

Transvaginal hydrolaparoscopy

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TRANSVAGINAL HYDROLAPAROSCOPY
A CLINICAL, ECONOMICAL AND PATIENT PERSPECTIVE

MARIA ANNA VAN KESSEL

TRANSVAGINAL HYDROLAPAROSCOPY:
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a clinical, economical en patient perspective

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TRANSVAGINAL HYDROLAPAROSCOPY: A CLINICAL, ECONOMICAL AND PATIENT PERSPECTIVE

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
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volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
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Maria Anna van Kessel

Promotores

Prof. dr. M.Y. Bongers

Prof. dr. B.W.J. Mol, Monash University, Australia

Copromotor

Dr. C.A.M. Koks, Máxima Medisch Centrum

Beoordelingscommissie

Prof. dr. M.A. Joore, voorzitter

Dr. R.J.T. van Golde

Prof. dr. A. Hoek, UMCG

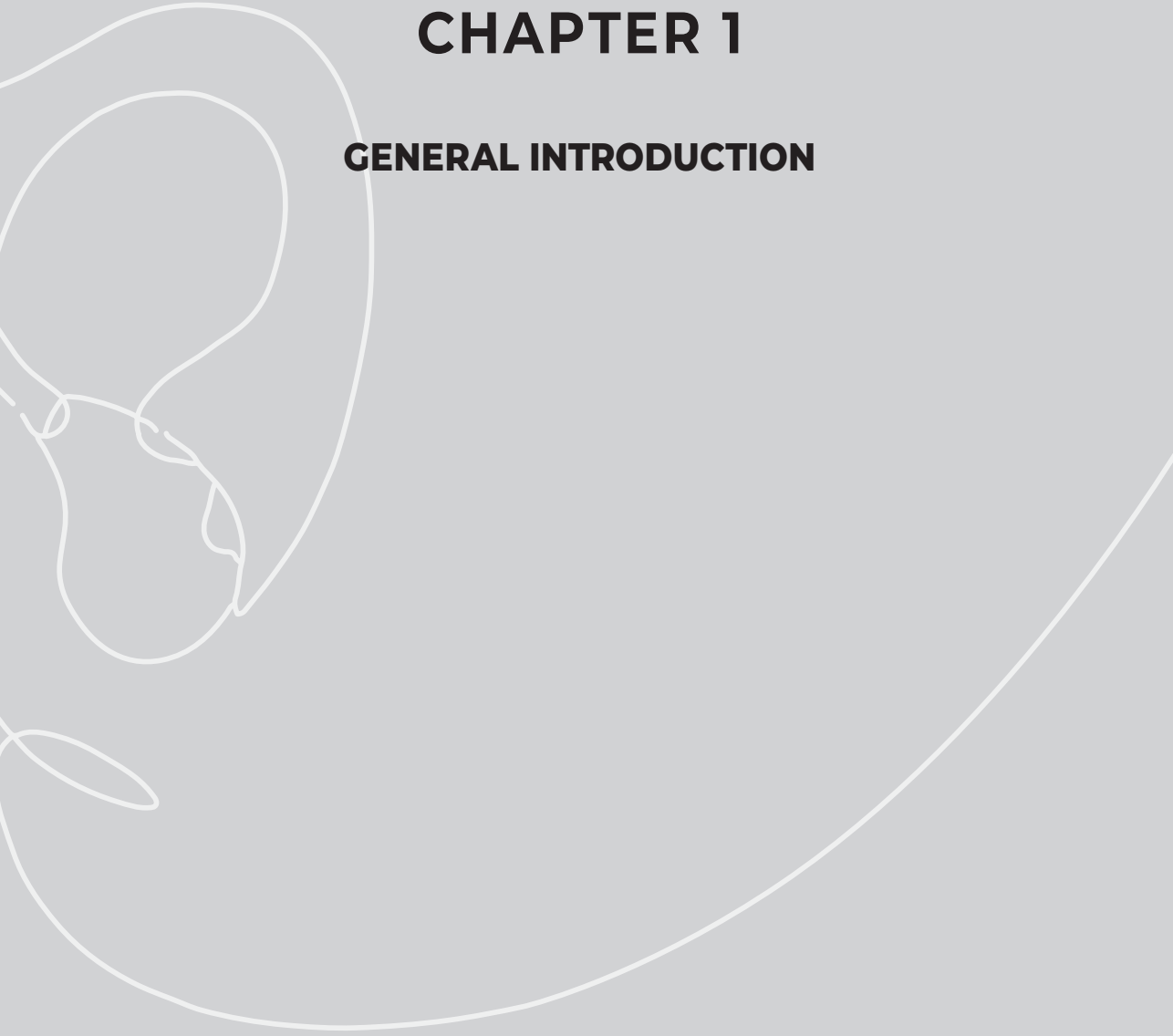
Prof. dr. V. Mijatovic, Amsterdam UMC

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CHAPTER 1

GENERAL INTRODUCTION



INTRODUCTION

Background and problem

Subfertility, which is defined as the non-occurrence of pregnancy after one year of unprotected intercourse, affects approximately one in six couples trying to conceive (Taylor 2003). Estimates suggest that between 48 million couples and 186 million individuals live with subfertility globally. (Mascarenhas et al. 2012, Boivin et al. 2007). Common causes of subfertility include ovulatory disorders, tuboperitoneal disease, uterine abnormalities, abnormalities of sperm and advancing female age. Infertility is unexplained if after thorough evaluation no diagnosis for the subfertility is found (Brugo Olmedo et al. 2001, Brandes et al. 2010).

Fallopian tube

The fallopian tubes play a major role in the female reproductive process. The fallopian tubes, named after their discoverer Gabriele Fallopio, connect the peritoneal cavity with the uterine cavity. The fallopian tube captures the oocyte after its release from the follicle, it transports spermatozoa towards the oocyte and it transports the fertilized oocyte towards the uterine cavity (Lyons et al. 2006). Dysfunction of the Fallopian tubes plays a role in 15-30% of subfertile women, depending on the population and the duration of subfertility (Evers 2002, Anyalechi et al. 2021). The fallopian tube can be affected in several ways. In women with endometriosis, local inflammation in response to endometrial-like tissue at extra-uterine sites, can lead to tubal blockage, adhesion formation or hydrosalpinges, and the endometriosis-induced inflammation response can also negatively impact sperm, oocyte and embryo viability (Hill et al. 2020). Pelvic inflammatory disease caused by sexual transmitted diseases such as Chlamydia Trachomatis, can lead to the formation of adhesions, proximal or distal tubal occlusion and disturbance of the ovum pickup mechanism (Hafner et al. 2015). Furthermore also women with a medical history of complicated appendicitis, pelvic surgery and ectopic pregnancy are at higher risk of having tuboperitoneal disease (Lutjeboer et al. 2009).

