	Bilateral tubal patency with only a ovarian cyst (dls performed 14 months after THL)	Cystectomy
	HSG (n = 12)	I. No naturally conceived pregnancy after expectant management of >6 months (n = 11) II. Ectopic pregnancy (n = 1)	I. -Concordant to initial test (n = 6) -Endometrioses ASRM grade I (n = 4) -Bilateral tubal occlusion with adhesions (n = 1) II. Ectopic pregnancy	I. -diagnostic (n = 6) -coagulation of endometrioses (n = 2) combined with adhesiolysis (n = 1) - leftsided tubectomy and rightsided tuboneostomy with adhesiolyses II. tubectomy
Unilateral tubal patency	THL (n = 1)	Abnormal THL	Bilateral tubal occlusion with hydrosalpinges	Tuboneostomy at both sides

	HSG (n = 5)	I. Abnormal HSG (n = 4) II. Inconclusive HSG (n = 1)	I. -Unilateral tubal patency with endometrioses (n = 1) -Bilateral tubal patency with endometrioses (n = 1) - Bilateral tubal patency with endometrioses and adhesions (n = 1) -Rudimentary uterine horn leftsided(n = 1) II. anatomic abnormality with a missing right tube and an inactive right ovary	I. -coagulation of endometrioses -coagulation of endometrioses -adhesiolyses and coagulation of endometrioses - clip placement on Fallopian tube left II. diagnostic
Bilateral tubal occlusion	THL (n = 1)	Abnormal THL	Bilateral tubal patency with endometrioses and adhesions	Adhesiolysis and coagulation of endometrioses
	HSG (n = 4)	I. Abnormal HSG (n = 3) II. Inconclusive HSG (n = 1)	I. -Bilateral tubal occlusion (n = 1) -Bilateral patency with endometrioses (n =2)	I. -diagnostic -coagulation of endometrioses (n=2)

			II. Bilateral tubal patency and no abnormalities	II. diagnostic
Bilateral tubal patency with other abnormalities	THL (n = 3)	Abnormal THL: I. endometrioses (n = 2) II. adhesions (n = 1)	I. bilateral tubal patency and endometrioses (n = 2) II. bilateral tubal patency and no abnormalities	I. coagulation of endometrioses (n =2) II. diagnostic
	HSG (n = 1)	Abnormal HSG (suspicion of adhesions)	Endometrioses	Coagulation of endometrioses
Unknown due to failure / inconclusive	THL (n = 2)	I. Failure (n = 1) II. Inconclusive due to adhesions in Douglas (n = 1)	I. bilateral tubal patency and endometrioses II. bilateral tubal occlusion and adhesions	I. coagulation of endometrioses II. diagnostic
	HSG (n = 0)			

Discussion

In this randomised trial, we showed that THL and HSG as primary invasive diagnostic tool in a low risk group of subfertile women, have a comparable capacity in terms of diagnosing tubal pathology and performance. With THL a DLS might be avoided but to the cost of a higher failure rate compared to HSG. Furthermore, THL is associated with a slight advantage in pain scores but HSG is found as acceptable as THL. To our knowledge, this is the first study comparing these two strategies as first invasive tubal test. Other studies comparing outpatient THL with HSG, performed both procedures in the same woman after HSG showed abnormalities [14–18], most of them retrospective studies. Cincinelli et al. [19] performed a small RCT with 23 women who underwent subsequently HSG and THL in whom the investigation sequence was randomized. They showed a lower pain score for THL compared to HSG with concordant results in 95.5%. Our study has limitations. The biggest limitation is the fact that the study is powered on our primary outcome and our sample size was not met. The latter was caused by the fact that the inclusion rate was much lower than anticipated, and attempts to fund our study to be able to continue recruiting were not successful. Furthermore, in this study we only included subfertile women with low risk for tubal disease. This might limit the generalizability in populations with high risk for tubal disease. Next, we observed a much higher DLS in the HSG group, which can be due to our study protocol, which stated that a DLS had to be performed after expectant management of six months or more when the Hunault model calculated a >30% chance of getting pregnant in 12 months. Nevertheless, DLS showed abnormalities in 5 out of 11 women with normal HSG. The disadvantage of THL is the high failure rate compared to HSG. This study shows a THL failure rate of 5.6%, which is comparable to known literature when THL is performed by experienced gynaecologists [20,21] and lower than during the learning curve of these gynaecologists [12]. The advantage of THL however, is that it tends to be able to show abnormalities as adhesions and endometriosis [22]. In our study population with low risk of tubal disease, we found adhesions and endometriosis in 7.1% despite the fact that the tubes were patent. In our opinion THL can be of benefit to these women as they might be helped with early treatment instead of expectant management. Van Kessel et al. showed a fecundity rate ratio of 0.42, which means less probability of a spontaneous intrauterine pregnancy per time unit for women with patent tubes but with the combination of endometriosis and adhesions, compared to women without endometrioses and adhesions [23]. On the other hand, however, HSG shows intrauterine abnormalities, that THL cannot detect. Furthermore, the usage of oil-based contrast during HSG could have had a therapeutic effect [24]. While we conclude that THL and HSG have a comparable diagnostic performance, with each of the procedures having a specific benefit, we have to wait for the live birth rates in both groups. This will determine whether one procedure should be preferred over the other.

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Chapter 5

Transvaginal hydrolaparoscopy versus hysterosalpingography in the work-up for subfertility: a randomized controlled trial.

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Key message

In subfertile women with a low risk of tubal pathology, a strategy for tubal patency testing using transvaginal hydrolaparoscopy was not inferior to a strategy using hysterosalpingography in predicting conception leading to a live birth or time to live birth at 24 months after randomization.

Abstract

Research question: Is transvaginal hydrolaparoscopy (THL) non-inferior to hysterosalpingography (HSG) as a first-line tubal patency test in subfertile women in predicting the chance of conception leading to live birth?

Design: A multicentre, randomized controlled trial in four teaching hospitals in the Netherlands, which randomized subfertile women scheduled for tubal patency testing to either THL or HSG as a first-line tubal patency test. The primary outcome was conception leading to live birth within 24 months after randomization.

Results: A total of 149 women were randomized to THL and 151 to HSG. From the intention-to-treat population, 83 women from the THL group (58.5%) conceived and delivered a live born child within 24 months after randomization compared with 82 women (55.4%) in the HSG group (difference 3.0%, 95% CI –8.3 to 14.4). Time to conception leading to live birth was not statistically different between groups. Miscarriage occurred in 16 (11.3%) women in the THL group, versus 20 (13.5%) women in the HSG group (RR = 0.66, 95% CI 0.34 to 1.32, P = 0.237), and multiple pregnancies occurred in 12 (8.4%) women in the THL group compared with 19 (12.8%) women in the HSG group (RR = 0.84, 95% CI 0.46 to 1.55, P = 0.58). Ectopic pregnancy was diagnosed in two women in the HSG group (1.4%) and none in the THL group (P = 0.499).

Conclusion: In a preselected group of subfertile women with a low risk of tubal pathology, use of THL was not inferior to HSG as a first-line test for predicting conception leading to live birth.

Introduction

Subfertility affects approximately 1 in 10 couples worldwide (Boivin et al. 2007, Datta et al. 2016), and tubal factors play a role in approximately 10-25% of them, depending on the duration of subfertility (Wilkes et al. 2009). Tubal pathology can be caused by infection such as Chlamydia Trachomatis, by adhesions due to previous surgery, or by endometriosis. In view of this, tubal testing is widely accepted as part of the first line diagnostic work-up for subfertility.

Hysterosalpingography (HSG) is traditionally performed as a first line tubal patency test. In a meta-analysis, HSG had a sensitivity of 46% and a specificity of 95% for the diagnosis of bilateral tubal pathology, with sensitivity of HSG being significantly lower in low-risk than in high-risk women (Broeze et al. 2011). Diagnostic laparoscopy has long been considered to be the 'gold standard' for tubal testing, but it is an invasive procedure, and it requires general anaesthesia. Transvaginal hydrolaparoscopy (THL) is an outpatient endoscopic technique, in which access to the pouch of Douglas is obtained by culdocentesis using the transvaginal route (Gordts et al. 1998). It allows a similar assessment of the pelvic cavity as with laparoscopy, including testing the patency of the tubes, and the presence of other pelvic pathology such as adhesions, endometriosis or an impaired tubo-ovarian contact. Different prospective studies comparing THL and laparoscopy in in subfertile women showed a high degree of concordance between the procedures (Campo et al. 1999, Casa et al. 2002, Watrelot et al. 2003).The diagnostic accuracy of THL compared to HSG has been validated in several studies and the agreement on tubal patency testing between the two procedures is good (Shibahara et al. 2001, Balsak et al. 2004). Compared with HSG, THL has been found to have a comparable diagnostic performance when used as a first-line test in subfertile women (Tros et al., 2019). Comparing HSG to THL, THL is superior in diagnosing endometriosis and peritubal adhesions (Shibahara et al. 2001, Cicinelli et al. 2001, Tros et al. 2019), whereas HSG gives more information about the uterine cavity. Transvaginal hydrolaparoscopy carried out under local anesthesia is well tolerated by the patient (Giampaolino et al. 2015) and in two randomized controlled trials, patients undergoing THL were found to have lower painscores than those undergoing HSG (Cicinelli et al. 2001, Tros et al. 2019).

The most important aspect of tubal testing however, is its prognostic capacity: it has to distinguish between women who can conceive a natural pregnancy and women who have a strongly reduced chance of conceiving, and therefore may need IVF or tubal surgery. Studies on the prognostic capacity of HSG have shown that women with unilateral tubal patency compared to women with bilateral patent tubes had only a mild reduction in the chance of a natural conceived pregnancy, whereas women with bilateral tubal occlusion had a significantly reduced chance of a natural conceived pregnancy (Mol et al. 1999, Verhoeve et al. 2011). Our previous study showed that, with THL as a first-line test, the likelihood of non-IVF conception is significantly reduced in women with bilateral tubal occlusion and in women with endometriosis and adhesions(van Kessel et al. 2018).

Although THL gives more information about pelvic abnormalities than HSG, it is unknown if this additional information leads to better treatment guidance for the subfertile couple. No studies have directly compared fertility outcomes after HSG and THL. In view of this, a randomized controlled non-inferiority trial was conducted to compare live birth rates in subfertile women undergoing tubal patency testing with transvaginal hydrolaparoscopy or HSG.

Materials and methods

Ethical approval

The study was conducted according to Good Clinical Practice guidelines. The study protocol was approved by the Institutional Review Board of the Amsterdam Medical Center (AMC, Amsterdam, the Netherlands) on 27 November 2012, and by the boards of directors of the other hospitals. The trial was registered in the Dutch Trial Registry (NTR3462). In each of the participating centres, patient counselling, data collection and monitoring was carried out by dedicated research nurses. All women provided written informed consent before randomization. The first patient was enrolled on 21 May 2013.

Study Population

Women were eligible for participation if they were undergoing a fertility work-up for subfertility with an indication for evaluation of tubal patency. Subfertility was defined as the non-occurrence of pregnancy after at least 1 year of unprotected intercourse. During their fertility work-up, couples had a complete history taken, a gynaecological examination, a transvaginal ultrasound in the follicular phase of the cycle and assessment of ovulation. Semen analysis was carried out at least once for each male partner.

Women were not eligible if they had a contraindication for THL, i.e. positive chlamydia polymerase chain reaction, before tubal testing or before tubal surgery, an immobile uterus or a retroverted uterus, evidence of endometriosis, masses or cysts in the pouch of Douglas or ovarian cysts interfering with THL. Women with a known allergy to iodine or methylene blue were not included.

Study design

Potential participants were recruited in four Dutch teaching hospitals (Amsterdam, Nieuwegein, Zwolle and Veldhoven). Eligible women were informed about the study by dedicated research nurses. After providing written informed consent, women were randomly allocated to a strategy starting with THL (experimental arm) or with HSG (control arm). Randomization was carried out by the doctors or research nurses with the use of a secure online randomization programme (ALEA, FormsVision), with random block sizes of two or four, stratified according to hospital.

Interventions

For women allocated to THL, the procedure was scheduled in the follicular phase of the menstrual cycle and carried out as described by Gordts et al. (1998). Two of the participating hospitals used the Storz re-usable system (KARL STORZ, Tuttlingen, Germany) and two used the disposable Fertiloscope (Fertility Focus, Warwick, UK). The procedure was carried out in an outpatient department. After inserting a speculum, the central part of the posterior cervix was infiltrated with a local anaesthetic. A tenaculum was placed on the posterior cervix and a balloon catheter was placed in the uterine cavity for chromopertubation.

Local anaesthesia was administered in the vaginal vault, 1–2 cm below the cervix. A small incision was made, and the trocar system was introduced. A Veress-like needle was inserted by a special needle loading system. Progressively, the dilatators and trocar were inserted into the pouch of

Douglas and replaced by a rigid 2.7-mm, wide-angel 30 optical system, and the pelvis was irrigated by a continuous infusion with warmed saline solution. The investigation started at the posterior uterine wall and moved laterally to identify the tubo-ovarian structures on the right and the left side consecutively. The ovarian surface was inspected first and, subsequently, the ovarian ligament, the ovarian fossa and the dorsal part of the ovary. Next, the fimbrial part of the Fallopian tubes and the tubo-ovarian contact were inspected. A dye test was conducted to test the patency of the tube. Throughout the whole procedure, continuous irrigation with warm saline kept the bowel and the tubo-ovarian structures afloat enabling clear vision. After the procedure, the fluid was drained from the pouch of Douglas. The puncture site in the posterior fornix was not sutured unless active bleeding was noted.

Hysteroscopy can be carried out directly after THL using the same optic and, in some hospitals, hysteroscopy is a systematic part of the procedure. In the present study, however, an additional office hysteroscopy was only carried out in case of suspected uterine anomaly or intrauterine pathology on ultrasound. In women allocated to THL, an additional diagnostic laparoscopy was carried out either if THL was inconclusive or if, during THL, the pouch of Douglas was not reached.

In women allocated to HSG, the procedure was scheduled in the follicular phase of the next cycle. The procedure was carried out in the radiology department according to hospital-specific protocols, by gynaecologists, residents or fertility doctors. The contrast medium (either water-soluble contrast) (Telebrix Hystero) (Guerbet, Villepinte, France) or oil-soluble contrast (Lipiodol Ultra-Fluide, Guerbet), according to hospital-specific protocols, was infused into the uterus with the use of a cervical vacuum cup, metal cannula (hysterophore) or balloon catheter. During the infusion of about 5–10 ml of contrast medium, four to six radiographs were obtained to evaluate the uterine cavity and the patency of both Fallopian tubes. The radiographs were examined by a gynaecologist, radiologist, or both.

In women assigned to HSG, an additional diagnostic laparoscopy was carried out when the HSG showed abnormalities, i.e. one-sided tubal occlusion, two-sided tubal occlusion or adhesions, or if HSG failed to show a reliable result. Furthermore, in women with a normal HSG, a diagnostic laparoscopy was scheduled if a pregnancy did not occur after 6–12 months, to rule out pelvic abnormalities that were not noticed by HSG.

Additional treatment

After completing the fertility work-up and tubal assessment, women were treated according to the National guideline of Dutch Society of Obstetrics and Gynecology 2021 (www.nvog.nl). In general, when no tubal pathology was evident, expectant management was advised when the probability of natural conception within 12 months was greater than 30% (Hunault et al., 2004). In couples with a probability less than 30%, intrauterine insemination with mild ovarian stimulation was advised. It was also advised in the presence of mild male subfertility (total motile sperm count 3–10 million), or after a period of expectant management without natural conception.

When severe tubal pathology was diagnosed, or when the couple did not conceive after three to six cycles of intrauterine insemination, couples were counselled for IVF or intracytoplasmic sperm injection. In women with hydrosalpinges, endometriosis or severe adhesions, surgery was scheduled for fertility-enhancing laparoscopic surgery.

Outcomes

The primary outcome was a conception leading to live birth within 24 months after randomization. Secondary outcomes were time to conception leading to live birth, miscarriage, ectopic pregnancy, multiple pregnancy and complications.

Data collection

In each of the participating centers, data were collected and monitored by dedicated research nurses.

Statistical Methods

Baseline characteristics of the participating women, stratified by allocation, were described using mean and SD for continuous variables and count and percentage for categorical variables. The prevalence of abnormalities found with THL and HSG were described using count and percentage. The primary outcome, the difference in conception leading to live birth within 24 months after randomization, was computed, including a 95% confidence interval.

For the secondary outcomes, Kaplan–Meier curves were constructed to assess the difference between groups in time to pregnancy and time to conception leading to live birth. The Log-rank test was used to test for differences in time to event between both groups.

Miscarriage and ectopic pregnancy within 24 months after randomization were compared with Pearson's Chi-squared test to assess differences in proportion. Fisher's exact test was used to assess differences in the proportion of women experiencing complications, i.e. bowel perforation, bladder perforation, bleeding and anaphylactic shock, because of the small cell counts.

All analyses were conducted according to intention-to-treat method. For the primary outcome, results were also computed according to the protocol that they received as a sensitivity analysis (per protocol). IBM SPSS version 26.0 and R version 3.3.3 were used for statistical analyses. P = 0.05 or lower was considered to be statistically significance.

Sample size calculation

For the sample size calculation, a 24-month live birth rate of 70% was assumed in both groups. To demonstrate non-inferiority of THL over HSG with a non-inferiority limit of 6%, 665 women were included per arm (total 1330) (alpha = 0.05, beta = 0.80).

As funding could not be obtained for the study, the study was limited to four centres, resulting in a slower than anticipated inclusion rate, and recruitment was halted after 300 inclusions.

Results

Trial participants

Between May 2013 and October 2016, 542 subfertile women were screened for eligibility in the trial, of whom 300 met the inclusion criteria and were willing to participate in the trial. Of these 300 women, 149 were randomly assigned to THL and 151 were assigned to HSG.

After randomization, five women in the THL group and one woman in the HSG group withdrew their informed consent, leaving 144 and 150 women for analysis. Baseline characteristics of the two groups are presented in TABLE 1.

TABLE 1 BASELINE CHARACTERISTICS

Characteristic	**THL (*n* = 144)**	**HSG (*n* = 150)**
Mean female age, years (+ SD)	31.6 (+/–3.9)	31.9 (+/–4.0)
Median BMI, kg/m^2 (IQR)	23.4 (21.0– 6.9)	23.3 (21.2–26.2)
Intoxications, *n* (%)		
• Smoking	27 (18.8)	25 (16.7)
• Alcohol	37 (25.7)	44 (29.3)
• Drugs	1 (0.7)	1 (0.7)
Type of subfertility, *n* (%)		
• Primary	102 (71.0)	124 (82.7)
• Secondary	42 (29.0)	26 (17.3)
Median duration of subfertility in months (IQR)	19 (16–26)	22 (17–30)
Ovulatory cycles, *n* (%)	108 (75.0)	129 (86.0)
Median VCM (IQR)	47.5 (17.25–98.5)	51.0 (22.0–118.0)
Positive chlamydia serology, *n* (%)	16 (11.1)	16 (10.7)

Between randomization and the scheduled procedure, 17 and 12 women conceived naturally in the THL group and HSG group, respectively. In the THL group, six women decided not to undergo any kind of tubal testing, and two women underwent HSG instead of THL. In the HSG-group, two women decided not to undergo tubal testing, whereas two women underwent THL instead of HSG. At 24 months after randomization, two women in the THL group and two women in the HSG-group were lost to follow-up. Therefore, with six women having withdrawn informed consent, and four women lost to follow-up, data on the primary outcome conception leading to live birth were available for 290 out of 300 women (FIGURE 1).

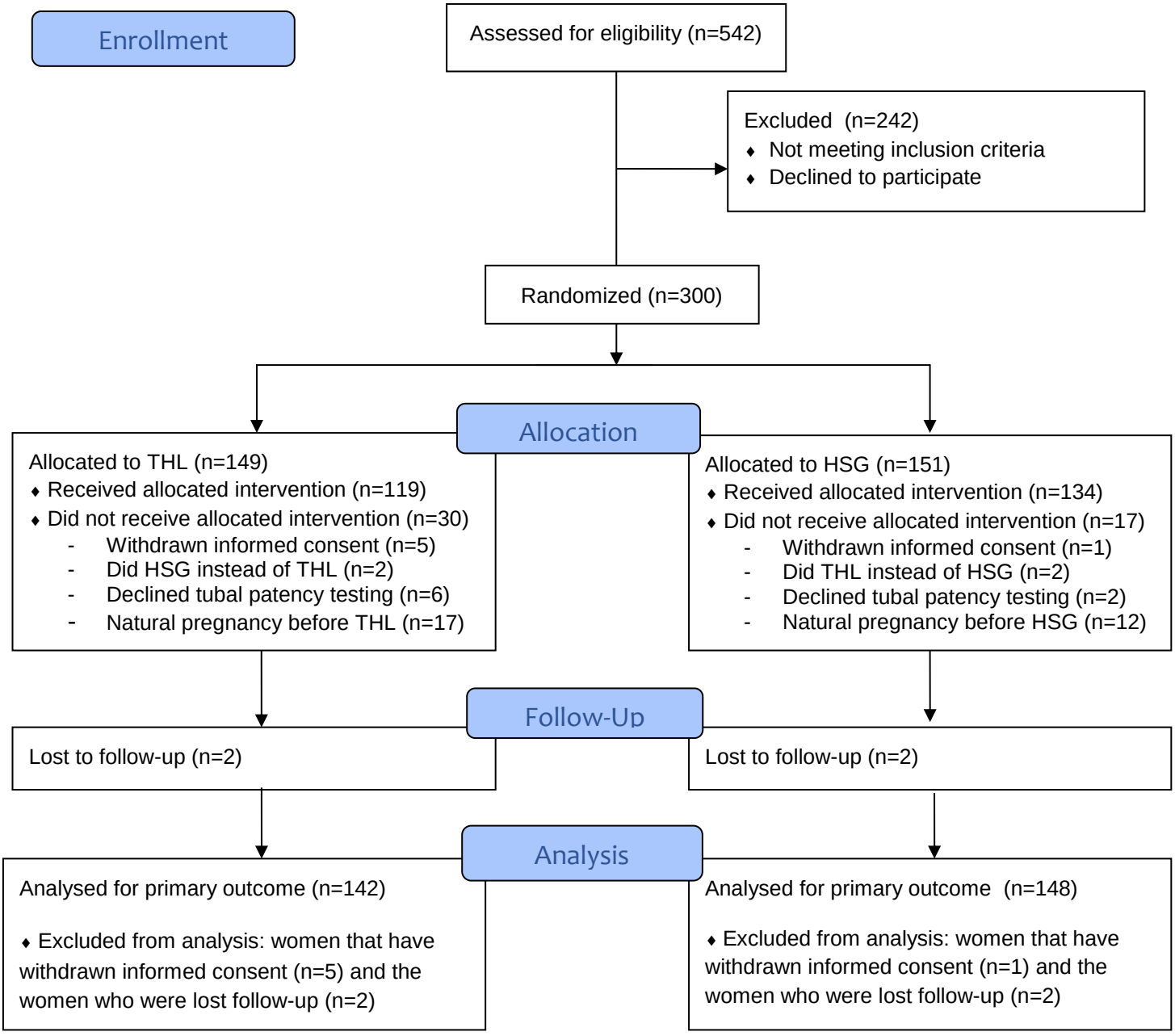

FIGURE 1 CONSORT 2010 flow diagram. Follow-up per randomization. HSG, hysterosalpingography, THL, transvaginal hydrolaparoscopy.

Result of tubal evaluation and treatment

Transvaginal hydrolaparoscopy showed bilateral tubal patency in 104 women out of the 119 women in the THL group who underwent the allocated intervention (87.4%) (TABLE 2). Unilateral tubal patency was seen in six women (5.0%) and bilateral tubal occlusion in one woman (0.8%). Furthermore, five women (4.2%) were diagnosed with endometriosis and, in six women (5.0%), pelvic adhesions were found. Additional hysteroscopies were not carried out in the THL group because no intrauterine pathologies were detected by transvaginal ultrasound. In the HSG group, 122 out of 134 women (91.0%) undergoing HSG had bilateral patent tubes. Unilateral tubal patency was found in eight women (6.0%) and bilateral tubal occlusion in three women (2.2%). Intrauterine abnormalities were detected in three women (2.2%). For HSG, oil-based contrast was used in 45 women (33.6%) and water-based contrast was used in 89 women (66.4%). Two women underwent an additional hysteroscopy because of intrauterine abnormalities.

In the THL group, four women (2.8%) suffered complications compared with one in the HSG group (P = 0.204). Two women had a bleeding of the vaginal wall that needed suturing, and one woman had a rectal perforation that was treated conservatively with antibiotics. One woman experienced a prolonged period of pain requiring painkillers. In the HSG group, one woman (0.7%) suffered cervical bleeding requiring one night of hospitalization.

TABLE 2 RESULTS OF TUBAL EVALUATION

	THL, *n* (%) (*n* = 119)	**HSG, *n* (%) (*n* = 134)**	***P*-value**
Results, *n* (%)			
• Bilateral tubal patency	104 (87.4)	122 (91.0)	0.351
• One-sided tubal occlusion	6 (5.0)	8 (6.0)	0.606
• Two-sided tubal occlusion	1 (0.8)	3 (2.2)	0.545
• Unknown, due to failure	8 (6.7)	1 (0.7)	0.014
Other abnormalities *n* (%)			
Endometriosis	5 (4.2)	0	NA
Adhesions	6 (5.0)	0	NA
Intrauterine abnormalities	0	3 (2.2)	NA

HSG, hysterosalpingography, NA, not applicable; THL, transvaginal hydrolaparoscopy.

Primary outcome

In the THL group, 83 out of 142 women for whom follow-up data were available (58.5%) conceived an intrauterine pregnancy leading to live birth within 24 months after randomization compared with 82 out of 148 (55.4%) in the HSG group (difference: 3.0% (95% CI –8.3 to 14.4). The difference in percentage of a live birth using the per-protocol sample was 2.0% (95% CI –10.4 to 14.5).

Secondary outcomes

The cumulative incidence of conception leading to live birth for both groups is presented in FIGURE 2. The Log-rank tests did not reveal significant differences in time to conception (P = 0.199) and time to conception leading to live birth (P = 0.308) between groups. The number of women who experienced a miscarriage was 16 (11.3%) in the THL group, compared with 20 (13.5%) in the HSG group (RR = 0.84, 95% CI 0.46 to 1.55, P = 0.581). In total, 12 (8.4%) women in the THL group experienced multiple pregnancies compared with 19 (12.8%) in the HSG group (P = 0.320). Ectopic pregnancy was only diagnosed in the HSG group in two women (1.4%) and not at all in the THL group (P = 0.499).

Figure 2: time to conception leading to live birth

Subsequent treatment after fertility evaluation in the two groups is presented in TABLE 3. Expectant management was advised in 47.9% of women in the THL group compared with 44.8% of women in the HSG group (P = 0.609). Similar percentages of women started with ovulation induction (5.9% in the THL group versus 6.0% in the HSG group, P = 1.000) and intrauterine insemination with or without mild ovarian stimulation (40.3% in the THL group versus 41.0% in the HSG group, P = 0.909).

In the THL group, IVF or intracytoplasmic sperm injection was scheduled in 1.7% compared with 2.2% in the HSG group (P = 1.000).
Fertility-enhancing laparoscopic surgery was carried out in five women (4.2%) in the THL group. The reasons for this were endometriosis (n = 3), adhesions (n = 1) and bilateral tuboneostomy because of hydrosalpinges (n = 1). In the HSG group, eight women (6.0%) underwent a therapeutic laparoscopy because of abnormalities. This was due to endometriosis (n = 5), endometriosis and adhesions (n = 1), tuboneostomy and adhesiolysis (n = 1) and clipping a rudimentary horn of the uterus (n = 1).

TABLE 3 TREATMENT AFTER FERTILITY EVALUATION

Treatment, *n* (%)	**THL, *n* (%) (*n* = 119)**	**HSG, *n* (%) (*n* = 134)**	***P*-value**
Expectant management	57 (47.9)	60 (44.8)	0.609
followed by IUI	29 (24.4)	32 (23.9)	1.000
Ovulation induction	7 (5.9)	8 (6.0)	1.000
IUI with and without MOS	48 (40.3)	55 (41.0)	0.909
followed by IVF	21 (17.6)	29 (21.6)	0.525
IVF/ICSI	2 (1.7)	3 (2.2)	1.000
Fertility-enhancing surgery	5 (4.2)	8 (6.0)	0.580
followed by IUI	1 (0.8)	4 (3.0)	0.374
followed by IUI and IVF	4 (3.4)	1 (0.7)	0.190

Discussion

This multicentre, randomized controlled trial showed that a strategy for tubal patency testing using THL was not inferior to a strategy using HSG when considering conception leading to live birth at 24 months after randomization in women with a low risk of tubal pathology.

The main limitation of our study was the sample size. Only the four Dutch hospitals that already carried out THL in their routine fertility work-up were able to participate in our trial owing to lack of funding. Therefore, the inclusion rate was lower than anticipated, compromising the statistical power; the study was halted after 3 years. With 300 women included, this is still, to the best of our knowledge, the largest study on this topic at the time of writing.

The study was conducted in a select group of women at low risk of tubal pathology, by excluding women with an immobile or retroverted uterus, evidence of endometriosis, ovarian cysts or an active infection with Chlamydia trachomatis. We found bilateral patent tubes without other abnormalities in more than 85% of our patients. Therefore, the results of our study should not be generalized to subfertile women with a high risk of tubal pathology.

The respective advantages and disadvantages of THL and HSG differ as they are different procedures. We have already shown that HSG and THL have a comparable diagnostic performance when used as a first-line diagnostic test in subfertile women (Tros et al., 2019). A potential advantage of THL over HSG is that THL gives information about other pelvic abnormalities, such as endometriosis and the tubo-ovarian contact. Use of THL as a first-line diagnostic test could, therefore, potentially benefit women with endometriosis and adhesions, as those might be helped with early treatment instead of expectant management.

It is still not certain if obtaining more information about pelvic abnormalities leads to a better fertility outcome. We have previously found that, with THL as a first-line diagnostic test, women with bilateral tubal occlusion and women with a combination of endometriosis and adhesions had significantly reduced chances of naturally conceived pregnancy compared with women with no abnormalities at THL (van Kessel et al., 2018). On the other hand, a study comparing HSG and diagnostic laparoscopy found the predictive capacity of the two procedures for naturally conceived pregnancy to be comparable. In that study, only bilateral tubal occlusion led to a severe reduction in the chances of a naturally conceived pregnancy (Verhoeve et al., 2011).

The disadvantage of THL is the higher rate of failed procedures and complications compared with HSG. The present study shows a failure rate of 6.7%, which is comparable to published data when THL is carried out by experienced gynaecologists (Verhoeven et al., 2004; van Tetering et al., 2007). Recent studies have shown that adding transabdominal ultrasound guidance to the introduction of the Veress needle can lead to a lower rate of failed procedures and complications (Sobek et al., 2008; Ma et al., 2012). An advantage of HSG is the possible therapeutic effect of tubal flushing when using oil-based contrast medium, leading to a higher rate of naturally conceived pregnancies (Dreyer et al., 2017). In the present randomized controlled trial, we used water-based contrast in two-thirds of women and oil-based contrast medium in one-third of women as a contrast-medium for HSG, depending on the local hospital protocol (Tros et al., 2019). The use of two different contrast media could lead to a potential bias but, owing to the small groups, it was not feasible to evaluate the differences between oil-based and water-based contrast in this study.

During THL, we used methylene blue to test the patency of the tubes, which is a water-based solution. To date, no studies have been published on the effect of tubal flushing with an oil-based solution after THL.

In conclusion, we found that a strategy for tubal patency testing using THL was not inferior to a strategy using HSG in cases of conception leading to live birth at 24 months after randomization, in women with a low risk of tubal pathology. On the basis of these results, neither procedure is preferable to the other.

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Conflict of interest

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Chapter 6

Visual tubal patency tests for tubal occlusion and hydrosalpinx.

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Abstract

Objectives

This is a protocol for a Cochrane Review (diagnostic). The objectives are as follows:

To determine and compare the diagnostic accuracy of visual tubal patency tests (hysterosalpingography (HSG), sonohysterosalpingography (sono-HSG), magnetic resonance hysterosalpingography (MR-HSG), and outpatient transvaginal hydrolaparoscopy (THL)) for the diagnosis of tubal occlusion.

Secondary objectives

To determine and compare the diagnostic accuracy of visual tubal patency tests (HSG, sono-HSG, MR-HSG, and outpatient THL) for the diagnosis of hydrosalpinx.