Tubal patency testing

The goal of the work-up of the subfertile couple is to determine the possible cause of the subfertility, and to determine which subsequent treatment would be possible and feasible. The work-up starts with a thorough medical history, a gynecological examination and a transvaginal ultrasound, followed by assessment of ovulatory function and analysis of the semen. Tubal patency testing is usually the last step in the diagnostic work-up, because it is the most invasive test.

Tubal patency testing is an important part of the workup of subfertile couples. Over the years different methods have been developed. Chlamydia Antibody testing (CAT) can be

used as a screening instrument, this test can identify which women have higher risk of tubal pathology due to Chlamydia infection, but it does not test the patency or visualize the fallopian tube. Testing tubal patency can be performed by imaging techniques such as Hysterosalpingography (HSG) and Hysterosalpingo Contrast Sonography (HyCoSy) and endoscopic techniques such as Diagnostic Laparoscopy (DLS) and Transvaginal Hydrolaparoscopy (THL). This thesis will focus mainly on THL and HSG.

THL

THL is first described by Gordts in 1998 (Gordts 1998). During this procedure access to the pouch of Douglas is obtained by culdocentesis using the transvaginal route. The pelvis is irrigated with warm saline (hydroflotation) and the pelvic structures can be visualised with a small endoscope, in their natural position and without manipulation. Patency of the tubes is investigated by chromopertubation with methylene blue. The procedure can be performed in an outpatient setting using local anaesthesia and is well tolerated by the patient. It allows an assessment of the pelvic cavity, including testing the patency of the tubes, and the presence of other pelvic pathology such as adhesions, endometriosis or an impaired tubo-ovarian contact. Fertiloscopy uses the same principle as THL, but during Fertiloscopy a microsalingoscopy and hysteroscopy is also performed during the same procedure to evaluate the mucosa of the tubes and the uterine cavity (Watrelet et al. 1998).

Existing publications have shown that THL is a safe method of tubal patency testing in women with a low risk of tubal pathology, and it has a low complication rate of 0.23-2%, after a learning curve of 50 procedures (Verhoeven et al. 2004, Gordt et al. 2021). The most common complication is a perforation of the rectum, which can be treated conservatively with antibiotics (Gordts et al. 2001). The procedure has proven to be well tolerated when performed under local anesthesia (Cicinelli et al. 2001), however in some hospitals THL is performed under conscious sedation. Moreover, THL is an accurate technique in comparison to conventional diagnostic laparoscopy, with a sensitivity between 80 and 92% and specificity up to 100% (Darai et al. 2000, Dechaud et al. 2001). In women with minimal endometriosis, THL may detect more subtle adhesions compared to conventional laparoscopy due to the watery distention medium (Gordts et al. 2000, Brosens et al. 2001).

HSG

HSG is a radiographic examination of the uterus and fallopian tubes and is introduced in 1914 (Rubin 1914). In a lot of countries it is the most common outpatient procedure of tubal patency testing in the workup for subfertility. When performing a HSG a catheter is inserted through the cervix into the uterus and a contrast medium instilled through the catheter with fluoroscopic images taking intermittently to evaluate the uterine cavity and

tubes. The procedure can either be performed with water-based contrast medium or oil-based contrast medium. In a retrospective survey study the most frequent complications was found to be intravasation of the contrast medium in 4.8% of the HSGs performed with oil-based contrast and in 1.3% of the HSGs with water-based contrast and PID was found in 0.3-0.4% of women (Roest et al. 2020). The exposure to radiation is around 3.6 mGY (Sulieyman et al. 2008). In a meta-analysis containing data of 4521 women, 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). HSG has been originally developed as a diagnostic instrument for tubal patency testing; however, recent studies show that there is also a therapeutic effect of tubal flushing with oil-based contrast medium. Dreyer et al. found that flushing with oil-based contrast medium compared to water-based contrast medium led to a higher ongoing pregnancy rate after 6 months (Dreyer et al. 2017), and also to an increase in live birth rate after a follow-up period of 5 years (van Welie et al. 2021).

The diagnostic accuracy of THL compared to HSG has been validated in some studies. The agreement on tubal patency testing between the two procedures is good (Cicinelli et al. 2001) however, THL is superior in diagnosing endometriosis and peritubal adhesions (Shibahara et al. 2001). In an outpatient setting THL is tolerated better and has lower pain scores compared to HSG (Cicinelli et al. 2001).

THESIS AIMS AND RATIONALE

Although THL gives more information about the pelvic cavity and about the presence of endometriosis and adhesions, it is unclear whether this additional information during the fertility work-up leads to a more effective fertility treatment for the subfertile couple and thus to better outcomes such as a higher pregnancy rate or a shorter time to pregnancy. Furthermore it is unclear if using THL as a tubal patency test in the fertility work-up would be cost-effective compared to a HSG as a tubal patency test. Also it is unknown if subfertile women would prefer one test over the other and what characteristics are important for their preference.

In order to address these gaps in the available literature, this thesis studies different factors of tubal patency testing with HSG versus THL in subfertile women. More precisely, the thesis aims to answer five research questions:

1. What is the prognostic capacity of transvaginal hydrolaparoscopy to predict non-IVF conception?
2. Is in the work-up for subfertility THL non-inferior to HSG in terms of conception leading to a live birth?

3. How is the cost-effectiveness of a strategy starting with THL compared to a strategy starting with HSG in the work-up for subfertility?
4. Is there a difference between quality of life in women after tubal patency testing with THL and HSG?
5. What aspects of a tubal patency test are most important to subfertile women in the work-up for subfertility?

OUTLINE OF THIS THESIS

Chapter 2 presents the outcome of a retrospective cohort study of subfertile women undergoing fertility examinations in four teaching hospitals, with THL as first line diagnostic test for tubal patency. After a follow-up period of 36 months we examined non-IVF conception rates (either spontaneous conception or a conception after ovulation induction or intrauterine insemination) and time to conception. We compared conception rates between groups of women with patent tubes, unilateral or bilateral tubal occlusion, and also between women with and without other tubo-peritoneal pathology such as endometriosis or adhesions diagnosed during THL.

Chapter 3 presents the results of our RCT comparing THL with HSG as first line patency test in the fertility work-up. Women with an indication for tubal patency testing, were randomised between THL or HSG. Their subsequent fertility treatment was depending on the result of their tubal patency test and according to the Dutch national protocols on subfertility care. Primary outcome was conception leading to a live birth. Secondary outcomes were time to pregnancy, ectopic pregnancies, miscarriage and multiple births.

Chapter 4 shows the cost-effectiveness analysis of THL versus HSG in the work-up for subfertility, which was performed alongside the randomised clinical trial. We compared the direct medical costs of the two procedures and the direct medical costs of the fertility and obstetric treatments. We calculated Incremental Cost Effectiveness Ratios (ICER's) and generated a cost-effectiveness plane to determine the cost-effectiveness of THL versus HSG.

Chapter 5 describes the results of an analysis of fertility related quality of life in women undergoing tubal patency testing by either THL or HSG. We evaluated fertility related quality of life alongside the aforementioned RCT, by using the FertiQoL, a validated questionnaire to measure fertility related quality of life in subfertile patients. We compared QoL six weeks after the procedure between the two groups of women.

Chapter 6 presents the results of our patient preference study. We evaluated subfertile women's preference by conducting a labeled Discrete Choice Experiment (DCE) on different aspects of THL and HSG as a first line test for detecting tubal pathology in the fertility work-up.

Chapter 7 provides a summary of this thesis which highlights the most important findings of the research and a general discussion of the studies presented in this thesis. It provides implications for clinical practice and suggestions for future research.

Chapter 8 presents a summary of this thesis in Dutch.

Chapter 9 is the impact paragraph.

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CHAPTER 2

THE PROGNOSTIC CAPACITY OF TRANSVAGINAL HYDROLAPAROSCOPY TO PREDICT NON-IVF CONCEPTION

M.A. van Kessel, R. Coenders-Tros, G.J.E. Oosterhuis, W.K.H. Kuchenbecker,
M.M.A Vernooij, M.Y. Bongers, B.W.J. Mol, C.A.M. Koks

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ABSTRACT

Transvaginal hydrolaparoscopy is performed to investigate tubal pathology in subfertile women. We studied the findings at THL and subsequent pregnancy rates in a retrospective multicenter cohort study. Between 2000 and 2011 1,033 subfertile women participated in our study. Primary outcome measure was intra-uterine pregnancy, either after natural conception or after treatment with intra-uterine insemination or ovulation induction. We calculated cumulative intra-uterine pregnancy rates using Kaplan-Meier analysis and fecundity rate ratios (FRR). THL showed bilateral patent tubes in 83%, one-sided tubal occlusion in 12.4% and bilateral tubal occlusion in 4.6% of women. Cumulative intra-uterine pregnancy rates after 36 months were 52% for women with bilateral patent tubes, 44% for one-sided tubal occlusion (FRR 1.04 (95% CI 0.78-1.39) and 7% for bilateral tubal occlusion (FRR 0.13 (95% CI 0.04-0.43). Endometriosis was diagnosed in 6.4%, adhesions in 9.1%, while 3.9% of women had both. Corresponding FRRs were 0.73 (95% CI 0.49-1.09), 0.68 (95% CI 0.46-1.02), and 0.42 (95% CI 0.20-0.84). In conclusion, women with bilateral tubal occlusion or the combination of endometriosis and adhesions found at THL have significantly reduced chances of natural conception.

Key words

Transvaginal hydrolaparoscopy, tubal pathology, infertility, prognostic capacity, fecundity rate ratio.

INTRODUCTION

Tubal pathology is one of the major causes of female subfertility, with a prevalence of about 30% in subfertile couples (Evers 2002, Brandes et al. 2010). In the diagnostic work-up of the subfertile couple, hysterosalpingography (HSG) is traditionally performed as the first method of invasive tubal patency testing. In a meta-analysis, HSG had a sensitivity of 46% and a specificity of 95% for the diagnosis of bilateral tubal pathology. In women at low-risk for tubal pathology, sensitivity of HSG was significantly lower than for women at high-risk (Broeze et al. 2010). For the diagnosis of peritubal adhesions HSG is less accurate, with reported sensitivity in detecting peritubal adhesions between 34 and 75%. (Fatum et al. 2002, Papaioanno et al. 2004). Moreover, HSG exposes women to radiation, and they need to be referred to the radiology department.

Diagnostic laparoscopy is traditionally considered as the gold standard for diagnosing tubal pathology, as it allows direct visualisation of the Fallopian tubes. However, laparoscopy is an invasive procedure with potential operative complications such as vascular and bowel damage, and it requires hospital admission and general anaesthesia. Transvaginal hydrolaparoscopy (THL) was first described by Gordts in 1998 (Gordts et al. 1998). In this procedure access to the pouch of Douglas is obtained by culdocentesis using the transvaginal route, after which hydroflotation is used for the exploration of the pelvis. Subsequently, tubo-ovarian structures can be visualised with a small scope, in their natural position and without manipulation. The procedure can be performed in an outpatient department using local anaesthesia.

Existing publications have shown that THL is a safe method with a low complication rate (WatreLOT et al.1999, Gordts et al. 2001, Verhoeven et al. 2004,Coenders-Tros et al. 2016) and that it has proven to be well tolerated when performed under local anaesthesia (Cicinelli et al. 2001, van Tetering et al. 2007, Coenders-Tros et al. 2016). Moreover, THL is a highly accurate technique in comparison to conventional diagnostic laparoscopy, with reported sensitivity between 80 and 92% and specificity up to 100% (Darai et al. 2000, Dechaud et al. 2001, WatreLOT et al. 2003, Tros et al. 2012).

When testing tubal patency; however, the most important feature of the test is its prognostic capacity. The test needs to distinguish between two categories: women who can still conceive using at least one of their Fallopian tubes and women who have a strongly reduced chance to conceive, thus emphasizing the need for IVF or tubal surgery. In our previous study (van Tetering et al. 2007) on the prognostic capacity of THL, we related the findings of THL to treatment-independent pregnancy rates and calculated fecundity rate ratios (FRR). We found that FRRs for one-sided tubal pathology, two-sided tubal pathology and adhesions/endometriosis were 0.59, 0 and 0.80, respectively.

In this article, we report our multicenter study with a large series of women undergoing THL as a first line diagnostic test for tubal pathology, performed in four teaching

hospitals in the Netherlands. We evaluated the incidence of abnormalities at THL, as well as its prognostic capacity by relating the findings of the procedure to the occurrence of non-IVF related conception.

MATERIALS AND METHODS

Participants

We studied subfertile women undergoing THL between January 2000 and December 2011 in four large teaching hospitals in the Netherlands (Maxima Medisch Centrum, Veldhoven; Medisch Spectrum Twente, Enschede; Isala, Zwolle and St. Antonius Ziekenhuis, Nieuwegein). In these hospitals, THL was performed as a first line tubal patency investigation in couples referred for fertility investigations, after attempting to conceive for at least 12 months. Findings at THL as well as other results of the basic fertility work-up were collected systematically in the clinical progress, while the occurrence of pregnancy and start of treatment was evaluated retrospectively. Ethical approval was not required for this study, according to Dutch regulations (<http://www.ccmo.nl/en/non-wmo-research>), because it was a retrospective study and only used anonymized patient data.

All women had a basic fertility work-up, including complete history, a gynaecological examination, a transvaginal ultrasound and assessment of ovulation. All women had Chlamydia Antibody Titre (CAT) and Chlamydia PCR performed, and an active infection was treated prior to the procedure. Women were not eligible for THL if there were contraindications for the procedure such as a fixed retroverted uterus, a history of severe pelvic inflammatory disease, rectovaginal endometriosis or a large ovarian cyst. Women with a contraindication for THL were scheduled for diagnostic laparoscopy with chromopertubation instead of THL.