To evaluate heterogeneity with regards to population characteristics (population risk stratification) and index test characteristics (contrastmedia, technology, operator skills).

Background

Infertility, defined as the failure to conceive within 12 months of regular unprotected sexual intercourse, occurs in at least 12% of the couples who wish to conceive (Datta 2016; Zhou 2018). Around 18% to 33% of couples with infertility present with tuboperitoneal pathologies such as blocked or damaged Fallopian tubes (Inhorn 2015; Wilkes 2009; Zheng 2019). As the Fallopian tubes are essential for transportation of the spermatozoa, the ovum and the embryo (Lyons 2006), bilateral occluded tubes exclude the chance of natural pregnancy. Therefore, bilateral tubal occlusion formed the basis of the development of in vitro fertilization (IVF) and was the earliest indication for IVF (Niederberger 2018).

Most diagnostic protocols for fertility assessment include a test to rule out tubal occlusion (ACOG 2019; NICE 2017). During such tubal patency tests, a contrast agent is flushed into the uterus and through the Fallopian tubes, visualizing tubal patency. Diagnostic laparoscopy with methylene blue dye tubal patency testing, also known as chromopertubation, is generally accepted as the reference standard (NICE 2017). However, due to its invasiveness and costs, alternative less invasive tests have been carried out as replacements. These visual tubal patency tests have evolved alongside the development of radiography, ultrasonography and laparoscopy, including hysterosalpingography (HSG), sono-hysterosalpingography (sono-HSG), magnetic resonance hysterosalpingography (MR-HSG), and outpatient transvaginal hydrolaparoscopy (THL). The choice of these visual tubal patency tests varies in different settings.

Visual tubal patency tests can be used to diagnose tubal, uterine and other pelvic conditions. The most important tubal conditions are bilateral tubal occlusion, unilateral tubal occlusion and hydrosalpinx. The diagnoses of these conditions will directly guide clinical management, so they will be the focus of this Cochrane Review.

Target condition being diagnosed

Target conditions of interest are tubal occlusion and hydrosalpinx.

1. Tubal occlusion: women with untreated bilateral occlusion have no chance of a natural pregnancy, as there is no way for the ovum and spermatozoa to meet, and these women can benefit from early IVF (Niederberger 2018). Therefore, women diagnosed with bilateral tubal occlusion are mostly offered IVF directly, although IVF is not available to all couples worldwide due to differences in health care systems and reimbursements. IVF can be preceded by laparoscopic surgery to optimize pelvic anatomy. Management in women with unilateral tubal blockage is more diverse, as in these women the patent Fallopian tube still facilitates transport of the ovum, spermatozoa and embryo. Mostly unilateral tubal patency is treated the same as bilateral tubal patency, as unilateral tubal patency does not reduce pregnancy outcomes significantly (Verhoeve 2011). There are studies reporting on lower odds of pregnancy when unilateral distal tubal occlusion is detected in comparison to proximal tubal occlusion (Tan 2018). This observed difference between proximal and distal tubal occlusion may result from inherent diagnostic limitations of HSG or may reflect different underlying pathologies that differentially affect pregnancy outcomes. However, proximal or distal occlusion cannot be identified by all index tests, so we will not differentiate between proximal or distal occlusion in this review.

2. Hydrosalpinx: the other condition of interest is hydrosalpinx. It refers to the distension of the Fallopian tube due to distal tubal occlusion and fluid accumulation, and the most common cause is a previous episode of pelvic inflammatory disease (Ng 2019). A hydrosalpinx has a negative impact on fertility outcomes through different mechanisms. Removal or ligation of the hydrosalpinx has a positive effect on clinical pregnancy rates before assisted reproductive technology (ART) (Melo 2020).

Other conditions that are not the focus of this review, but can be detected during visual tubal patency tests, are endometriosis (which can be visualized during THL), peritoneal/pelvic adhesions (sono-HSG and THL) and intrauterine pathology (HSG and sono-HSG). Endometriosis is seen in about 25% to 40% of women with infertility (Carson 2021; Ozkan 2008). Pelvic adhesions, caused by previous surgery, pelvic inflammatory disease or endometriosis, may interfere with ovum pickup if they are distorting the anatomy of the ovary and Fallopian tube. Intrauterine pathology as myomas, polyps or intrauterine adhesions, as well as congenital uterine anomalies, can be detected by some of the visual tubal tests. These intracavitary conditions might all have some effect on fertility outcomes (ASRM 2017; Parry 2019).

Index test(s)

We will consider the following four main groups of index tests.

1. Hysterosalpingography (HSG): this uses serial X-ray or fluoroscopy images during injection of an iodine-containing contrast medium through the cervical canal into the uterus and subsequently the Fallopian tubes. DiKerent instruments, such as a reusable metal cannula (hysterophore or Jarcho cannula), a 5-French balloon catheter or a (modified) cervical vacuum cup device, as well as different iodine-containing contrast media, oil-based or water-based, can be used. HSG is contraindicated in women with an allergy to iodine-containing contrast media. HSG is a safe and widely accepted procedure in the outpatient setting, but it needs to be performed in a radiology department. HSG is well-tolerated, although more painful than sono-HSG (Dreyer 2014) or THL (Tros 2019). In addition to

its advantage of evaluating the uterine cavity and tubal patency, it has a potential therapeutic effect when an oil-soluble contrast medium is used, with a higher chance of clinical pregnancy and live birth rates (Wang 2019; Wang 2020). Choice of contrast medium, operator skill and the observer interpreting the HSG are likely to be potential sources of heterogeneity (Mol 1996).

2. Sono-hysterosalpingography (sono-HSG): this includes both hysterosalpingo-foam sonography (HyFoSy) and hysterosalpingo-contrast sonography (HyCoSy). Overall, this test is based on ultrasound, in which an echogenic medium is used to assess the uterine cavity and tubal patency. Many different sono-HSG techniques are performed, with differences in two- or three-dimensional ultrasound modality; vaginal or abdominal ultrasound; contrast type (commercially available foam as well as normal saline, saline and air or galactose, or combinations of these); or the usage of colour Doppler sonography (Maheux-Lacroix 2014). The advantages of these tests are that they can be performed in an outpatient setting without a radiology department (offering the possibility of a one-stop fertility evaluation), and are generally well tolerated (Dreyer 2014). Furthermore, when compared to HSG, the procedure does not require exposure to radiation or iodinecontaining contrast media (Ludwin 2019). In addition to tubal patency, the uterine cavity and myometrium, as well as both ovaries, can be assessed during the procedure (Saunders 2011). It is likely that choice of contrast, operator skill and test technology influence the diagnostic quality.

3. Magnetic resonance hysterosalpingography (MR-HSG): this is similar to HSG. It uses MR-imaging instead of X-ray or fluoroscopy, and the contrast medium is a gadolinium-based solution, available from different manufactures and prepared in different ways (Li 2021). Similar to HSG, the procedure can be performed in an outpatient setting when a radiology department is available, and it is well tolerated (Unterweger 2002; Volondat 2019). It also avoids exposure to radiation and iodine-containing contrast media, and can be used to diagnose (deeply infiltrating) endometriosis, uterine and ovarian anomalies. In comparison to sono-HSG, the advantage of MR-HSG is that is not operator dependent, with a better reproducibility (Li 2021; Volondat 2019).

4. Transvaginal hydrolaparoscopy (THL): also known as transvaginal endoscopy or fertiloscopy, this technique uses hydroflotation for exploration of the pelvic cavity. A small diameter optic is inserted transvaginally through an incision in the vaginal posterior fornix, after the pelvis is filled with warm normal saline for pelvic cavity distention. By using a dye, mostly methylene blue, tubal patency can be tested (Gordts 1998). Different instruments, disposable or reusable, can be used for THL (Coenders-Tros 2016). THL is a known, safe and well tolerated procedure, which can be performed in an outpatient setting under local anaesthesia (Coenders-Tros 2016;Shibahara 2007;Tros 2019). An advantage is the direct visualization of the female genital tract, thus allowing the evaluation of hydrosalpinx, endometriosis, and pelvic adhesions next to the tubal blockage. It is possible that the experience of the operator influences the success rate of THL.

Clinical pathway

There has been a wide range of variation in visual tubal patency tests during fertility workup, at both national and international levels (ACOG 2019; NICE 2017). In general, a comprehensive medical history is obtained as the first step to explore the possible causes of female-factor infertility. Next, physical examination and transvaginal ultrasound assessment are performed. In some settings, tubal patency is always then tested (ACOG 2019; NICE 2017), while in other settings, tubal testing is

considered based on findings from medical history, physical examination and serological testing (chlamydia antibody testing; CAT) and only women with a high risk for tubal pathology will undergo tubal testing (FMS 2015). Women are usually considered as having a high risk for tubal pathology when they have had a history of chlamydia infection or a positive CAT, pelvic inflammatory disease or peritonitis, or when they have been diagnosed with endometriosis or have had pelvic surgery in the past (Coppus 2007; Luttjeboer 2009).

A visual tubal patency test can be used as a triage or as a replacement test. When used as a triage test, women will undergo laparoscopy only when occlusion is suspected or the visual tubal patency test shows indeterminate findings. However, the aim of laparoscopy in current practice is more often to select women who may benefit from therapeutic laparoscopy, rather than to select women for diagnostic laparoscopy. For example, in the Federation Medical Specialists (FMS) guideline (FMS 2015), visual tubal patency tests are performed in high risk women as a triage test to select women who require laparoscopy. Laparoscopy without prior visual tubal patency testing is reserved only for those women with severe endometriosis or hydrosalpinges, where the diagnostic procedure and therapeutic laparoscopy are combined at the same time. In most other settings a visual tubal patency test is used as a replacement for the reference standard. The outcome of this test will then be used to determine if fertility treatment is necessary. Fertility treatment can be therapeutic laparoscopy or assisted reproduction, depending on the availability and preferences of the doctor and person undergoing treatment. An example is the NICE guideline (NICE 2017), in which women with low risk for tubal pathology are offered a visual tubal patency test and those with high risk are offered a laparoscopy. Depending on the results, women with tubal obstruction can be offered tubal surgery, when appropriate expertise is available, or assisted reproduction directly.

The choice of visual tubal patency tests also varies in different settings, depending on the preference and skills of the clinician, the preference of the couples with infertility and the availability of tubal testing methods in the clinic. In different geographical and economic contexts, costs, availability and the accessibility of these testing methods will differ. However, if available and accessible, this protocol hopes to answer the question of which visual tubal patency test should be advised above others as a replacement test for laparoscopy to diagnose tubal patency.

Alternative test(s)

Alternative tests are not applicable, as all visual tubal patency tests will be reviewed in this protocol.

Rationale

Over the last two decades, new tubal patency tests (e.g. MR-HSG) have been emerging, as well as new contrast media or test technology for existing tubal patency tests. Therefore, it is important to summarise all the evidence on the accuracy of individual tests, and to compare different tests' accuracies. However, there is no Cochrane Review on this topic. As visual tubal patency tests are all less invasive than diagnostic laparoscopy and are well-tolerated in an outpatient setting, it seems fair to offer such a test instead of the reference standard diagnostic laparoscopy. Nevertheless, the diagnostic accuracy of these tests is less acknowledged in clinical decision-making about the choice of tubal testing method. Currently, there is no consensus in terms of how different types of visual tubal patency test compare to each other. Before replacing the reference standard, it is important

to understand the diagnostic accuracy of each individual visual patency test and to compare the diagnostic accuracy when possible. Couples with infertility will benefit from this research as it will guide clinicians to select the most suitable visual tubal patency test for the individual couple.

Objectives

To determine and compare the diagnostic accuracy of visual tubal patency tests (hysterosalpingography (HSG), sono-hysterosalpingography (sono-HSG), magnetic resonance hysterosalpingography (MR-HSG), and outpatient transvaginal hydrolaparoscopy (THL)) for the diagnosis of tubal occlusion.

Secondary objectives

To determine and compare the diagnostic accuracy of visual tubal patency tests (HSG, sono-HSG, MR-HSG, and outpatient THL) for the diagnosis of hydrosalpinx.
To evaluate heterogeneity with regards to population characteristics (population risk stratification) and index test characteristics (contrast media, technology, operator skills).

Methods

Criteria for considering studies for this review

Types of studies

We will include studies on the diagnostic test accuracy of a single index test and studies on the comparative diagnostic test accuracy of two or more index tests.

For the diagnostic test accuracy of a single index test, we will include single-gate studies, in which one of the index tests (defined below) is compared with the reference standard within a timeframe in which the tubal status is unlikely to be changed (within three months).

For the comparative diagnostic test accuracy of two or more index tests, we will include the two following types of studies.
1. Studies with fully-paired direct comparisons. In these studies, the participants receive two or more index tests and the reference standard.
2. Randomized controlled trials that directly compares two or more index tests. In all arms, the index test should be followed by diagnostic laparoscopy as the reference standard.

We will exclude two-gate studies, as these study designs are likely to overestimate sensitivity and specificity. Furthermore, we will exclude studies with the primary endpoint of prognostic capacity for fertility outcomes, as well as diagnostic accuracy studies for sterilization purposes. We will exclude studies with a sample size of fewer than 50 participants, given the relatively low prevalence of bilateral tubal occlusion across all risk groups. Although this threshold may be considered arbitrary, both sensitivity and specificity could be unreliable or biased in studies with smaller sample size.

Participants

We will include participants with infertility undergoing a visual tubal patency test and a diagnostic laparoscopy. We will include participants who have been trying to conceive for one year or more, both with low and high risk of tubal pathology, as well as unselected participants (i.e. participants undergoing a visual tubal patency test without knowing about their risk of having tubal pathology). High risk incorporates all women with a positive history of pelvic inflammatory disease/chlamydia or who are CAT positive, those with extensive abdominal or tubal surgery in the past, and those with abnormalities like endometrioses/possible hydrosalpinx discovered during physical examination. Participants with low risk on tubal pathology are those with no previously mentioned conditions for high risk. We will include participants who have had previous tubal testing only when the outcome of this test was not used to select the participants, as we will not include studies with a two-gate design. We will exclude participants undergoing tubal testing after refertilization (surgery to undo a tubal sterilization).

Index tests

We will include the following types of index texts.

- HSG, with either oil-based or water-based contrast.
- MR-HSG, including all techniques/MR-protocols or contrast media used.
- THL, transvaginal endoscopy or fertiloscopy, conducted with reusable instruments or disposable trocars.
- Sono-HSG (including HyFoSy and HyCoSy), used with commercially available foam, saline, saline and air or galactose, or combinations of these. We will exclude studies conducted with contrast that is no longer available (Echovist; galactose microparticles; Bayer Schering Pharma AG, Berlin, Germany) (Welie 2020). Furthermore, we will include studies that use two or three-dimensional modality, with or without colour doppler.

Target conditions

We will consider tubal occlusion as a dichotomous diagnosis for all tests, i.e. occluded or patent (not occluded). As the unit of analysis will be at the individual level, due to its clinical importance, we will treat bilateral tubal occlusion and at least one-sided tubal occlusion as two separate conditions, instead of a threshold. Similarly, we will also consider hydrosalpinx as a dichotomous diagnosis.

Reference standards

Laparoscopy with methylene blue dye tubal patency testing is the reference standard. All participants in the included studies should undergo this reference standard to avoid verification bias. We will only include video-assisted laparoscopy, as this is less operator-dependent. We will exclude studies on direct visualization laparoscopy or those using CO2-pertubation or indigo carmine dye for tubal testing during laparoscopy, as well as the use of other dyes currently unknown to the authors. In addition, we will exclude studies with laparotomic tubal testing, and studies with another reference standard, for example using one of the index tests as the reference standard.

Search methods for identification of studies

Electronic searches

In collaboration with the Cochrane Gynaecology and Fertility (CGF) Group's Information Specialist, we will search the following electronic databases:

- CENTRAL (Cochrane Central Register of Controlled Trials) via the Cochrane Register of Studies Online (CRSO), web platform, to search from 1968 to present (Appendix 1);
- MEDLINE, Ovid platform, to search from 1968 to present (Appendix 2);
- Embase, Ovid platform, to search from 1980 to present (Appendix 3);
- CINAHL (Cumulative Index to Nursing and Allied Health Literature; EBSCO platform, to search from 1968 to present (Appendix 4).