Procedure

Women received both oral and written information about THL prior to the procedure. THL was performed in the outpatient department using local anaesthesia or conscious sedation, by a gynaecologist specialized in the procedure. THL was performed as described by Gordts (Gordts et al.1998), using the Fertiloscope™ (Fertility focus®, Warwick, UK) in one hospital (Medisch Spectrum Twente) while in the three other hospitals (Maxima Medisch Centrum, St. Antonius Ziekenhuis and Isala) the Storz re-usable system (Storz®, Tuttlingen, Germany) was used. The procedure was performed with the woman in the dorsal gynaecological position. After disinfecting the vagina, 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 ultracaine was performed in the vaginal vault and a small incision was made, after which the trocar system was inserted and infusion of warm saline in the pelvic cavity. Investigation started at the posterior uterine wall, subsequently the tubo-ovarian structures were seen and a dye test with methylene blue 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. Antibiotics were not prescribed routinely, but only in cases where complications occurred or when severe tubal pathology was diagnosed. THL was considered to be complete if evaluation of the tubo-ovarian structures, pelvic sidewalls and the cul-de-sac was possible, or if pathology was diagnosed requiring fertility enhancing surgery or IVF.

Follow-up

After completion of tubal assessment, women were treated according to the guidelines of the Dutch Society for Obstetrics and Gynaecology (www.nvog.nl). In couples with unexplained subfertility, the Hunault prediction model (Hunault et al. 2004) was used to calculate the prognosis to conceive naturally. In case of normal Fallopian tubes and a good prognosis to conceive naturally (>30%) according to the Hunault model, women were managed expectantly for 6-12 months. In case of a poor prognosis to conceive naturally (<30%), or when no pregnancy occurred after a 12 month period of expectant management, women were treated with intra-uterine insemination (IUI) with ovarian stimulation and if required followed by IVF. When severe tubal pathology was diagnosed at THL, i.e. bilateral tubal occlusion, severe endometriosis or peritubal adhesions, couples were counselled for either IVF or (if the gynaecologist thought this was feasible) laparoscopic fertility enhancing surgery.

Follow-up of fertility outcome was derived by examining the couples' medical records. The follow-up period ended at 36 months or at the occurrence of an intra-uterine pregnancy (either naturally, with ovulation induction or IUI), or on the day of IVF-treatment or fertility enhancing surgery was started, or on the day the woman was lost to follow-up.

Analysis

Cumulative non-IVF pregnancy rates were calculated for each category of findings, using Kaplan-Meier analysis. This analysis expressed the time to pregnancy (TTP). TTP was censored on the day IVF or operative treatment was started, or when the woman was lost to follow-up.

Subsequently, fecundity rate ratios (FRR) and 95% confidence intervals for the occurrence of naturally conceived pregnancy were calculated for THL findings through

Cox regression modelling. A FRR 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. In addition, we determined FRRs for other potential prognostic factors such as age, primary subfertility and the duration of subfertility. To adjust the FRRs of THL findings for these prognostic factors, multivariable analysis was performed.

To study whether the non-informative censoring was a reasonable assumption for women in whom follow-up was censored due to the start of IVF or tubal surgery, we compared three known risk factors for subfertility between women who started IVF or tubal surgery and the group of women: female age, parity and duration of subfertility, measured as the time between starting to attempt to conceive and the first consultation. Since women with a favourable profile may not have started treatment (because they conceived before considering treatment), we compared the risk factors of treated women with the women who did not conceive or start treatment. We used t-test and a χ^2 test statistics for these comparisons. P-values < 0.05 were considered to indicate statistical significance.

RESULTS

Between 2000 and 2011, 1,103 women underwent THL in our hospitals. We excluded 70 women from the study, because either they underwent THL for tubal patency testing after tubal ligation reversal surgery or because they were referred from another hospital just for tubal patency testing by THL without any other treatment or follow-up in our hospitals. Thus, data of 1,033 women were available for evaluation in our study. The characteristics of these women are shown in table I. In our cohort we found positive Chlamydia serology in 107 women (10.4%). Of the 1,033 procedures, successful access to the pouch of Douglas was achieved in 986 (95.5%) of women. Subsequently, complete evaluation of the pelvic cavity was possible in 952 women (92.2%).

Table I Baseline characteristics at the time of procedure (n=1033)

Characteristics		
Age (mean - years)	31.9	25-39 (5-95th percentile)
Duration of infertility (mean - months)	22.6	11-48 (5-95th percentile)
Primary infertility (n - %)	745 (72.1%)	
Ovulatory cycles (n - %)	896 (86.7%)	
Normal semen analysis (n - %)	855 (82.7%)	
Positive Chlamydia serology (n - %)	107 (10.4%)	

The findings of THL are shown in table II. Among 790 women with bilateral patent tubes, 678 women (85.8%) had no further pelvic pathology and in 112 women (14.2%) THL showed bilateral patent tubes but with endometriosis, adhesions or the combination of both.

Table IIa Primary outcomes of transvaginal hydrolaparoscopy (n=1033)

Access to pouch of Douglas – no. (%)	986 (95.4%)
Complete visualisation – no (%)	952 (92.0%)
Complications – no. (%)	26 (2.5%)
perforation of bowel	9 (0.9%)
perforation of posterior uterine wall	8 (0.8%)
bleeding	4 (0.4%)
infection	5 (0.5%)
allergic reaction	0

Table IIb Findings of transvaginal hydrolaparoscopy (n=952)

Tubal patency	Pelvic abnormalities				Total
	None	Endometriosis	Adhesions	Both	
Bilateral tubal patency	678	47	42	23	790
One-sided tubal occlusion	72	13	25	8	118
Two-sided tubal occlusion	17	1	20	6	44
Total	767	61	87	37	952

In the group of women with bilateral patent tubes, 239 women were treated expectantly, 73 women started ovulation induction and 413 women were treated with IUI. Direct referral for IVF was scheduled in 56 women, usually for other reasons such as mild male subfertility and 9 women were treated with fertility enhancing surgery. THL showed unilateral tubal occlusion in 118 women, of whom 72 women (61.0%) had no pelvic abnormalities and 46 women (39.0%) had unilateral tubal occlusion with endometriosis, adhesions or the combination of both. In this group of women, 30 women started with an expectant management, 9 women were treated with ovulation induction, 54 women were treated with IUI, 13 women were referred for IVF and 12 women underwent fertility enhancing surgery.

Among the 44 women with bilateral tubal occlusion, 17 women (38.6%) had no further pelvic pathology and in 27 women (61.4%) bilateral tubal occlusion combined with the finding of endometriosis and/or adhesions was found. Of these 44 women, 8 women did not want ART or laparoscopic surgery and were therefore managed expectantly. Another 9 women underwent laparoscopy at which at least patency of one tube was found; of these, one woman did not receive treatment, one woman was treated with ovulation induction and 7 women were treated with IUI. Furthermore, 13 women were referred for IVF and fertility enhancing surgery was scheduled for 14 women (figure I).

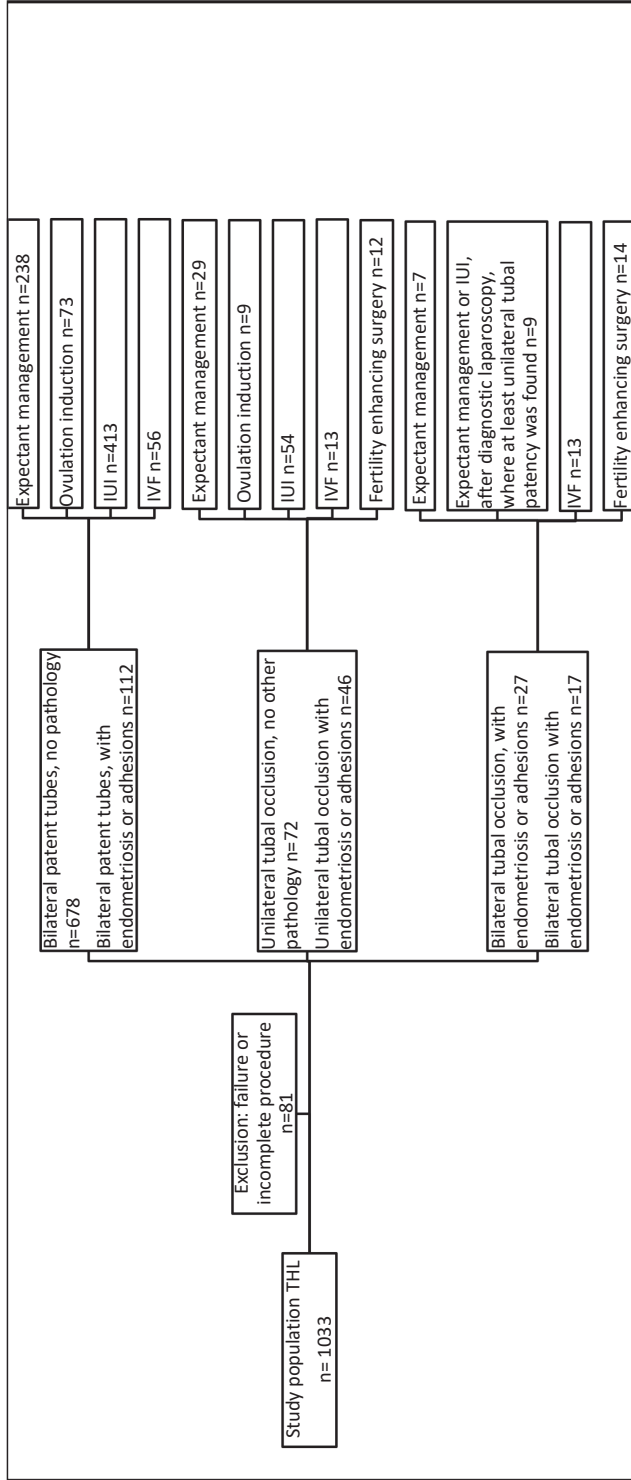


Figure 1 Flowchart with findings of THL and treatment

When we compared risk factors between treated women and women not referred for treatment in our data set, we observed the profile of the 117 women that were treated with IVF or tubal surgery was comparable to the profile of the 835 women that were managed expectantly or treated with ovulation induction or IUI. There was no significant difference in age (mean age 31.7 years versus 32.2 years), and women that had a previous pregnancy were equally distributed in the two groups (222 women, 26.6% versus 38 women, 32.5%). On the other hand, the duration of subfertility was slightly longer for women treated with IVF or tubal surgery (21.2 months versus 25.8 months, p-value 0.01). During follow-up, almost half of the studied women conceived, either naturally or with ovulation induction (287 women, 30.1%) or after IUI (176 women, 18.4%). There were 376 (39.5%) who had a conception leading to a singleton live birth, whereas three (0.3%) women delivered a twin pregnancy. The women with twin pregnancies had all been treated with ovulation induction or IUI with ovarian stimulation. Miscarriage occurred in 71 (7.5%) women and in seven (0.7%) women second trimester intra-uterine fetal death occurred. Furthermore, six (0.6%) women had an ectopic pregnancy; their THL results showed tubal pathology in three women and were normal in the other three women. Figure II shows time to pregnancy in a Kaplan-Meier curve for women with bilateral patent tubes (n=790), one-sided tubal occlusion (n=118), and bilateral tubal occlusion (n=44). Cumulative natural intra-uterine pregnancy rates after 36 months were 52%

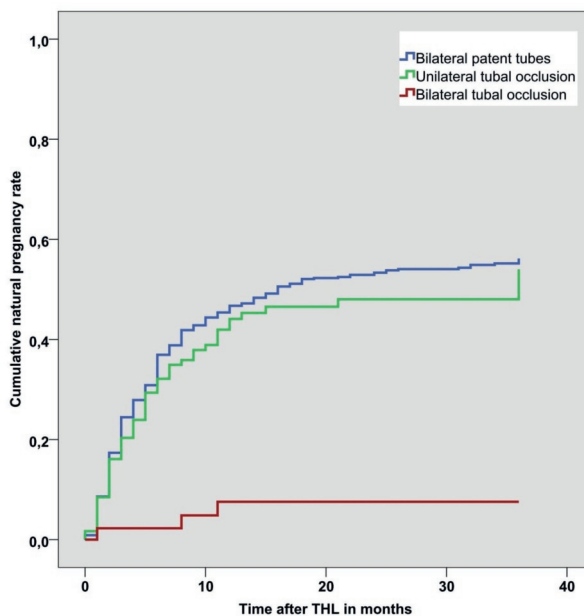


Figure II Kaplan-Meier curve showing time to pregnancy after THL for different outcomes on tubal patency testing at THL

(n=408) for women with bilateral patent tubes, 44% (n=52) for women with one-sided tubal occlusion and 7% (n=3) for women with bilateral tubal occlusion at THL. Singleton live birth rates were 42% (n=334) for women with bilateral patent tubes, 34% (n=40) for women with one-sided tubal occlusion and 4.5% (n=2) for women with bilateral tubal occlusion at THL. The follow-up period ended at 36 months or at the occurrence of an intra-uterine pregnancy (either naturally, with ovulation induction or IUI), or on the day IVF-treatment or fertility enhancing surgery was started, or on the day the woman was lost to follow-up. The number of women who were still under study at 12 and 24 months respectively, was 315 and 117 for women with bilateral patent tubes, 38 and 13 for women with one-sided tubal occlusion, 11 and 5 for women with bilateral occlusion. Figure III shows a Kaplan-Meier curve for women without pelvic abnormalities (n=767), women with endometriosis (n=61), women with adhesions (n=87) and women with the combination of adhesions and endometriosis (n=37). The number of women who were still under study at 12 and 24 months respectively, was 296 and 101 for women without pelvic abnormalities, 27 and 14 for women with endometriosis, 28 and 15 for women with adhesions and 13 and 5 for women with the combination of adhesions and endometriosis.