For each database, we will use both index and free terms, and synonyms related to: infertility, tubal pathology, hysterosalpingography, hydrolaparoscopy, MR-HSG and sono-HSG. We will also search trial registries for trials comparing two or more index tests, and for other eligible observational studies. We will search ClinicalTrials.gov (clinicaltrials.gov/), International Standard Randomised Controlled Trial Number (ISRCTN) registry (www.isrctn.com/), and the World Health Organization (WHO) International Clinical Trials Platform (ICTRP) Search portal (apps.who.int/trialsearch/). As the reference test, laparoscopy with methylene blue dye tubal patency testing, was first reported in 1968 (Ansari 1968), we will use this as the earliest search date for those databases with an inception date prior to 1968.

Searching other resources

We will screen the reference lists of included studies and relevant systematic reviews for any additional trials. We will also search for ongoing and unpublished studies by approaching clinical experts and trialists in this field.

Data collection and analysis

Selection of studies

Two authors (RT and KR) will independently screen retrieved studies for eligibility on the basis of their titles and abstracts. If the study is potentially eligible, the same two authors will independently evaluate the full text for eligibility. A third author (CK or RW) will be involved to solve any disagreement at both stages. Where studies have multiple publications, we will collate multiple reports of the same study under a single study ID with multiple references. We will perform the study selection process in Covidence 2021 or other similar online platforms.

Data extraction and management

Two review authors (RT and KR) will perform the data extraction independently. When there is a disagreement between the two authors, a third author (CK or RW) will be consulted in the discussion. We will design a data extraction form for this review and pilot-test the form on three studies. We will collect the following data from the included studies: general information (first author, year of publication, country), participant characteristics (age, inclusion/exclusion criteria, numbers of participants, risk stratification (high/low risk for tubal pathology or unselected population), index test/reference standard details, two-by-two table for each outcome (true positives, true negatives, false positives, and false negatives), inconclusive tests and adverse events. When data for two-by-two tables are not available, we will calculate these data from the test accuracy results (sensitivity, specificity, positive predictive value and negative predictive value). Next, we will collect data on test-specific related conditions found. We will contact study investigators for information when needed.

Handling of inconclusive results

We will consider both valid inconclusive (intermediate or borderline) results and invalid inconclusive (indeterminate or uninterpretable) results in the analysis, as suggested by Shinkins 2013. Participants with valid inconclusive results may receive further fertility treatment in clinical practice, but may also have another test in other settings. Therefore, we will treat all valid inconclusive results as positive (i.e. occluded) in the main analysis and as negative in a sensitivity analysis. Participants with invalid inconclusive results or procedure failures are more likely to have another test or a different index test in clinical practice, and some of these women may have conditions relevant to tubal pathology. Therefore, we will exclude invalid inconclusive results from the main analysis and treat them as positive (i.e. occluded) in a sensitivity analysis. We will evaluate the robustness of the findings by using different methods to handle the inconclusive results. Please refer to Sensitivity analyses.

Assessment of methodological quality

We will use the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool for the assessment of methodological quality of all included studies (Whiting 2011). We will evaluate the four domains in QUADAS-2 (patient selection, index test, reference standard, and flow and timing) for risk of bias, and the first three domains for concerns regarding applicability. For comparative diagnostic test accuracy studies, we will use the QUADAS-C tool (Yang 2021b) (Appendix 5). Two review authors (RT and KR) will evaluate the methodological quality of all included studies independently; we will resolve disagreements by involving a third author (CK or RW). We will pilot test both tools and only repeat this if it demonstrates problems during the first round.

Statistical analysis and data synthesis

Diagnostic test accuracy for each index test

We will perform the analysis for each index test separately. We will perform random-effects meta-analysis in a bivariate model (Chu 2006). For each index test, we will present pairs of sensitivity and specificity with their 95% confidence intervals (CIs) for each study, as well as the pooled sensitivity and specificity, in a forest plot. We will then present the summary receiver operating characteristic (SROC) plot with summary points, and incorporate the seven domains of the QUADAS-2 tool into this SROC plot.

Unit of analysis

We will analyse the data on a participant level in the analysis, as this is more clinically relevant. However, if per participant data are not available and per tube is the unit of analysis in the majority of included studies, we will consider performing analysis on a per tube basis.

Comparative diagnostic test accuracy for different index tests

Direct comparison

We will include studies directly reporting two or more index tests compared with the reference standard in the primary analysis of comparative diagnostic test accuracy of different index tests. We will add a covariate for type of test in the bivariate model to compare the differences in test accuracy, and perform a likelihood ratio test to compare models (Takwoingi 2021). We will also present linked SROC plots, linking estimates of two different index tests from the same studies.

Indirect comparison

As indirect comparisons are prone to bias, we will only perform them as additional analyses if there are limited studies for direct comparisons. In this case, we will include studies that include one or more index test. We will evaluate the comparative diagnostic accuracy between HSG and other tests.

Procedure failure and adverse events

We will tabulate procedure failure and adverse events for all index tests and the reference test. We will use Stata (Stata 2019) and MetaDTA, an interactive online application for meta-analysis of DTA studies (Freeman 2019). When necessary, we will also use Review Manager 5.4.1 (Review Manager 2020).

Investigations of heterogeneity

We will consider the following in the assessments of heterogeneity.

- Population characteristics: population risk stratification (high risk, low risk and unselected risk for tubal pathology).
- Index tests characteristics: HSG (oil versus water based contrast media; operator skills), sono-HSG (2D/3D versus 2D; different contrast media; use of colour doppler or not; operator skills), MR-HSG (different viscosity contrast media), THL (operator skills).

All these covariates are categorical variables. We will fit the models separately in different subgroups and perform visual inspections of SROC.

Sensitivity analyses

We will perform the following sensitivity analyses.

- Different approaches to handling inconclusive results:
    - treating valid inconclusive results as negative (i.e. patent);
    - treating invalid inconclusive results are positive (occluded).
- Limiting to studies at low risk of bias in the index tests and reference standard domains.

Assessment of reporting bias

We do not plan to evaluate reporting bias in this systematic review because statistical investigation of publication and reporting bias is not routinely recommended in DTA systematic reviews, as stated in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Macaskill 2010; Salameh 2020).

Summary of findings and assessment of the certainty of the evidence

For diagnostic accuracy of individual index tests, we will assess the certainty of the evidence according to the GRADE guidance 21 (Schünemann 2020a; Schünemann 2020b). We will evaluate risk of bias, indirectness, inconsistency and imprecision, but will not assess publication bias for the reasons mentioned in Assessment of reporting bias. We will produce summary of findings tables for each index test, but these will be limited to one outcome only (bilateral tubal occlusion). We will present the number of studies/participants, study design, certainty assessment (risk of bias, indirectness, inconsistency and imprecision), summary of findings (numbers and 95% confidence intervals for both the index test and the reference standard on true positives, false negatives, true negatives and false positives), and certainty of evidence in the summary of findings tables.

For comparative diagnostic accuracy of different index tests, we will evaluate the certainty of the evidence according to the GRADE guidance 31 (Yang 2021a). We will evaluate the same four domains as mentioned above for diagnostic accuracy of individual index tests. We will not consider indirect comparisons (between-study comparisons), given that evidence resulting from indirect comparisons is likely to be of low certainty and the methodological work in this area is under development (Yang 2021a). We will also produce summary of findings tables for comparative diagnostic accuracy if more than two studies are included for each comparison, but will be limited to one outcome only (bilateral tubal occlusion). We will present the number of studies/participants, study design, certainty assessment (risk of bias, indirectness, inconsistency and imprecision), summary of findings (numbers and 95% confidence intervals for both index tests on true positives, false negatives, true negatives, false positives and the differences of these between the two tests), and certainty of evidence in the summary of findings tables.

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Appendices

Appendix 1. CENTRAL via the Cochrane Register of Studies Online (CRSO) search strategy

Web platform
To search from 1968 onwards

1 MESH DESCRIPTOR Fallopian Tube Diseases EXPLODE ALL TREES
2 MESH DESCRIPTOR Fallopian Tubes EXPLODE ALL TREES
3 ((tubal or tube or tubes or peritubal) adj3 (patent or patency or pathology or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic)):TI,AB,KY
4 (fallopian* adj3 (patent or patency or pathology or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic)):TI,AB,KY
5 (oviduct* adj3 (patent or patency or pathology or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic)):TI,AB,KY
6 ((salpinges or salpinx) adj3 (patent or patency or pathology or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic)):TI,AB,KY
7 Salpingitis:TI,AB,KY
8 (Hydrosalpin* or pyosalpin* or h?ematosalpin*):TI,AB,KY
9 Endosalping*:TI,AB,KY
10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11 MESH DESCRIPTOR Laparoscopy EXPLODE ALL TREES
12 hysterolaparoscop*:TI,AB,KY
13 hystero-laparoscop*:TI,AB,KY
14 (Laparoscop* and (fallopian* or chromopertubation or diagnos* or sensitivity or specificity or patency or patent or dye or methylene or LSC)):TI,AB,KY
15 (laparoscop* adj10 predictive value):TI,AB,KY
16 (laparoscop* adj10 receiver operating characteristic):TI,AB,KY
17 (Laparoscop* and likelihood ratio*):TI,AB,KY
18 (LSC and fallopian*):TI,AB,KY
19 mini-laparoscop*:TI,AB,KY
20 micro-laparoscop*:TI,AB,KY
21 microlaparoscop*:TI,AB,KY
22 minilaparoscop*:TI,AB,KY
23 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
24 MESH DESCRIPTOR Hysterosalpingography EXPLODE ALL TREES
25 (hysterosalpingo* or salpingogra* or salpingoscop*):TI,AB,KY
26 (hydrolaparoscop* or fertiloscop*):TI,AB,KY
27 (sonohysterosalping* or SonoVue*):TI,AB,KY
28 (HSG or HSSG or MRHSG):TI,AB,KY
29 (HyCoSy or HyCoUs):TI,AB,KY

30 hysteroscop*:TI,AB,KY
31 (foam sonogra*):TI,AB,KY
32 HyFoSy:TI,AB,KY
33 MESH DESCRIPTOR Magnetic Resonance Imaging EXPLODE ALL TREES
34 MESH DESCRIPTOR Magnetic Resonance Spectroscopy EXPLODE ALL TREES
35 #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34
36 #23 OR #35
37 #10 AND #36
38 MESH DESCRIPTOR Fallopian Tube Patency Tests EXPLODE ALL TREES
39 #37 OR #38

Appendix 2. MEDLINE search strategy
Ovid platform
To search from 1968 onwards

1 exp fallopian tube diseases/ or pelvic inflammatory disease/ or salpingitis/
2 exp Fallopian Tubes/
3 ((tubal or tube or tubes or peritubal) adj3 (patent or patency or pathology or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic)).tw.
4 (fallopian* adj3 (patent or patency or patholog* or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic)).tw.
5 (oviduct* adj3 (patent or patency or patholog* or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic)).tw.
6 ((salpinges or salpinx) adj3 (patent or patency or patholog* or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic)).tw.
7 Salpingitis.tw.
8 (Hydrosalpin* or pyosalpin* or h?ematosalpin*).tw.
9 Endosalping*.tw.
10 or/1-9
11 exp Laparoscopy/
12 hysterolaparoscop*.tw.
13 (Laparoscop* and (fallopian* or chromopertubation or diagnos* or sensitivity or specificity or patency or patent or dye or methylene or LSC)).tw.
14 (laparoscop* adj10 predictive value).tw.
15 (laparoscop* adj10 receiver operating characteristic).tw.
16 (Laparoscop* and likelihood ratio*).tw.
17 (LSC and fallopian*).tw.
18 (minilaparoscop$ and (fallopian* or diagnos*)).tw.
19 (microlaparoscop$ and (fallopian* or diagnos*)).tw.
20 mini-laparoscop*.tw.
21 micro-laparoscop*.tw.
22 or/11-21
23 Hysterosalpingography/
24 Hysterosalpingo-Contrast Sonography.af.
25 HyCoSy.af.
26 HyFoSy.af.
27 or/23-26
28 (hysterosalpingo* or salpingogra* or salpingoscop*).tw.

29 (hydrolaparoscop* or fertiloscop*).tw.
30 (sonohysterosalping* or SonoVue*).tw.
31 (HSG or HSSG or MRHSG).tw.
32 (HyCoSy or HyCoUs).tw.
33 hysteroscop*.tw.
34 hystero-laparoscop*.tw.
35 foam sonogra*.tw.
36 HyFoSy.tw.
37 exp Magnetic Resonance Imaging/ or exp Magnetic Resonance Spectroscopy/
38 or/28-37
39 22 or 27 or 38
40 10 and 39
41 Fallopian Tube Patency Tests/ or Fallopian Tube Diseases/dg [Diagnostic Imaging]
42 40 or 41
43 exp animals/ not humans.sh
44 42 not 43

Appendix 3. Embase search strategy
Ovid platform
To search from 1980 onwards

1 exp uterine tube disease/
2 ((tubal or tube or tubes or peritubal) adj2 (patent or patency or pathology or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic)).tw.
3 (fallopian* adj2 (patent or patency or patholog* or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic)).tw.
4 (oviduct* adj2 (patent or patency or patholog* or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic)).tw.
5 ((salpinges or salpinx) adj2 (patent or patency or patholog* or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic)).tw.
6 Salpingitis.tw.
7 (Hydrosalpin* or pyosalpin* or h?ematosalpin*).tw.
8 Endosalping*.tw.
9 or/1-8
10 exp laparoscopy/
11 hysterolaparoscop*.tw.
12 hystero-laparoscop*.tw.
13 (Laparoscop* and (fallopian* or chromopertubation or diagnos* or sensitivity or specificity or patency or patent or dye or methylene or LSC)).tw.
14 (laparoscop* adj10 predictive value).tw.
15 (laparoscop* adj10 receiver operating characteristic).tw.
16 (Laparoscop* and likelihood ratio*).tw.
17 (LSC and fallopian*).tw.
18 (minilaparoscop$ and (fallopian* or diagnos*)).tw.
19 (microlaparoscop$ and (fallopian* or diagnos*)).tw.
20 mini-laparoscop*.tw.
21 micro-laparoscop*.tw.
22 or/10-21

23 exp hysterosalpingography/ or hysterosalpingography dye injection set/
24 Hysterosalpingo-Contrast Sonography.af.
25 HyCoSy.af.
26 HyFoSy.af.
27 or/23-26
28 (hysterosalpingo* or salpingogra* or salpingoscop*).tw.
29 (hydrolaparoscop* or fertiloscop*).tw.
30 (sonohysterosalping* or SonoVue*).tw.
31 (HSG or HSSG or MRHSG).tw.
32 (HyCoSy or HyCoUs).tw.
33 hysteroscop*.tw.
34 foam sonogra*.tw.
35 HyFoSy.tw.
36 exp nuclear magnetic resonance imaging/ or exp nuclear magnetic resonance spectroscopy/
37 or/28-36
38 22 or 27 or 37
39 9 and 38
40 exp tubal patency test/
41 uterine tube disease/di [Diagnosis]
42 40 or 41
43 39 or 42

Appendix 4. CINAHL search strategy
Ebsco platform
To search from 1968 onwards

#	Query
S37	S35 OR S36
S36	(MM "Fallopian Tube Patency Tests")
S35	S12 AND S34
S34	S22 OR S33
S33	S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32
S32	(MH "Magnetic Resonance Imaging") OR (MH "Magnetic Resonance Spectroscopy+")
S31	TX HyFoSy or TX (mini-laparoscopy)
S30	TX foam sonogra*
S29	TX hysteroscop* or TX (hystero-laparoscop*)
S28	TX (HyCoSy or HyCoUs)
S27	TX (HSG or HSSG or MRHSG)
S26	TX (sonohysterosalping* or SonoVue*)
S25	TX (hydrolaparoscop* or fertiloscop*)
S24	TX (hysterosalpingo* or salpingogra* or salpingoscop*)
S23	(MM "Hysterosalpingography") or TX (micro-laparoscop*)
S22	S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21
S21	TX (microlaparoscop* and (fallopian* or diagnos*))
S20	TX (minilaparoscop* and (fallopian* or diagnos*))
S19	TX (LSC and fallopian*)
S18	TX (laparoscop* and likelihood ratio*).
S17	TX (laparoscop* and predictive value).
S16	TX (laparoscop* and receiver operating characteristic)
S15	TX (Laparoscop* and (fallopian* or chromopertubation or diagnos* or sensitivity or specificity or patency or patent or dye or methylene or LSC))
S14	TX hysterolaparoscop*