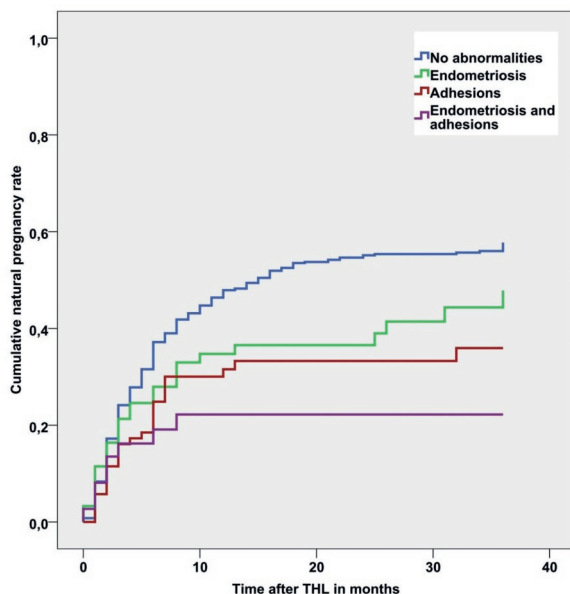


Figure III Kaplan-Meier curve showing time to pregnancy after THL for the different findings of THL

Table III shows the results of the Cox proportional hazard regression analysis. In the univariable analysis, the FRRs for women with one-sided and two-sided bilateral tubal occlusion were 0.93 (95% CI 0.49-1.09) and 0.10 (95% CI 0.03-0.31), respectively. Women with endometriosis only, adhesions only or with the combination of both endometriosis and adhesions had FRRs of 0.73 (95% CI 0.49-1.08), 0.56 (95% CI 0.38-0.81) and 0.35 (95% CI 0.17-0.71), respectively.

In our model for multivariable analysis we used the findings of THL, as well as age, primary subfertility and the duration of subfertility. Positive chlamydia serology did not add value to the model. Our multivariable analysis showed the FRRs for women with one-sided tubal occlusion and bilateral tubal occlusion to be 1.04 (95% CI 0.78-1.39) and 0.13 (95% CI 0.04-0.43), respectively. Women with endometriosis only, adhesions only or with the combination of both endometriosis and adhesions had FRRs of 0.73 (95% CI 0.49-1.09), 0.68 (95% CI 0.46-1.02) and 0.42 (95% CI 0.20-0.84), respectively.

Table III Results of Cox regression analysis (n=952)

	Univariable analysis			Multivariable analysis	
	n	FRR	95%CI	FRR	95%CI
Bilateral tubal patency	790	1	0.68-1.19	1	
Unilateral tubal occlusion	118	0.93	0.49-1.09	1.04	0.78-1.39
Bilateral tubal occlusion	44	0.10	0.03-0.31	0.13	0.04-0.43
Endometriosis	61	0.73	0.49-1.08	0.73	0.49-1.09
Adhesions	87	0.56	0.38-0.81	0.68	0.46-1.02
Endometriosis and adhesions	37	0.35	0.17-0.71	0.42	0.20-0.84
Primary infertility	692	0.87	0.71-1.06	0.82	0.66-1.01
Duration of subfertility (months)	952	0.97	0.96-0.98	0.97	0.96-0.98
Female age (years)	952	0.96	0.94-0.96	0.96	0.94-0.96

DISCUSSION

In this study, we performed THL in a large group of subfertile women as a first-line method of tubal patency testing. We found that women diagnosed with bilateral tubal occlusion or with the combination of endometriosis and adhesions had significantly reduced conception chances. Furthermore, in the group of women with either adhesions or endometriosis we found they might have a limited reduction of their fertility potential, although in the multivariable analysis this was not significant. One-sided tubal occlusion had no impact on the fertility prospects whatsoever.

Strengths and limitations

Our study was a cohort study, in which THL was used in a clinical setting and its findings had medical consequences. In an ideal situation, the prognosis of natural conception would be studied in the absence of fertility treatment, but since effective treatment options are available, follow-up without treatment would be ethically unacceptable.

The problem of informative censoring in the prediction of natural conception has been described in previous literature (Mol et al. 1999, van Geloven et al. 2012). Both the Kaplan-Meier analysis and the Cox regression analysis, although commonly used for the prediction of conception, may be leading to an overestimation. Both methods assume non-informative censoring: women for whom the follow-up period ends without the occurrence of a natural pregnancy, and for whom the time to pregnancy observation is thus censored, are from that time on assumed to have a similar pregnancy prognosis to women who remain in follow up (van Geloven et al. 2012). In our cohort, we compared characteristics of the women that underwent IVF or tubal surgery to the women that were managed expectantly or treated with ovulation induction or IUI, and found no statistical differences on the prognostic factors of age and parity. We did find a slight but significant difference between the duration of subfertility between both groups of women.

Furthermore, in our study, the prognostic capacity of THL could only be compared with other diagnostic techniques by using data from known literature. To our knowledge, a direct prospective comparison of the prognostic capacity for non-IVF pregnancy of THL to other diagnostic techniques such as HSG, HyCoSy or laparoscopy still needs to be assessed. Therefore, a randomized controlled trial (NTR3462) is currently being conducted in the Netherlands, comparing prognostic capacity of THL and HSG as well as women's preferences and cost-effectiveness.

We related the findings at THL to non-IVF conception in subfertile couples, with a follow-up period of 36 months. In our study, women with one-sided tubal occlusion on THL had fertility prospects similar to that of women with bilateral patent tubes. Indeed, previous studies on the capacity of tubal patency tests to predict natural conception, showed that unilateral tubal occlusion compared with bilateral tubal patency only mildly reduces chances of non-IVF pregnancy without statistically different fecundity rate ratios. For HSG, FRRs for one-sided tubal occlusion were 0.80 (Mol et al. 1999) and 0.81 (Verhoeve et al. 2011) respectively. For laparoscopy, FRRs for one-sided tubal occlusion was 0.56 (Mol et al. 1999) and 0.85 (Verhoeve et al. 2011). All these ratios have wide overlapping confidence intervals crossing unity, showing that there might be a reduction of FRR when one-sided tubal occlusion is diagnosed, but there is no statistically significant difference from the FRR of the women with bilateral patent tubes. Our FFR for one-sided tubal occlusion was close to 1. This might have several explanations. First, the

one-sided tubal occlusion might be an artefact, caused by pressure differences between the two tubes, thus mimicking the tube with highest pressure as occluded. Second, one patent tube might be sufficient for conception, as has been seen in for example in a study showing no significant difference between salpingectomy and salpingostomy in women undergoing surgery for ectopic pregnancy (Mol et al. 2014).

For women with THL showing bilateral tubal occlusion chances to conceive without IVF were significantly reduced (FRR 0.10 (95% CI 0.03-0.31)). Although unexpected, in the group of 44 women in which THL showed bilateral tubal occlusion 3 women conceived naturally an intra-uterine pregnancy. In two of these women, a subsequently performed diagnostic laparoscopy showed at least one-sided tubal patency; the other woman conceived an intra-uterine pregnancy while she was scheduled for IVF treatment. An explanation of these apparent discordant findings might be the occurrence of tubal spasm during THL. Therefore, when THL finds bilateral tubal occlusion in the absence of any other pelvic abnormalities we perform a subsequent diagnostic laparoscopy to rule out false positive findings.

On the other hand, women with at least one patent tube had good natural fertility prospects. Further prognostic assessment might be useful in these couples (Bensdorp et al. 2017). Positive chlamydia serology has been reported to decrease natural conception chances (Coppus et al. 2011, Steiner et al. 2015) In our cohort we found positive chlamydia serology in 10.4% of women, of whom 75% had open tubes. In our multivariate analysis; however, positive chlamydia serology did not add value to the model.

In our study, the complication rate was 2.5%. Perforation of the rectum was the most common complication and it occurred 9 times (0.9%). All of these cases were managed expectantly with antibiotics if needed and the women recovered uneventfully. Our complication rate of THL is comparable with previous studies (Gordts et al., 2000, 2001; Shibahara et al.), but higher than reported in other large cohorts (Gordts et al. 2011, Verhoeven et al. 2004). Gordts et al reported a total of 24 bowel injuries (0.65%) in 3667 procedures, in an international retrospective survey (Gordts et al. 2011). An explanation for these differences, is that in our cohort all gynecologists were starting to perform the procedure and the higher number of complications depicts their learning curve. Coenders-Tros previously reported a decrease in complications of THL from 5% within the first 50 procedures to 0.7% after 100 procedures (Coenders-Tros et al. 2016). In comparison, for HSG, the two most common complications are bleeding and infection. Large series have reported that that 0.3% to 1.3% of women undergoing hysterosalpingography (HSG) developed infectious morbidity (Stumpf and March 1980). For laparoscopy previous studies showed complication rates between 1.84 and 4.64 in 1000 women (Jansen et al. 1997, Capron et al. 1998).

The diagnostic accuracy of THL compared with HSG has been validated in several studies. The agreement of tubal patency testing between the two procedures is good, but THL is superior in diagnosing endometriosis (Cicinelli et al. 2001) and peritubal adhesions (Shibahara et al. 2001). Since we excluded women with endometriomas, ovarian cysts, evidence of rectovaginal endometriosis or retroverted uteri in our study, our cohort consists of women with a low risk of tubal pathology. We found a low incidence of bilateral tubal occlusion diagnosed by THL in our cohort (4.6%). The incidence of endometriosis and/or adhesions; however, is almost 20%. If the combination of endometriosis and adhesions is observed with THL, the chances of a naturally conceived pregnancy are significantly reduced.

When HSG is used as a first line tubal patency test, in most hospitals a subsequent diagnostic laparoscopy is performed if HSG shows abnormalities, or a pregnancy is not achieved in 6 to 12 months. Taking this into consideration, the advantage of THL is that subsequent diagnostic laparoscopy has no additional diagnostic value if THL has already shown bilateral tubal patency and no further pelvic abnormalities. Coenders-Tros et al showed that in this Dutch cohort diagnostic laparoscopy was avoided in approximately 70% of women with no pelvic pathology (Coenders-Tros et al. 2016), this is comparable with previous literature (Watrelet 1999 et al., Gordts et al. 2000, Dechaud et al. 2001, Watrelet et al. 2003).

An important issue is that tubal patency testing might also have a therapeutic effect. While meta-analysis of prior randomized trials already indicated beneficial effect from tubal flushing during HSG (Mohiyiddeen et al. 2015), a recent clinical trial showed clear benefit of oil-based tubal flushing (39.7% versus 29.1%; RR 1.37; 95% CI 1.16 to 1.61) (Dreyer et al. 2017). It remains a question if there is a therapeutic effect of THL and whether oil-flushing after a THL also would increase pregnancy rates.

In summary, our study confirms that THL is a feasible and reliable technique for tubal patency testing and pelvic exploration in subfertile women. We showed that the prognosis for non-IVF conception is significantly reduced in women with bilateral tubal occlusion, as well as in women with the combination of endometriosis and adhesions. Since the latter category of pathologic findings cannot be diagnosed using HSG, it is our opinion that by using THL as a first line investigation, women with tubal or peritubal pathology, who have a reduced chance of conceiving naturally, are distinguished from women more likely to conceive naturally at an early stage of fertility treatment.

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CHAPTER 3

TRANSVAGINAL HYDROLAPAROSCOPY VERSUS HYSTEOSALPINGOGRAPHY IN THE WORK-UP FOR SUBFERTILITY: A RANDOMIZED CONTROLLED TRIAL

M.A. van Kessel, R. Tros, S.M.J. van Kuijk, G.J.E. Oosterhuis, W.K.H. Kuchenbecker,
M.Y. Bongers, B.W.J. Mol, C.A.M. Koks

† *The authors consider that the first two authors should be regarded as joint First Authors*

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ABSTRACT

Research question

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

Design

We performed a multicenter randomized controlled trial (RCT) (NTR3462) in four teaching hospitals in the Netherlands, randomizing sub-fertile 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

We randomized 149 women to THL and 151 to HSG. From the intention to treat (ITT) population, 83 women from the THL group (58.5%) conceived a live-born child within 24 months after randomization compared to 82 women (55.4%) in the HSG group (difference 3.0% (95% CI: -8.3 – 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 – 1.32), $p = 0.237$) and multiple pregnancies occurred in 12 (8.4%) women in the THL group compared to 19 (12.8%) women in the HSG group (RR = 0.84 (95% CI: 0.46 – 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 sub-fertile women with a low risk of tubal pathology, use of THL was non-inferior to HSG as a first-line test in terms of conception leading to live birth.