S13 (MM "Laparoscopy")
S12 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
S11 TX Endosalping*
S10 TX (Hydrosalpin* or pyosalpin* or h?ematosalpin*)
S9 TX Salpingitis
S8 TX salpinges or salpinx*
S7 TX oviduct*
S6 TX fallopian*
S5 TX ((tubal or tube or tubes or peritubal) NR3 (patent or patency or pathology or infertil* or subfertil* or factor* or disten* or occlusion* or occluded or damage* or adhesion* or lesion* or blockage* or blocked or block or disease* or obstruct* or fibrosis or fibrotic))
S4 (MM "Fallopian Tubes")
S3 (MM "Salpingitis")
S2 (MH "Pelvic Inflammatory Disease")
S1 (MM "Fallopian Tube Diseases+")

Appendix 5. Tailored QUADAS-2 and QUADAS-C tools to the review question

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Domain 1: Patient Selection			
Information to support judgment	*Describe methods of patient selection.* *Describe included patients (previous testing, presentation, intended use of index test, and setting). Describe how patients were allocated to receive each of the index tests. If randomization was used to assign individual patients (or clusters of patients) to index tests, describe the randomization process.*		
Single test accuracy (QUADAS-2)		**Answers for _____ (test A)***	**Answers for _____ (test B)***
Signaling questions	1.1 Was a consecutive or random sample of participants enrolled? • Yes: if participants eligible for the study were randomly selected or consecutively selected within a certain time frame • No: if participants were selected using other procedures (e.g. based on clinician's or participant's preference or by convenience) • Unclear: when provided data are insufficient to assess the enrollment of participants	Yes/No/Unclear	Yes/No/Unclear
	1.2 Was a case-control design avoided? (Not applicable as case-control studies will be excluded)	-	-

	1.3 Did the study avoid inappropriate exclusions? • Yes: if the study avoided inappropriate exclusions (e.g. only excluding participants after refertilization or participants who do not meet the criteria for infertility) • No: if participants were excluded inappropriately (e.g. based on prior knowledge about tubal pathology such as confirmed tubal patency or occlusion) • Unclear: if insufficient information on exclusion criteria is available	Yes/No/Unclear	Yes/No/Unclear
Risk of bias	1.4 Could the selection of patients have introduced bias? • Low: if all signaling questions are answered with "yes" • High: if at least one signaling questions are answered with "no" • Unclear: if at least one signaling questions were answered with "unclear" and no signaling questions are answered with "no"	Low/High/Unclear	Low/High/Unclear
Concerns regarding applicability	1.5 Are there concerns that the included patients do not match the review question? • Low: if the participants represent an unselected or well defined low or high risk population • High: if participants with known tubal occlusion or patency are included • Unclear: if there is insufficient information available to make a judgement about applicability	Low/High/Unclear	Low/High/Unclear
Comparative accuracy (QUADAS-C)		**Answers for the test comparison**	
Signaling questions	C1.1 Was the risk of bias for each index test judged 'low' for this domain?	Yes/No	
	C1.2 Was a fully paired or randomized design used?	Yes/No/Unclear	
	C1.3 Was the allocation sequence random?†	Yes/No/Unclear/ Not applicable	
	C1.4 Was the allocation sequence concealed until patients were enrolled and assigned to index tests?†	Yes/No/Unclear/ Not applicable	
Risk of bias	C1.5 Could the selection of patients have introduced bias in the comparison?	Low/High/Unclear	

** Example when the comparison is between two index tests. Additional columns can be added for each additional test in the comparison. † Only applicable to randomized designs*

See the QUADAS-C Guidance Document for more detailed explanations.

C1.1: Answer 'yes' if the risk of bias judgment for single test accuracy (question 1.4 in QUADAS-2) was 'low' for each index test.
C1.2: Answer 'yes' if one of the following methods was used for allocating patients to index tests: (1) each patient receiving all of the index tests (fully paired design) or (2) random allocation of patients to one of the index tests (randomized design).
C1.3: Answer 'yes' if the study generated a truly random allocation sequence, for example, computer-generated random numbers and random number tables.
C1.4: Answer 'yes' if the study used appropriate methods to conceal allocation, such as central randomization schemes and opaque sealed envelopes.
C1.5: Risk of bias can be judged 'low' if questions C1.1 to C1.4 were answered 'yes' (questions C1.3 and C1.4 are only applicable to randomized designs). If at least one question was answered 'no', users should consider a 'high risk of bias' judgment if the bias associated with the design feature is of such concern that the entire domain is deemed problematic. If C1.2 was answered 'no', strongly consider 'high risk of bias'.

Domain 2: Index Test			
Information to support judgment	*Describe the index tests and how they were conducted and interpreted.* *For paired comparative studies, describe the order in which the index tests were performed.*		
Single test accuracy (QUADAS-2)		**Answers for _____ (test A)**	**Answers for _____ (test B)**
Signaling questions	2.1 Were the index test results interpreted without knowledge of the results of the reference standard? • Yes: if the index test was performed prior to the reference test or if the index test interpreter was blinded to the reference test result. • No: if the reference standard was performed before the index test and the index test interpreter was not blinded to this result • Unclear: If the above mentioned was not provided in the full text.	Yes/No/Unclear	Yes/No/Unclear
	2.2 If a threshold was used, was it pre-specified? (Not applicable as this is a dichotomous diagnosis)	-	-
Risk of bias	2.3 Could the conduct or interpretation of the index test have introduced bias? • Low: if signaling questions are answered with yes only • High: if one or both signaling questions are answered with “no” • Unclear: if at least one signaling questions were answered with “unclear” and no signaling questions are answered with “no”	Low/High/Unclear	Low/High/Unclear
Concerns regarding applicability	2.4 Are there concerns that the index test, its conduct or its interpretation differ from the review question? • Low: If the index test technology and the way the test has been applied and interpreted in the study match the pre-stated requirements in the review question (HSG/MR-HSG/sono-HSG/THL, performed and interpreted	Low/High/Unclear	Low/High/Unclear

	by trained person /expert i.e. not within learning curve) • High: If there are differences in index test technology, execution, and interpretation between the study and the review question (e.g. if index test is not performed and interpreted by trained person / expert). • Unclear: if insufficient information is available		
Comparative accuracy (QUADAS-C)		**Answers for the test comparison**	
Signaling questions	C2.1 Was the risk of bias for each index test judged 'low' for this domain?	Yes/No	
	C2.2 Were the index test results interpreted without knowledge of the results of the other index test(s)?‡	Yes/No/Unclear/ Not applicable	
	C2.3 Is undergoing one index test <u>unlikely</u> to affect the performance of the other index test(s)?‡ • Yes: if the order of index tests was determined by randomisation • No: if one index test was always performed after the other index test. • Unclear: if insufficient information about the order of the tests.	Yes/No/Unclear/ Not applicable	
	C2.4 Were the index tests conducted and interpreted without advantaging one of the tests? • Yes: if the index tests are performed and interpreted by personnel with comparable level of experience or training • No: if one index test was performed or interpreted by a more experienced person whereas the other index test was performed or interpreted by a less experienced person • Unclear: if insufficient information about level of experience or training.	Yes/No/Unclear	
Risk of bias	C2.5 Could the conduct or interpretation of the index tests have introduced bias in the comparison?	Low/High/Unclear	

‡ Only applicable if patients received multiple index tests (fully or partially paired designs)

C2.1: Answer 'yes' if the risk of bias judgment for single test accuracy (question 2.3 in QUADAS-2) was 'low' for each index test.

C2.2: Answer ‘yes’ if index test A was interpreted blind to the results of index test B and vice versa. Blinding is not necessary if none of the index tests involve subjective interpretation.
C2.3: Answer ‘yes’ if one index test cannot influence or interfere with the results of subsequently performed index test(s). Examples of such influence or interference include distortion of sampling area (biopsies) and patient fatigue (questionnaires).
C2.4: Answer ‘yes’ if there were no differences between the index tests that may unfairly benefit one of the tests. An example of such a difference is when index test A was performed by an expert and index test B by a nonexpert. Differences between tests that reflect clinical practice are acceptable, in which case ‘yes’ is appropriate.
C2.5: Risk of bias can be judged ‘low’ if signaling questions C2.1 to C2.4 were answered ‘yes’ (C2.2 and C2.3 are only applicable to fully or partially paired designs). If at least one question was answered ‘no’, users should consider a ‘high risk of bias’ judgment if the bias associated with the design feature is of such concern that the entire domain is deemed problematic.

Domain 3: Reference Standard			
Information to support judgment	*Describe the reference standard, how it was conducted and interpreted, and whether any of the index tests were part of the reference standard.*		
Single test accuracy (QUADAS-2)		**Answers for _____ (test A)**	**Answers for _____ (test B)**
Signaling questions	3.1 Is the reference standard likely to correctly classify the target condition? • Yes: if the final diagnosis is based on laparoscopy with blue dye testing • No: if the final diagnosis is not based on the reference standard result • Unclear: if there is not enough sufficient information on the reference standard provided	Yes/No/Unclear	Yes/No/Unclear
	3.2 Were the reference standard results interpreted without knowledge of the results of the index test? • Yes: if the reference test interpreter was blinded to the index test result. • No: if the reference test interpreter was not blinded to the index test result. • Unclear: when blinding is not clearly reported or where blinding cannot be assumed based on provided information.	Yes/No/Unclear	Yes/No/Unclear
Risk of bias	3.3 Could the reference standard, its conduct, or its interpretation have introduced bias? • Low: if signaling questions were answered with yes only • High: if one or both signaling questions were answered with "no" • Unclear: if at least one signaling questions were answered with "unclear" and no signaling questions are answered with "no"	Low/High/Unclear	Low/High/Unclear

Concerns regarding applicability	3.4 Are there concerns that the target condition as defined by the reference standard does not match the review question? • Low: if the reference standard, as used in the study, detects the target condition defined in the review question (one- or two-sided tubal occlusion and/or hydrosalpinx). • High: if the reference standard, as used in the study, does not detect the same (form of) target condition as defined in the review question (e.g. number of tubes with occlusion instead of one- or two-sided tubal occlusion at a participant level) • Unclear: if there is insufficient information available to make a judgement about applicability for this domain	Low/High/Unclear	Low/High/Unclear
Comparative accuracy (QUADAS-C)		**Answers for the test comparison**	
Signaling questions	C3.1 Was the risk of bias for each index test judged 'low' for this domain?	Yes/No	
	C3.2 Did the reference standard avoid incorporating any of the index tests?	Yes/No/Unclear	
Risk of bias	C3.3 Could the reference standard, its conduct, or its interpretation have introduced bias in the comparison?	Low/High/Unclear	

C3.1: Answer 'yes' if the risk of bias judgment for single test accuracy (question 3.3 in QUADAS-2) was 'low' for each index test.
C3.2: Answer 'yes' if none of the index tests were part of the reference standard. Note that this issue is different from blinding (signaling question 3.2 in QUADAS-2).
C3.3: Risk of bias can be judged 'low' if signaling questions C3.1 and C3.2 were answered 'yes'. If at least one question was answered 'no', users should consider a 'high risk of bias' judgment if the bias associated with the design feature is of such concern that the entire domain is deemed problematic.

Domain 4: Flow and Timing			
Information to support judgment	*Describe any patients who did not receive the index tests or reference standard or who were excluded from the analysis.* *Describe the time interval and any interventions between the index tests and the reference standard. Describe the time interval and any interventions between the index tests being compared.*		
Single test accuracy (QUADAS-2)		**Answers for _____ (test A)**	**Answers for _____ (test B)**
Signaling questions	4.1 Was there an appropriate interval between index tests and reference standard? • Yes: if the index test and reference standard were performed within 3 months • No: if the index test and reference standard were performed beyond 3 months • Unclear: if the study does not report the interval between the index test and reference standard.	Yes/No/Unclear	Yes/No/Unclear
	4.2 Did all patients receive a reference standard? • Yes: if all participants underwent a reference test. • No: if not all participants underwent a reference test (for example only those with positive test result). • Unclear: if it is not mentioned which participants received a reference test.	Yes/No/Unclear	Yes/No/Unclear
	4.3 Did all patients receive the same reference standard? • Yes: if all participants underwent laparoscopy with blue dye testing • No: if the index test positives or index test negatives underwent a different reference test • Unclear: if this was not reported	Yes/No/Unclear	Yes/No/Unclear
	4.4 Were all patients included in the analysis? • Yes: if all participants were included in the analysis.	Yes/No/Unclear	Yes/No/Unclear

	• No: if some participants were excluded from the analysis. • Unclear: if not clearly reported.		
Risk of bias	4.5 Could the patient flow have introduced bias? • Low: if signaling questions were answered with yes only • High: if one or both signaling questions were answered with "no" • Unclear: if at least one signaling questions were answered with "unclear" and no signaling questions are answered with "no"	Low/High/Unclear	Low/High/Unclear
Comparative accuracy (QUADAS-C)		**Answers for the test comparison**	
Signaling questions	C4.1 Was the risk of bias for each index test judged 'low' for this domain?	Yes/No	
	C4.2 Was there an appropriate interval between the index tests? • Yes: if the interval between index tests was within 3 months • No: if the interval between index tests was more than 3 months • Unclear: if the time interval between the index tests was unclear or not reported	Yes/No/Unclear	
	C4.3 Was the same reference standard used for all index tests?	Yes/No/Unclear	
	C4.4 Are the proportions and reasons for missing data similar across index tests?	Yes/No/Unclear	
Risk of bias	C4.5 Could the patient flow have introduced bias in the comparison?	Low/High/Unclear	

C4.1: Answer 'yes' if the risk of bias judgment for single test accuracy (question 4.5 in QUADAS-2) was 'low' for each index test.
C4.2: For many index tests, 'appropriate' would constitute performing the tests at the same time after patient enrolment. This excludes the possibility of disease progression or change in patient management. Some index tests have different 'diagnostic windows' and are ideally performed at different timepoints; subject-matter expertise is required to determine this.
C4.3: Answer 'yes' if either (1) a single reference standard was used in all patients or (2) multiple reference standards were used (e.g., either surgery or follow-up) and these reference standards were the same for patients receiving index test A and patients receiving index test B.

C4.4: Missing data occurs if test results are unavailable, invalid, inconclusive, or if patients are excluded from the analysis. Answer 'yes' if there is no missing data, or if the proportion and reasons for missing data are similar for index test A and index test B.
C4.5: Risk of bias can be judged 'low' if signaling questions C4.1 to C4.4 were answered 'yes'. If at least one question was answered 'no', users should consider a 'high risk of bias' judgment if the bias associated with the design feature is of such concern that the entire domain is deemed problematic.

Contributions of authors

RT, CK, BWM and RW conceived and designed the review. KR, MYB and VM contributed to the development of the protocol. RT and RW drafted the protocol. All authors revised the protocol critically for important intellectual content and approved the final version.

Declarations of interest

RT is PhD student, writing a thesis on transvaginal hydrolaparoscopy.
KR is a PhD student, focusing on hysterosalpingography.
CK is copromotor for RT's thesis and co-author on several articles on visual tubal patency tests.
VM reports receiving travel and speakers' fees as well as research grants from GUERBET LLC, Merck and Ferring.
MYB has no relevant conflicts to disclose.
BWM is supported by an NHMRC (National Health and Medical Research Council) Investigator grant (GNT1176437). BWM reports consultancy for ObsEva and GUERBET LLC. BWM has received research funding from Ferring and Merck.
RW has no relevant conflicts to disclose.

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Chapter 7

General discussion and future perspectives

General discussion

Transvaginal hydrolaparoscopy is a technique to evaluate tubal patency and can be used in an outpatient setting, as described by Gordts [1] in 1998. However, when starting this thesis, literature did not provide clear answers what one could expect when adopting this technique throughout. The idea arose that the capacity of THL to visualize endometriosis and adhesions directly on the video screen, could potentially be an advantage to other visual tubal patency tests which have a more indirect way of visualizing. The aim of this thesis was to study the capacity of transvaginal hydrolaparoscopy for diagnosing tubal pathology as a first-choice tubal patency test in an outpatient setting. In this chapter the research questions will be discussed according to our findings and in relation to available literature as well as directions for future research will be given.

Is THL feasible as an outpatient tubal patency test in terms of performance, learning curve reflected by failures and complications, and tolerability?

Performance of THL is described by several research groups around the globe [2-9]. Most of these research groups show data of THL performed by a small number of gynaecologists. Some of them have performed over 1000 procedures which is not applicable to the Dutch situation. We therefore performed a retrospective study in four hospitals and included over 1100 women who had a THL as first choice tubal patency test (Chapter 2). Also, the initial procedures performed by the 16 different gynaecologists were taken into account. We studied performance of the THL in terms of four categories: 1. complete evaluation, 2. incomplete evaluation procedure, 3. incomplete non diagnostic procedure and 4. failure. We concluded THL has a good performance which is supported by the 89.7% complete evaluation of tubal as well as pelvic state together with 2.5% of incomplete evaluation procedure in which pelvic abnormalities like endometriosis or adhesions prevent a complete evaluation. Performance of THL in other studies was likewise, from 92% [8] to 96% [6] and 96.2% [10] in respectively 106, 109 and 160 THLs from single operator experience. The performance of THL by highly experienced gynaecologist is 96.8% in a single operator experience of 1000 THLs [5], 98.26% in a total of 2288 procedures performed by 6 gynaecologists [3] and 99.05% in a single operator experience with 1490 THLs [4].

The complication rate of 2.6% shown in Chapter 2 is comparable to the literature. However, our data are at the upper limit [3, 7, 11]. All but one complication could be managed conservatively, which is in line with these previous reviews [7, 11]. In the review of Gordts from 2008 [11], 27 publications on THL with a total of 2843 procedures were included. In this study the complication rate was 0.74% overall, including 0.35% bowel injuries. They concluded that major complications never occurred and bowel injuries can be treated conservatively with antibiotics. The reason for this is the small diameter of the instruments used (3.9 to 6mm) and that bowel injuries mostly occur extra-peritoneal. The rather high complication rate in our study (Chapter 2) is reflecting the learning curve of the participating gynaecologists as the complication rate dropped from respectively 5% when performing <50 procedures, to 2% when performing 50-100 procedures to 0.7% when performing >100 procedures. Other studies describing learning curves are performed by Gordts et al [12] and Franz et al. The first undertook a multinational retrospective survey which stated a learning curve of 50 procedures based on the significant decrease in bowel injuries from 1.35% to 0.25% respectively when performing up to 50 procedures and over 50 procedures. This study included data on bowel injury of one of our participating centers as well. Franz et al. [13] described learning curve as a

decrease in length of surgery, where they proposed a learning curve of 20 procedures for diagnostic THL and 40 procedures for operative THL. The complication rate for the trainee in this study however was 5% in his first 60 procedures.

Failure is a known default in THL. In our retrospective cohort (Chapter 2) 6.8% failures occurred, whereas 5.4% failures were seen in our later performed randomised controlled trial (RCT) (Chapter 4). Pre-peritoneal Veress needle- or trocar placement was the main reason for failure, accounting for 3.5% in both studies. Peritoneal tenting, which happens when the Verres needle or trocar is not placed briskly enough, is said to happen more often during the learning curve [3, 8, 14]. We did see less failures when a gynaecologist had performed over 100 procedures compared to less than 100 (respectively 6.3% failures versus 8.1% failures). When looking at the proposed learning curve threshold of 50 procedures, the risk on failure was 8.1% when over 50 THLs were performed compared to 7.8% under 50 procedures. In our RCT however, all gynaecologists were experienced and past their learning curve and still in 5.4% of the procedures a failure occurred (Chapter 4). The explanation is most likely a poor patient selection. Although a relative contra indication, in our retrospective cohort 31 women with a retroverted uterus underwent a THL. They had a higher risk on complications (12.9%) and failures (29.1%) (Chapter 2). Furthermore obesity, vaginismus or pelvic floor dysfunction or cervical problems accounted for the other failures. These problems can be foreseen during physical examination. In Dutch teaching hospitals, the doctors explaining and planning THL with their patients, are mostly not the ones performing the THL. This can be an explanation for the unfortunate scheduling of those women for a THL.

Regarding tolerability, in Chapter 2 low pain scores were given by women undergoing THL with an average of 4.0 (range 0-10 on a visual analogue scale; 0 meant no pain at all and 10 the worst pain one could imagine). Next, in Chapter 4 we showed THL to be less painful than HSG with a pain score of 4.7 vs 5.4 (range 0-10).The acceptability scores, defined as the willingness to undergo the same procedure under the same circumstances again and as the willingness to recommend the procedure to friends or family on a VAS from zero (total willingness, total recommendation) to ten (no willingness nor recommendation at all), were 1.5 in Chapter 2 and 2.6 in Chapter 4 with no statistical difference with the HSG group. We therefore conclude that outpatient THL is well tolerated by women. Only five other studies reported on pain during THL [3, 15, 16, 17, 18]. Van Tetering et al. [18] uses a cohort of patients which is included in our retrospective cohort as well. Although the four studies [3, 15, 16, 17] all report acceptable pain scores and high acceptability, a comparison with our data is hard to make as these studies do not report a mean pain score for the whole procedure but separate scores for parts of the procedure.

In conclusion, THL is feasible as outpatient tubal patency test with a fair performance of 92% evaluations of tubal status and pelvic pathology, a complication rate of 2.6 to 2.7% and failure rate of 5.4 to 6.3%, low pain scores and high acceptability. The learning curve takes at least 50 procedures reflected by a decline in complications of 5% to 2%. However, when performed over 100 procedures, complication rate drops to 0.7% and more over failure rate drops to 6.3%. The latter can further be reduced with better patient selection.

What is the diagnostic accuracy of outpatient THL compared to the current reference standard laparoscopy?

Although diagnostic laparoscopy with tubal patency testing is nowadays omitted in fertility assessments [19-21], it is still considered as reference standard to investigate tubal patency as well as tubo-peritoneal pathology. Several studies compared diagnostic accuracy of THL to diagnostic laparoscopy with dye (DLS). First, pilot studies to assess the feasibility and accuracy of THL under general anaesthesia in a small number of women were performed [1, 22]. In these studies, comparable accuracy was concluded, although filmy adhesions on the ovarian surface were seen more often during THL. Hereafter, five studies were performed comparing THL with DLS [23-27]. Sensitivity in these studies was calculated between 70-100% and specificity between 20-100% for diagnosing tubal occlusion, adhesions and endometriosis. Endometriosis was found to be detected better with THL in two studies of the group of Gordts et al. [14, 29], though Nawroth et al. [24] found THL to be less accurate in detecting endometriosis. To our knowledge, we presented the largest retrospective cohort of women who underwent THL and DLS (Chapter 3). We found a sensitivity and specificity of finding abnormalities (tubal pathology, endometrioses and/or adhesions) of respectively 100 and 22.2%. This can be explained by the fact that just a few women underwent laparoscopy when their THL showed no abnormalities, which was not the case in the above mentioned studies. In the group of failed and non-diagnostic THLs, abnormalities during DLS were found in 32.6% whereas only 5.4% abnormalities were seen in the group of complete evaluations and incomplete evaluation procedures. Again, this stresses the need for good physical examination and (transvaginal) ultrasonography before scheduling a THL. Next, in our RCT (Chapter 4) in only 8 women of the THL group a laparoscopy was carried out as no laparoscopies were performed when THL showed bilateral tubal patency and no need for therapeutic laparoscopy was found. In two women diagnostic laparoscopy was performed because THL failed or was incomplete, and in both abnormalities were found. The other six women underwent therapeutic laparoscopy. Concordant results between THL and diagnostic/therapeutic laparoscopy were found in 71.4%. The two discordant cases are debatable as in one woman a large timeframe between both tests existed and in the other woman adhesions were detected during THL, which were not seen during laparoscopy. THL detecting more adhesions than laparoscopy was seen more often in previous studies [22, 28]. Thus, when looking at the current available evidence, THL seems to be comparable to DLS in diagnostic accuracy. The outcome of the protocol described in Chapter 6 will shed more light on the question if THL is the best visual tubal patency test to replace DLS.

Can THL replace HSG as a first-choice tubal patency test; what is the capacity of these tests to diagnose tubal pathology and their performance in safety, pain and acceptability?

For over a century HSG is mostly used as first-choice tubal patency test. Although DLS is considered the reference standard, it is often omitted when HSG does not show any abnormalities. HSG is a safe, less invasive and less expensive procedure compared to DLS and also has a therapeutic effect when an oil-soluble contrast medium is used [30]. But, HSG has drawbacks. Its sensitivity of 65% and specificity of 83% in diagnosing tubal pathology seems to be lower than what is described for THL [31]. Next, there is need for a radiology department and exposure to ionizing radiation for both woman and healthcare workers. Several studies compared THL to HSG [15,16, 32-35]. To our knowledge only one small RCT was performed [16], in which 23 subfertile women without obvious pelvic pathology were divided in two groups by randomisation. One group underwent THL and mini-hysteroscopy followed by HSG in 7 days. The second group underwent HSG followed by THL and mini-hysteroscopy in 7 days. They concluded in 95.5% concordance between HSG and THL regarding tubal patency, THL detected endometriosis in 2 women and THL was found to be less painful than

HSG. Other studies were small retrospective studies in which THL was performed after abnormal HSG [15, 32, 33] and two small prospective studies in which THL was offered before/instead of laparoscopy after abnormal HSG [34, 35]. These studies showed in general a fair agreement between HSG and THL, but the latter showed more peritubal adhesions and endometriotic lesions. Furthermore, THL showed no abnormalities in several cases after abnormal HSG thus preventing 50 - 80% of these women to undergo the more invasive laparoscopy [34, 35]. In our RCT (Chapter 4) we included 300 subfertile women, who were randomised to a strategy with THL or HSG as first-choice tubal test. Bilateral tubal occlusion was detected in one versus three women (0.9% versus 2.2%) of the THL group and HSG group, while unilateral tubal occlusion was detected in seven (6.2%) versus eight (5.9%) women, respectively. Normal findings were seen in 96 (79.3%) women randomised to THL and in 119 (87.5%) in women randomised for HSG (RR 0.91 95%CI 0.81–1.01, p = 0.08). In 9 (7.4%) women of the THL group other abnormalities (adhesions, endometriosis, ovarian cyst) were found compared to 3 (3.7%) women of the HSG group in which intra uterine abnormalities and hydrosalpinx were found. Failures were seen more in the THL group (n = 8, 5.6%) than in the HSG group (n = 1, 0.7%) (p = 0.014). Complications did not differ significantly between the groups (THL n = 4; 2.8% vs HSG n = 1; 0.7%) (p = 0.20). The pain score was significantly less for THL (VAS 4.7 (SD: 2.5)) than for HSG (VAS 5.4 (SD:2.5)) (p 0.038). The acceptability rate of THL and HSG was high and comparable. The concordance in findings during the initial tubal test and DLS (8 in THL group vs 22 in HSG group) did not differ significantly between both groups (p = 1.00). We therefore conclude THL and HSG have a comparable capacity in diagnosing tubal pathology, though they have different test characteristics as THL is able to show pelvic abnormalities but not uterine where HSG does show intra uterine pathology but is less able to discover pelvic abnormalities. It thus seems plausible THL can replace HSG as first choice tubal test, though prognostic capacity and costs must be taken into account as well.

Does a strategy with outpatient THL as first choice tubal patency test lead to as many live births when compared to a strategy with HSG?

Prognostic capacity of THL was first described in a small retrospective study of Fujiwara [33]. They performed THL in 36 patients after HSG and found 20 pregnancies (natural, by intra uterine insemination (IUI) or assisted reproductive technology (ART)) out of 35 women. In eleven of the pregnant women, the THL findings differed for HSG. Next, Van Tetering et al [18] conducted a retrospective study of 272 women and found fecundity rate ratio's (FRRs) for one-sided tubal pathology, two-sided tubal pathology and adhesions/endometriosis were 0.59, 0 and 0.80 respectively. FFR expresses the probability of non-IVF intra uterine pregnancy per time unit for women with a specific feature, relative to the probability in those without that feature. They concluded THL is capable to predict natural ongoing pregnancy. We used our retrospective cohort (Chapter 2) as well for calculating the FFRs [36]. Cumulative intrauterine pregnancy rates after 36 months were 52% for women with bilateral patent tubes, 44% for one-sided tubal occlusion (FRR 1.04; 95% confidence interval [CI], 0.78 to 1.39) and 7% for bilateral tubal occlusion (FRR 0.13; 95% CI, 0.04 to 0.43). Endometriosis was diagnosed in 6.4%, and adhesions in 9.1%, while 3.9% of women had both. Corresponding FRR were 0.73 (95% CI, 0.49 to 1.09), 0.68 (95% CI, 0.46 to 1.02) and 0.42 (95% CI, 0.20 to 0.84). In this study we concluded that both bilateral tubal occlusion or a combination of endometriosis and adhesions found on THL significantly reduced chances of natural conception. In Chapter 5 however, we directly compared the prognostic capacity of THL to that of HSG. Although our study was underpowered and therefore, we cannot draw strict conclusions, it is the first and

largest direct comparison currently available. Regarding our primary outcome, 83 women (58.5%) of the THL group (n = 142) conceived of a live born child within 24 months after randomisation compared to 82 women (55.4%) in the HSG group (n = 150) (difference 3.0% (95% CI: -8.3 – 14.4)). Time to conception leading to live birth was not statistically different in both groups. In this RCT we did not find evidence that the advantage of THL over HSG to detect endometriosis and adhesions better leads to a better prognostic capacity, like we did in our retrospective cohort. Nor did we find differences in treatment after completing fertility workup. This might be due to the fact the study was underpowered. Therefore, when taking all available evidence into account, a strategy for subfertile women with outpatient THL as first choice tubal patency test is non-inferior compared to a strategy with HSG.

Can THL replace diagnostic laparoscopy as reference standard?

Diagnostic laparoscopy with tubal patency testing is still considered to be the reference standard, though several visual tubal patency tests are available. Next to THL and HSG, sono-hysterosalpingography (sono-HSG) and magnetic resonance-hysterosalpingography (MR-HSG) have been developed and studied as visual tubal patency tests. Sono-HSG is an ultrasound technique in which an echogenic medium is infused into the uterine cavity to assess the cavity and tubal patency. MR-HSG is similar to HSG, but instead of using fluoroscopy it uses MR-imaging. Which test is used, differs from protocol to doctors' preference and availability of equipment in the setting of the fertility assessment. Furthermore, some protocols differentiate between women with low and high risk on having tubal pathology and recommend to use different tests in these group. Visual tubal patency tests have a common advantage, which is the less-invasive character of the tests and the tolerability in an outpatient or office setting in contrast to laparoscopy. It therefore only seems fair to investigate which visual tubal patency test can replace DLS best for diagnosing tubal patency. The protocol to answer this question is shown in Chapter 6. In this protocol the target conditions are tubal occlusion and hydrosalpinx as these conditions can be diagnosed by all tests. Furthermore, both conditions require fertility treatment. Bilateral tubal occlusion is the indicator for in vitro fertilization (IVF) as natural conception changes are practically zero [37]. Hydrosalpinx has a negative impact on fertility for women undergoing ART and clinical pregnancy rates for IVF are better when removed [38]. Other conditions like endometriosis or adhesions however, cannot be detected by all tests and treatment is debatable. This does not mean these other conditions should not be taken into account. In chapter 2 endometriosis or adhesions or both were detected in 115 women with bilateral patent tubes (11,3%). In chapter 5 bilateral tubal patency with endometrioses or adhesions was seen in 6.7% of the women undergoing THL. Van Kessel et al. showed [36] when both endometriosis and adhesions are detected by THL the chance of natural pregnancy declines. This may imply tubal patency tests which can detect pelvic adhesions and endometriosis might be preferred over those which cannot detect pelvic abnormalities. However, the question is, if this outcome is due to non-informative censoring. Non-informative censoring assumes the pregnancy prognosis is equal to patients for whom the follow up period ends (in this case due to treatment) without the occurrence of natural pregnancy as to patients who remain in follow up [39]. When a patient has open tubes but other pathology is seen, a doctor can decide to start treatment, because he/she considers the chance of natural conception to be low. Therefore, the chance of natural conception is likely to be lower for treated patients. As concluded in chapter 3, THL has a high concordance to DLS and is comparable in diagnostic accuracy and thus is able to replace DLS as

reference standard. We must wait for the results of this review study however, if THL is the best candidate.

Future perspectives

Overall THL is a promising technique, with many similarities to DLS. However, in the past two decades the uptake of this technique has not been one would expect. Just like with the former culdoscopy, gynaecologist remain sceptical and keep using the “old fashioned” HSG or the newer sono-HSG for all different reasons [29]. With the upcoming procedure named transvaginal natural orifice transluminal endoscopic surgery (vNOTES) [40], which gains a lot of interest, THL might become more popular as well. vNOTES is a surgical procedure with aesthetically (no external scars) advantages for patients and better ergonomics for the surgeon because of the use of the transvaginal route just like THL. Therefore, possibilities to use THL for other diagnostic and small surgical purposes can gain more interest [41].

Though already established for HSG [30], the therapeutic effect of tubal flushing with oil-based contrast medium has to be studied for other tubal patency tests as well. Currently, a THL-oil pilot study (NTR NL8696) is carried out which is a first step in this matter. If its therapeutic effect of tubal flushing has been proven in other tubal tests next to HSG, the next step should be comparing the therapeutic and prognostic capacities and, in this way, the best strategy for subfertile women. For lasting affordable healthcare, cost effectiveness should as well be taken into account when investigating these different strategies.

Next, to help bringing offspring in this world, we should also think how to save our earth for future generations. With the alarming report of the Lancet Countdown in mind, sustainability should always be a part of clinical trials [42]. For example, life cycle assessments can be performed to compare which strategy has the lowest carbon footprint [43]. Furthermore, prevention of causes of subfertility is another possibility for reducing health costs and resources. Potential options are awareness of safe sex, affordable and available contraception methods and safe abortion. These measures might prevent tubal infertility by lowering the change on sexually transmitted diseases and pelvic inflammatory disease. Next, prevention of obesity and reducing unhealthy habits as smoking will help in effectuating more natural pregnancies and thus less tubal patency testing. When we work on all these different approaches, less tubal patency tests have to be performed. But when it is necessary, the best in terms of diagnostic and prognostic capacity, tolerability, cost effectiveness and sustainability should be used, which may be well THL.

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Chapter 8

Impact paragraph

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The Fallopian tubes are necessary for the transport of spermatozoa, ovum and embryo. Their fimbriae have to move freely to pick up the ovum, store it in the folds of the tube and wait for spermatozoa to fertilize it after which the cilia sweep the zygote to the uterus. When tubes are blocked or dysfunctional, this process can be disturbed. Tubal infertility, which is the result of damage or infection to the Fallopian tubes, accounts for around 20% of all subfertility diagnoses. Tubal testing is therefore offered during subfertility workup.

Transvaginal hydrolaparoscopy (THL) is one of the available visual tubal patency tests. THL uses the transvaginal route to enter the pelvis after warm saline is infused. With a 30 degrees optical endoscope connected to a video camera system and monitor, the whole pelvis is inspected for adhesions, endometriosis or other pathology. Furthermore, tubal patency is tested by flushing a blue dye through the tubes. THL allows both the gynaecologist to visualize potential fertility declining abnormalities directly and the woman in question to witness the whole procedure at the same time. In terms of direct visibility, THL is comparable to diagnostic laparoscopy (DLS), the reference standard for testing tubal patency. However, a big advantage of THL compared to DLS is THL can be performed under local anaesthesia where as DLS requires general anaesthesia and thus hospitalization. The fact that THL can visualize the pelvis and internal female organs a direct manner, next to testing tubal patency, is why some gynaecologists prefer THL over other visual tubal patency tests. Though, THL is only practiced by a small number of gynaecologists in four hospitals/clinics in the Netherlands. In most Dutch hospitals as well in the Dutch guideline for fertility workup hysterosalpingography (HSG) is the preferred tubal patency test. HSG is a visual tubal patency test like THL, but can only visualize tubal pathology and no other pelvic pathology. To the contrary of THL, it does so in an indirect way. HSG uses serial X-rays or fluoroscopy to evaluate the shape of the uterine cavity and the patency of the Fallopian tube by injecting a radiopaque medium through the cervical canal into the uterus and subsequently the tubes. When an oil-soluble contrast medium is used, HSG has a therapeutic effect as well, with a higher chance of clinical pregnancy and birth compared to the use of a water-based contrast medium. But when HSG shows abnormalities, these have to be confirmed with DLS. This is a major drawback compared to THL.

The question at hand is if THL is a procedure which gynaecologists should embrace or should forget. In other words, is THL comparable to or even better than HSG and DLS in diagnosing fertility declining pathology with the same safety and tolerability for women undergoing this procedure?

In this thesis we showed THL to be an accurate, safe and tolerable procedure in diagnosing tubal and pelvic pathology, comparable to both HSG and DLS. When compared to HSG, THL has:

- the ability to omit diagnostic laparoscopy
- an acceptable but higher complication rate (2.6% for THL versus 0.7% for HSG) without major complications
- lower pain scores
- comparable acceptability
- a higher failure rate (5.6% for THL versus 0.7% for HSG)
- the ability to select women suitable for therapeutic laparoscopy

When compared to DLS, THL has:

- no need for general anaesthesia and hospitalization
- a high sensitivity (how many women are correctly identified as having tubal pathology, endometriosis and/or adhesions) but low(er) specificity (how many women are correctly identified as having no tubal pathology, endometriosis and/or adhesions)

This means that the current gynaecologist performing THL, can continue to offer this to women as tubal patency test for completing their fertility workup. If other gynaecologists want to start performing THL, they should take two points of concern from this thesis into account. First, the learning curve takes up to 50 procedures before the complication rate drops. To minimalize the number of complications a small permanent executive team can help to maximize the exposure and experience. Second, to decline failure rate, we discussed better patient selection. This can be done by training of all staff counselling women for tubal testing and making them aware of the contra-indications of THL. This can help unnecessary cancellations prior to THL or complications of THL which will protect the women concerned. Especially those with a (fixed) retroverted uterus should not be counselled for THL as this thesis showed an almost fivefold higher chance on complications.

Nowadays it depends where a subfertile woman has her fertility work-up, what kind of tubal test she is offered to undergo. When the HSG shows abnormalities, DLS is the next step. But when all Dutch gynaecologist would perform THL instead of HSG, an unnecessary diagnostic laparoscopy could be omitted and only in case of pelvic or tubal abnormality a therapeutic laparoscopy can be scheduled when necessary. Furthermore, THL can be beneficial for the understanding and counselling of the woman and her partner because they can watch the THL procedure directly on the video screen. In this way, the gynaecologist can show and explain possible abnormalities directly which is more patient friendly.

With this thesis we have provided evidence why THL should be acknowledged and have a more prominent place in the work-up of subfertile women. Ongoing research from our THL-group will show if THL, just like HSG, also has a therapeutic effect when an oil-soluble contrast medium is used.

A next step is conducting the “Visual tubal patency tests for tubal occlusion and hydrosalpinx” Cochrane review in which we will try to find the visual tubal patency test which can replace diagnostic laparoscopy. As this study is published on the Cochrane website and will be freely available for physicians and patients worldwide, both our target groups (fertility doctors / gynaecologists and subfertile women) can be reached.

Chapter 9

Summary / Samenvatting

Summary

Every 6 out of 1000 women per year visit their general practitioner because of subfertility which is defined as the failure to achieve a successful pregnancy after 12 months or more of regular, unprotected sexual intercourse. Tubal infertility is a result of damage and/or infection to the Fallopian tubes and is diagnosed in around 10-30% of the subfertile women. This is why fertility workup is usually completed with tubal patency testing. One of the known visual tubal patency tests is transvaginal hydrolaparoscopy (THL). This technique uses the transvaginal route to enter the pelvic cavity after filling it with warm saline. Because of the use of a video camera system and monitor, it allows the gynaecologist to visualize potential fertility declining abnormalities directly as it allows the woman in question to witness the whole procedure at the same time. Before implementing THL in more hospitals than the current four, the performance of THL as well as a comparison of THL, standard care and standard reference must be studied.

Therefore, this thesis focuses on the capacity of transvaginal hydrolaparoscopy for diagnosing tubal pathology as a first-choice tubal patency test in an outpatient setting. **Chapter 1** gives an introduction on subfertility as well as on different visual tubal patency tests as on THL. The aim of this thesis is described as well as the questions this thesis will try to answer.

Chapter 2 describes a large retrospective cohort of subfertile women undergoing THL as first-choice tubal patency test. In this study the feasibility of performing transvaginal hydrolaparoscopy (THL) in an outpatient setting was evaluated. We studied all THL procedures performed as a primary diagnostic tubal patency test in an outpatient setting in subfertile women starting from the initial THL in four large hospitals. Baseline characteristics were obtained, as well as the outcome of the procedures in terms of success, complications and findings by examining medical records. We used a uniform visual analogue scale (VAS) score document to collect data on pain and acceptability prospectively and compared two methods of pain relief. We studied a total of 1,103 women who underwent THL. Successful access to the pouch of Douglas was achieved in 1028 women (93.2%), and 1,017 women had a complete evaluation (92.2%). Double-sided tubal patency was found in 844 women (83%), unilateral tubal patency in 127 women (12.5%) while in 46 women (4.5%) bilateral occluded tubes were diagnosed. Endometriosis alone was seen in 64 women (6.3%), adhesions alone in 87 women (8.6%) and both endometriosis and adhesions in 42 women (4.1%). Complications occurred in 29 (2.6%) women, including 10 perforations of the rectum (0.9%), 8 perforations of the posterior uterine wall (0.7%) and 5 infections/pelvic inflammatory diseases (PIDs) (0.5%). Bleeding of the vaginal wall requiring intervention and hospital admissions due to pain was seen in 4 (0.4%) and 2 women, respectively (0.2%). The average pain score was rated 4.0 (±2.4 SD) on a VAS from 0 to 10 with 0 meaning no pain at all with no difference in different types of pain relief. Acceptability was rated 1.5 (±2.1 SD). The main limitation of the study is its retrospective character and the fact that only a fourth of the women were asked for pain- and acceptability scores. Nevertheless, we concluded it is feasible to perform THL in an outpatient setting, reflected by a low complication- and failure-rate and a high patients' satisfaction. Therefore, THL can be used as a primary method for tubal assessment in an outpatient setting. Further randomised studies are needed to assess whether THL is superior to other methods and strategies for tubal assessment in terms of prognostic capacity and cost-effectiveness.

In **Chapter 3** the findings the findings of outpatient THL in comparison to diagnostic laparoscopy combined with chromo perturbation in subfertile women. From the database of the in **Chapter 2** described retrospective study, we studied all subfertile women who underwent a THL and a conventional laparoscopy as part of their fertility work up in the period between 2000-2011. Findings at THLs were compared with findings at diagnostic and therapeutic laparoscopies. We defined tubal occlusion, endometriosis and adhesions as abnormalities. We found 1103 women who underwent THL, out of a total of 1119 women. A complete evaluation or incomplete but diagnostic procedure could be performed in 989 (89.7%) and 28 (2.5%) respectively. An incomplete non-diagnostic procedure was performed in 11 (1.0%) women. Failure of THL occurred in 75 women (6.8%) and 40 of these women (3.6%) underwent laparoscopy subsequently. Laparoscopy was performed in a total of 126 patients with a median time interval of 7 weeks (IQR 3-13 weeks). Of 64 patients who successfully underwent both THL and laparoscopy concordant findings were found in 53 women and discordant results in 11 women, 6 of which were caused by tubal spasm. Sensitivity of THL in detecting abnormalities was 100% and specificity was 22.2% with a likelihood ratio of 1.29. We concluded that THL in an outpatient setting can detect anatomical abnormalities comparable to the, more invasive, reference standard diagnostic laparoscopy. If THL succeeds, there is no need to add a diagnostic laparoscopy in the work-up.

Chapter 4 presents the results of a randomised clinical trial to assess the capacity of transvaginal hydrolaparoscopy (THL) versus hysterosalpingography (HSG) as a primary tool to diagnose tubal pathology. We performed a multicenter RCT (NTR3462) in 4 teaching hospitals in the Netherlands, comparing THL and HSG as first line tubal test in subfertile women. The primary outcome of this trial was cumulative live birth rate at 24 months which is presented in **Chapter 5**. Here, we present the secondary outcomes, the diagnostic findings of both THL and HSG as well as performance defined as failures, complications and pain- and acceptability scores. Between May 2013 and October 2016, we allocated 149 women to THL and 151 to HSG, of which 17 women in the THL group (11.4%) and 12 in the HSG group (7.9%) conceived naturally before the scheduled procedure, while 13 HSGs and 5 THLs were not performed for other reasons (withdrawal of informed consent, not willing to undergo tubal testing and protocol violations). A total of 119 THLs and 134 HSGs were carried out. Failures were seen more in the THL group (n=8, 5.6%) than in the HSG group (n=1, 0.7%) (p=0.014). Complications did not differ significantly between the groups (THL n=4; 2.8% vs HSG n = 1; 0.7%) (p = 0.20). Bilateral tubal occlusion was detected in one versus three women (0.9% versus 2.2%) of the THL group and HSG group, while unilateral tubal occlusion was detected in seven (6.2%) versus eight (5.9%) women, respectively. Normal findings were seen in 96 (79.3%) women randomised for THL and in 119 (87.5%) women randomised for HSG (RR 0.91 95%CI 0.81 to 1.01, p = 0.08). The pain score was significantly less for THL (VAS 4.7 (SD: 2.5)) than for HSG (VAS 5.4 (SD:2.5)) (p 0.038). The acceptability rate of THL and HSG was high and comparable. We concluded THL and HSG have a comparable capacity in diagnosing tubal pathology with comparable performance in safety, pain and acceptability.

In **Chapter 5** the primary outcome “conception leading to live birth within 24 months after randomisation” of the in **Chapter 4** described RCT is presented. The research question of this trial is whether THL is non-inferior to HSG as a first-line tubal patency test in subfertile women in predicting the chance of conception leading to live birth. As described above a multi-centre, randomised controlled trial in four teaching hospitals in the Netherlands was performed, which randomised subfertile women scheduled for tubal patency testing to either THL or HSG as a first-line tubal patency test. A total of 149 women were randomised to THL and 151 to HSG. From the intention-to-

treat population, 83 women from the THL group (58.5%) conceived and delivered a live born child within 24 months after randomisation compared with 82 women (55.4%) in the HSG group (difference 3.0%, 95% CI –8.3 to 14.4). Time to conception leading to live birth was not statistically different between groups. Miscarriage occurred in 16 (11.3%) women in the THL group, versus 20 (13.5%) women in the HSG group (RR = 0.66, 95% CI 0.34 to 1.32, P = 0.237), and multiple pregnancies occurred in 12 (8.4%) women in the THL group compared with 19 (12.8%) women in the HSG group (RR = 0.84, 95% CI 0.46 to 1.55, P = 0.58). Ectopic pregnancy was diagnosed in two women in the HSG group (1.4%) and none in the THL group (P = 0.499). This led to the conclusion that in a preselected group of subfertile women with a low risk of tubal pathology, use of THL was not inferior to HSG as a first-line test for predicting conception leading to live birth.

Chapter 6 describes a diagnostic test accuracy (DTA) Cochrane Review protocol named "Visual tubal patency tests for tubal occlusion and hydrosalpinx". The primary objective is to determine and compare the diagnostic accuracy of visual tubal patency tests (hysterosalpingography (HSG), sono-hysterosalpingography (sono-HSG), magnetic resonance hysterosalpingography (MR-HSG), and outpatient transvaginal hydrolaparoscopy (THL)) for the diagnosis of tubal occlusion. Secondary objectives are:

- To determine and compare the diagnostic accuracy of visual tubal patency tests (HSG, sono-HSG, MR-HSG, and outpatient THL) for the diagnosis of hydrosalpinx.
- To evaluate heterogeneity with regards to population characteristics (population risk stratification) and index test characteristics (contrast media, technology, operator skills).

The rationale for this review is that all visual tubal patency tests are well tolerated in an outpatient setting and are less invasive than DLS, the current reference standard. Therefore, it seems fair to offer such a test instead of DLS. However, no (Cochrane) review about the evidence of the accuracy of individual tests and about the comparison of different tests' accuracies exists. This must be known first, before replacing the reference standard. Therefore, a literature search will be performed including studies on the diagnostic test accuracy of a single index test (HSG, sono-HSG, MR-HSG and THL) and studies on the comparative diagnostic test accuracy of two or more index tests. Only studies with participants with infertility, both with high and low risk of tubal pathology as well as unselected participants, undergoing a visual tubal patency test and a diagnostic laparoscopy will be included.

In **Chapter 7** the general discussion in relation to available literature as well as future perspectives are described.

Nederlandse samenvatting

Transvaginale hydrolaparoscopie bij de diagnose van tubapathologie

Per jaar bezoeken 6 op de 1000 vrouwen per jaar hun huisarts vanwege subfertiliteit, wat wordt gedefinieerd als het niet bereiken van een succesvolle zwangerschap na een periode van 12 maanden of meer met regelmatige, onbeschermde geslachtsgemeenschap. Tubaire sub/infertiliteit

dat het gevolg is van beschadiging en/of infectie van de tubae oftwel eileiders, wordt vastgesteld bij ongeveer 10-30% van de subfertiele vrouwen. Dit is de reden waarom vruchtbaarheidsonderzoek meestal wordt gecompleteerd met het testen van de doorgankelijkheid van deze tubae genaamd tubatesten. Een van deze tubatesten, is transvaginale hydrolaparoscopie (THL). Deze techniek maakt gebruik van de transvaginale route om de bekkenholte te bekijken nadat deze is gevuld met warme zoutoplossing. Door gebruik te maken van een videocamerasysteem en monitor kan de gynaecoloog afwijkingen direct visualiseren en tegelijkertijd kan de vrouw in kwestie de hele procedure volgen. Voordat THL in meer dan de huidige vier ziekenhuizen wordt geïmplementeerd, zullen de prestaties van THL moeten worden bestudeerd en vergeleken worden met de huidige zorg en de gouden standaard. Daarom richt dit proefschrift zich op de bekwaamheid van transvaginale hydrolaparoscopie als eerste keus tubatest in een poliklinische setting.

Hoofdstuk 1 geeft een inleiding over subfertiliteit en over de verschillende tubatesten en over THL. Het beschrijft het doel van dit proefschrift en de vragen die gesteld worden. **Hoofdstuk 2** beschrijft een groot retrospectief cohort van subfertiele vrouwen die THL ondergaan als eerste keus tubatest. In deze studie werd de haalbaarheid van het uitvoeren van THL in een poliklinische setting geëvalueerd. We bestudeerden alle THL-procedures die werden uitgevoerd in vier grote ziekenhuizen bij subfertiele vrouwen in een poliklinische setting. Hierbij werd THL als eerste keus onderzoek ingezet om de doorgankelijkheid van de eileiders te testen. Door medische dossiers te onderzoeken werden patiënt-kenmerken achterhaald, evenals de uitkomst van de procedures in termen van succes, complicaties en bevindingen. We gebruikten een uniforme visueel analoge schaal (VAS) score-formulier om prospectief gegevens te verzamelen over pijn en aanvaardbaarheid van het onderzoek en vergeleken twee methoden voor pijnverlichting. We bestudeerden in totaal 1.103 vrouwen die een THL ondergingen. Succesvolle toegang tot de bekkenholte werd bereikt bij 1028 vrouwen (93,2%) en in 1017 vrouwen de evaluatie was compleet (92,2%). Dubbelzijdige doorgankelijke tubae werden gevonden bij 844 vrouwen (83%), enkelzijdige doorgankelijke tuba bij 127 vrouwen (12,5%) terwijl bij 46 vrouwen (4,5%) dubbelzijdig afgesloten tubae werden gediagnosticeerd. Endometriose werd gezien bij 64 vrouwen (6,3%), adhesies bij 87 vrouwen (8,6%) en zowel endometriose als adhesies bij 42 vrouwen (4,1%). Complicaties traden op bij 29 (2,6%) vrouwen, waaronder 10 perforaties van het rectum (0,9%), 8 perforaties van de uterusachterwand (0,7%) en 5 infecties/bekkenontstekingen (pelvic inflammatory disease / PID) (0,5%). Bloeding van de vaginawand waarvoor een interventie nodig was en ziekenhuisopnames vanwege pijn, werden gezien bij respectievelijk 4 (0,4%) en 2 (0,2%) vrouwen. De gemiddelde pijnscore werd beoordeeld als 4,0 (± 2,4 SD) op een VAS van 0 tot 10, waarbij 0 betekent dat er helemaal geen pijn is en 10 de ergste pijn die men kent. Er was geen verschil in verschillende soorten pijnverlichting. Aanvaardbaarheid, gedefinieerd als de bereidheid voor het opnieuw ondergaan van de procedure als nodig, werd beoordeeld met 1,5 (± 2,1 SD). De belangrijkste beperking van het onderzoek is het retrospectieve karakter en het feit dat slechts een vierde van de vrouwen werd gevraagd naar pijn- en aanvaardbaarheidsscores. We concludeerden dat het haalbaar is om THL uit te voeren in een poliklinische setting, weerspiegeld door een laag complicatie-percentage, een laag percentage niet gelukte ingrepen en een hoge patiënttevredenheid. THL kan daarom worden gebruikt als een primaire methode voor het beoordelen van de eileiders in een poliklinische setting. Verdere gerandomiseerde studies zijn nodig om te beoordelen of THL superieur is aan andere methoden en strategieën voor de beoordeling van de eileiders in termen van prognostische capaciteit en kosteneffectiviteit.

In **Hoofdstuk 3** worden de bevindingen van poliklinische THL vergeleken met diagnostische laparoscopie gecombineerd met tubatesten bij subfertiele vrouwen. Uit de database van de in **Hoofdstuk 2** beschreven retrospectieve studie hebben we alle subfertiele vrouwen bestudeerd die in de periode 2000-2011 een THL en een conventionele laparoscopie ondergingen als onderdeel van hun vruchtbaarheidsonderzoek. Bevindingen bij THL's werden vergeleken met bevindingen bij diagnostische en therapeutische laparoscopieën. We definieerden dubbelzijdig afgesloten tubae, endometriose en adhesies als afwijkingen. We vonden 1103 vrouwen die THL ondergingen, op een totaal van 1119 vrouwen. Een volledige evaluatie of een onvolledige maar diagnostische procedure kon worden uitgevoerd in respectievelijk 989 (89,7%) en 28 (2,5%). Bij 11 (1,0%) vrouwen werd een onvolledige niet-diagnostische procedure uitgevoerd. Falen van THL trad op bij 75 vrouwen (6,8%) en 40 van deze vrouwen (3,6%) ondergingen vervolgens laparoscopie. Laparoscopie werd uitgevoerd bij in totaal 126 patiënten met een mediane tijdsinterval van 7 weken (IQR 3-13 weken). Van 64 patiënten die met succes zowel THL als laparoscopie ondergingen, werden concordante bevindingen gevonden bij 53 vrouwen en discordante resultaten bij 11 vrouwen, waarvan er 6 werden veroorzaakt door tubaire spasmen. De sensitiviteit van THL bij het opsporen van afwijkingen was 100% en de specificiteit was 22,2% (LR 1,29). We concludeerden dat THL in een poliklinische setting anatomische afwijkingen kan detecteren die vergelijkbaar zijn met de, meer invasieve, gouden standaard diagnostische laparoscopie. Als THL succesvol wordt uitgevoerd, hoeft er geen diagnostische laparoscopie meer verricht te worden.

Hoofdstuk 4 presenteert de resultaten van een gerandomiseerde klinische studie om het vermogen van transvaginale hydrolaparoscopie (THL) versus hysterosalpingografie (HSG) te beoordelen als primair onderzoek voor het diagnosticeren van eileider afwijkingen. We hebben een multicenter RCT (NTR3462) uitgevoerd in 4 perifere opleidingsziekenhuizen in Nederland, waarbij THL en HSG werden vergeleken als eerstelijns eileider onderzoek bij subfertiele vrouwen. De primaire uitkomst van deze studie was het cumulatieve geboortecijfer na 24 maanden, welke wordt gepresenteerd in **Hoofdstuk 5**. Hier presenteren we de secundaire uitkomstmaten namelijk de diagnostische bevindingen van zowel THL als HSG, evenals de prestaties van THL en HSG gedefinieerd als percentage gelukte en niet gelukte procedures, complicaties en pijn- en aanvaardbaarheidsscores. Tussen mei 2013 en oktober 2016 zijn 149 vrouwen gerandomiseerd voor THL en 151 voor HSG. Hiervan werden 17 vrouwen in de THL-groep (11,4%) en 12 in de HSG-groep (7,9%) op natuurlijke wijze zwanger vóór de geplande procedure, terwijl 13 HSG's en 5 THL's om andere redenen niet werden uitgevoerd (intrekking van toestemming, niet bereid om een tubatest te ondergaan en protocolschending). In totaal werden 119 THL's en 134 HSG's uitgevoerd. Niet gelukte procedures werden vaker gezien in de THL-groep (n=8; 5,6%) dan in de HSG-groep (n=1; 0,7%) (p=0,014). Complicaties tussen beide groepen verschilden niet significant (THL n=4; 2,8% versus HSG n = 1; 0,7%) (p = 0,20). Dubbelzijdig afgesloten tubae werd gedetecteerd bij respectievelijk één en drie vrouwen van de THL- en HSG-groep (0,9% versus 2,2%), terwijl bij respectievelijk zeven (6,2%) en acht (5,9%) vrouwen een eenzijdige afgesloten tuba werd gedetecteerd. Normale bevindingen werden gezien bij 96 (79.3%) vrouwen gerandomiseerd voor THL en bij 119 (87.5%) vrouwen gerandomiseerd voor HSG (RR 0.91 95%CI 0.81 tot 1.01, p = 0.08). De pijnscore was significant lager voor THL (VAS 4,7 (SD: 2,5)) dan voor HSG (VAS 5,4 (SD:2,5)) (p 0,038). De aanvaardbaarheids-score van THL en HSG was hoog en vergelijkbaar. We concludeerden dat THL en HSG een vergelijkbare capaciteit hebben in het diagnosticeren van tubaire afwijkingen met vergelijkbare prestaties op het gebied van veiligheid, pijn en aanvaardbaarheid.

In **Hoofdstuk 5** wordt de primaire uitkomstmaat “conceptie leidend tot levendgeborene binnen 24 maanden na randomisatie” van de in **Hoofdstuk 4** beschreven RCT gepresenteerd. De onderzoeksvraag van deze studie is of THL als eerstelijns tubatest bij subfertiele vrouwen niet inferieur is aan HSG bij het voorspellen van de kans op conceptie die leidt tot een levendgeborene. Zoals hierboven beschreven werd een multicenter, gerandomiseerde studie uitgevoerd in vier perifere opleidingsziekenhuizen in Nederland, waarbij subfertiele vrouwen die waren ingepland voor een tubatest gerandomiseerd werden voor THL of HSG als een eerstelijns onderzoek. In totaal werden 149 vrouwen gerandomiseerd naar THL en 151 naar HSG. Analyse volgens het intention-to-treat principe, liet zien dat 83 vrouwen uit de THL-groep (58,5%) binnen 24 maanden na randomisatie een levend geboren kind ter wereld brachten in vergelijking met 82 vrouwen (55,4%) in de HSG-groep (verschil 3,0%, 95% CI -8,3 tot 14,4). De tijd tot conceptie die leidde tot een levend geboren kind was statistisch niet verschillend tussen de groepen. Een miskraam trad op bij 16 (11,3%) vrouwen in de THL-groep, versus 20 (13,5%) vrouwen in de HSG-groep (RR = 0,66, 95% BI 0,34 tot 1,32, P = 0,237), en meerlingzwangerschappen kwamen voor bij 12 (8,4 %) vrouwen in de THL-groep vergeleken met 19 (12,8%) vrouwen in de HSG-groep (RR = 0,84, 95% BI 0,46 tot 1,55, P = 0,58). Buitenbaarmoederlijke zwangerschappen werden gediagnosticeerd bij twee vrouwen in de HSG-groep (1,4%) en niet in de THL-groep (P = 0,499). Dit leidde tot de conclusie dat in een voorgeselecteerde groep van subfertiele vrouwen met een laag risico op tubaire afwijkingen het gebruik van THL als eerstelijns tubatest voor het voorspellen van conceptie leidend tot levendgeborenen niet inferieur was aan HSG.

Hoofdstuk 6 beschrijft een Cochrane Review-protocol voor diagnostische testnauwkeurigheid (diagnostic test accuracy - DTA) genaamd " Visual tubal patency tests for tubal occlusion and hydrosalpinx ". Het primaire doel is het bepalen en vergelijken van de diagnostische nauwkeurigheid van visuele tubatesten (hysterosalpingografie (HSG), sono-hysterosalpingografie (sono-HSG), magnetische resonantie hysterosalpingografie (MR-HSG) en poliklinische transvaginale hydrolaparoscopie (THL)) voor de diagnose van doorgankelijkheid van de tubae. Secundaire doelstellingen zijn:

- Het bepalen en vergelijken van de diagnostische nauwkeurigheid van visuele tubatest (HSG, sono-HSG, MR-HSG en poliklinische THL) voor de diagnose van hydrosalpinx.

- Het evalueren van heterogeniteit met betrekking tot populatie-kenmerken (stratificatie van hoog en laag risico op tubaire afwijkingen en ongeselecteerden qua risico) en indextest-kenmerken (contrastmedia, technologie, vaardigheden van de uitvoerende).

De rationale voor dit review is dat alle visuele tubatesten goed worden verdragen in een poliklinische setting en minder invasief zijn dan DLS, de huidige gouden standaard. Daarom lijkt het eerlijk om een dergelijke test aan te bieden in plaats van DLS. Er bestaat echter geen (Cochrane) review over de diagnostische nauwkeurigheid van de verschillende tubatesten noch een vergelijking tussen al deze verschillende onderzoeken. Dit moet eerst bekend zijn, voordat de gouden standaard wordt vervangen. Daarom zal een zoekstrategie op bestaande literatuur worden uitgevoerd, waarbij studies naar de diagnostische testnauwkeurigheid van een enkele indextest (HSG, sono-HSG, MR-HSG en THL) en studies naar de vergelijkende diagnostische testnauwkeurigheid van twee of meer indextests zullen worden geïncludeerd. Alleen studies met subfertiele deelnemers, zowel met een hoog en laag

risico op tubaire afwijkingen als met niet-geselecteerde deelnemers, die een visuele tubatest én een diagnostische laparoscopie ondergaan, zullen worden opgenomen.

In **Hoofdstuk 7** worden de algemene discussie in relatie tot bestaande literatuur en toekomstperspectieven beschreven.

Appendices

Abbreviations

ART	artificial reproductive technique
CAT	Chlamydia antibody titer
CGF	Cochrane Gynaecology and Fertility
CINAHL	Cumulative Index to Nursing and Allied Health Literature
DLS	diagnostic laparoscopy
DTA	diagnostic test accuracy
HSG	hysterosalpingography
ICTRP	International Clinical Trials Platform
ISRCTN	International Standard Randomised Controlled Trial Number registry
MR-HSG	magnetic resonance hysterosalpingography
NTR	Nationaal trial register
PID	pelvic inflammatory disease
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
RCT	randomised controlled trial / randomised clinical trial
RR	relative risk
SD	standard deviation
Sono-HSG	sono-hysterosalpingography (includes hysterosalpingo-foam sonography and hysterosalpingo-contrast sonography)
SPSS	Statistical Package for the Social Sciences
STD	sexual transmitted disease
THL	transvaginal hydrolaparoscopy
VAS	visual analogue scale
vNOTES	transvaginal natural orifice transluminal endoscopic surgery
WHO	World Health Organization

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Curriculum vitae

Rachel Tros werd geboren op 21 december 1981 in Schoorl als de jongste van drie dochters van Nol Tros en Lida Tros-Schotvanger. Na het behalen van haar VWO diploma met Latijn in 1999, startte zij met de studie Geneeskunde aan de Universiteit van Amsterdam waar ze na een wetenschappelijke stage “cervical cancer and HPV” in Addis Abeba, Ethiopië, in 2004 haar doctoraal behaalde en vervolgens haar artsexamen in 2007.
Na een jaar in het Kennemer Gasthuis, Haarlem als ANIOS verloskunde & gynaecologie te hebben gewerkt, kwam Rachel in 2008 in het VUmc als ANIOS verloskunde. Vanuit deze functie werd zij aangenomen voor de opleiding tot gynaecoloog per januari 2009 in het Medisch Spectrum Twente, Enschede, (opleider G.J.E. Oosterhuis) van waaruit de eerste stappen richting dit promotietraject werden gezet. Na drie mooie jaren in Enschede werd de opleiding voortgezet in het VUmc (opleider J.I.P. de Vries), waar zij in haar laatste jaar differentieerde bij de benigne gynaecologie onder leiding van Judith Huirne.
In januari 2016 rondde Rachel haar opleiding af, waarna ze als chef de Clinique startte in St. Antonius ziekenhuis, Nieuwegein en Leidsche Rijn. Vanaf augustus 2016 werkt Rachel als gynaecoloog binnen de pijler benigne gynaecologie, eerst vanuit VUmc op locatie Louwesweg, later in VUmc en na de lateralisatie in 2020 op locatie AMC van het Amsterdam UMC.

Rachel woont samen met haar man Christof en hun kinderen Norah (2012) en Thijn (2015) in Ouderkerk aan de Amstel.