Key words: Tubal testing / tubal pathology / transvaginal hydrolaparoscopy / hysterosalpingography / TVE / transvaginal endoscopy

INTRODUCTION

Subfertility affects approximately 1 in 10 couples worldwide (Datta et al. 2016, Boivin et al. 2007), 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 was found to have 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 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). We found that THL has a comparable diagnostic performance compared to HSG, 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. THL performed under local anaesthesia is well-tolerated by the patient (Giampaolino et al. 2015) and in two RCT's, THL patients were found to have lower pain scores 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 to conceive, and therefore may need IVF or tubal surgery. Studies on the prognostic capacity of HSG showed 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 naturally conceived pregnancy (Verhoeve et al. 2011, Mol et al. 1999). Our previous study showed that with THL as a first-line test, the likelihood of non-IVF conception is significantly reduced not only in women with bilateral tubal occlusion, but also as in women with endometriosis and adhesions (van Kessel et al. 2018).

Although THL gives more information about pelvic abnormalities than HSG, it is not known whether or not this additional information leads to better treatment guidance for the sub-fertile couple. There have been no studies directly comparing fertility outcomes after HSG and THL. In view of this, we conducted a randomized controlled non-inferiority trial to compare live birth rates in sub-fertile women undergoing tubal patency testing with transvaginal hydrolaparoscopy or HSG.

MATERIALS AND METHODS

Ethical approval

The study was performed according to Good Clinical Practice (GCP) guidelines. The study protocol was approved by the Institutional Review Board of the Amsterdam Medical Center (AMC, Amsterdam, the Netherlands) on 27th 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 centers, patient counseling, data collection and monitoring was performed by dedicated research nurses. All women provided written informed consent prior to randomization. The first patient was enrolled on 21st May 2013.

Study population

Women were eligible 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 one year of unprotected intercourse. During their fertility work-up, couples had a complete history taken, a gynecological examination, a transvaginal ultrasound in the follicular phase of the cycle and assessment of ovulation. Semen analysis was performed at least once for each male partner.

Women were not eligible if they had a contraindication for THL (i.e. positive Chlamydia PCR, prior tubal testing or prior 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 written informed consent, women were randomly allocated to a strategy starting with THL (experimental arm) or with HSG (control arm). Randomization was performed by the doctors or research nurses with the use of a secure online randomization program (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. THL was performed as described by Gordts (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 performed in an out-patient department. After insertion of a speculum, the central part of the posterior cervix was infiltrated with local anesthetic. A tenaculum was placed on the posterior cervix and a balloon catheter was put in the uterine cavity for chromopertubation.

Local anaesthesia was performed 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 dilators and trocar were inserted into the pouch of Douglas and replaced by a rigid 2.7 mm wide-angle 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, both the fimbrial part of the Fallopian tubes and the tubo-ovarian contact were inspected. 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 posterior fornix was not sutured unless active bleeding was noted.

Hysteroscopy can be performed directly after THL using the same optic, and in some hospitals, hysteroscopy is a systematic part of the procedure. In this study however an additional office hysteroscopy was only performed in case of suspected uterine anomaly or intrauterine pathology on ultrasound. In women allocated to THL an additional diagnostic laparoscopy was performed 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 performed in the radiology department according to hospital-specific protocols, by gynecologists, residents or fertility doctors. The contrast medium (either water-soluble contrast (Telebrix Hystero, Guerbet) 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 approximately 5 to 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 gynecologist and/or radiologist.

In women allocated to HSG an additional diagnostic laparoscopy was performed when the HSG showed abnormalities (like 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 to 12 months, to rule out pelvic abnormalities that were not noticed by HSG.

Additional treatment

After the completion of the fertility work-up and tubal assessment, women were treated according to the Dutch national guidelines (www.nvog.nl). When there was no tubal pathology, in general, expectant management was advised when the probability of natural conception within 12 months was >30% (Hunault et al. 2004). In couples with a probability <30%, intrauterine insemination with mild ovarian hyperstimulation (IUI-MOH) was advised. IUI-MOH was also advised when there was 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 3-6 cycles of intra-uterine insemination, couples were counselled for IVF or ICSI. 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 collection and monitoring were performed by dedicated research nurses.

Statistical methods

Baseline characteristics of the participating women, stratified by allocation, were described using mean and standard deviation 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 (CI).

For the secondary outcomes, we constructed Kaplan Meier curves 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 performed to assess differences in the proportion of women experiencing complications (bowel perforation, bladder perforation, bleeding, anaphylactic shock), because of the small cell counts.

All analyses were performed according to intention to treat (ITT). For the primary outcome, we also computed results according to the protocol that they received as a sensitivity analysis (per protocol, or PP). We used IBM SPSS version 26.0 and R version 3.3.3. P-values of 0.05 or lower were considered to indicate statistical significance.

Sample size calculation

For the sample size calculation, we assumed a 24-month live birthrate of 70% in both groups. In order to demonstrate non-inferiority of THL over HSG with a non-inferiority limit of 6%, we planned to include 665 women per arm (total 1330) (alpha .05, beta .80). Since we could not obtain funding for the study, the study was limited to 4 centers resulting in a slower than anticipated inclusion rate, and recruitment was halted after 300 inclusions.

RESULTS

Trial participants

Between May 2013 and October 2016, a total of 542 sub-fertile 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 can be found in Table 1.

Table 1. Baseline characteristics

Characteristic	THL (n=144)	HSG (n=150)
Mean female age (+ SD)	31.6 (+/- 3.9)	31.9 (+/-4.0)
Median BMI (IQR)	23.4 (21.0 - 26.9)	23.3 (21.2 – 26.2)
Intoxications		
Smoking	27 (18.8%)	25 (16.7 %)
Alcohol	37 (25.7%)	44 (29.3%)
Drugs	1 (0.7%)	1 (0.7%)
Type of subfertility		
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	108 (75.0 %)	129 (86.0%)
Median VCM (IQR)	47.5 (17.25-98.5)	51.0 (22.0-118.0)
Positive Chlamydia serology	16 (11.1%)	16 (10.7%)

Abbreviations:

BMI: Body mass index, kg/m².

VCM: (volume x concentration x percentage progressively moving spermatozoa)

IQR: interquartile range

Between randomization and the scheduled procedure 17 and 12 women conceived naturally in the THL group and HSG group, respectively. In the THL group, 6 women decided not to undergo any kind of tubal testing, and 2 women underwent HSG instead of THL. In the HSG-group, 2 women decided not to undergo tubal testing, while 2 women underwent THL instead of HSG. At 24 months after randomization, 2 women in the THL-group and 2 women in the HSG-group were lost to follow-up. Therefore, with withdrawn informed consent of 6 women and 4 women that were lost to follow-up, data on the primary outcome conception leading to live birth, were available for 290 of 300 women (Figure 1: Consort diagram).

Result of tubal evaluation and treatment

THL showed bilateral tubal patency in 104 women out of the 119 women in the THL-group that underwent the allocated intervention (87.4%) (Table 2). Unilateral tubal patency was seen in 6 women (5.0%) and bilateral tubal occlusion in one woman (0.8%). Furthermore 5 women (4.2%) were diagnosed with endometriosis and in 6 women (5.0%) pelvic adhesions were found. We did not perform additional hysteroscopies 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.

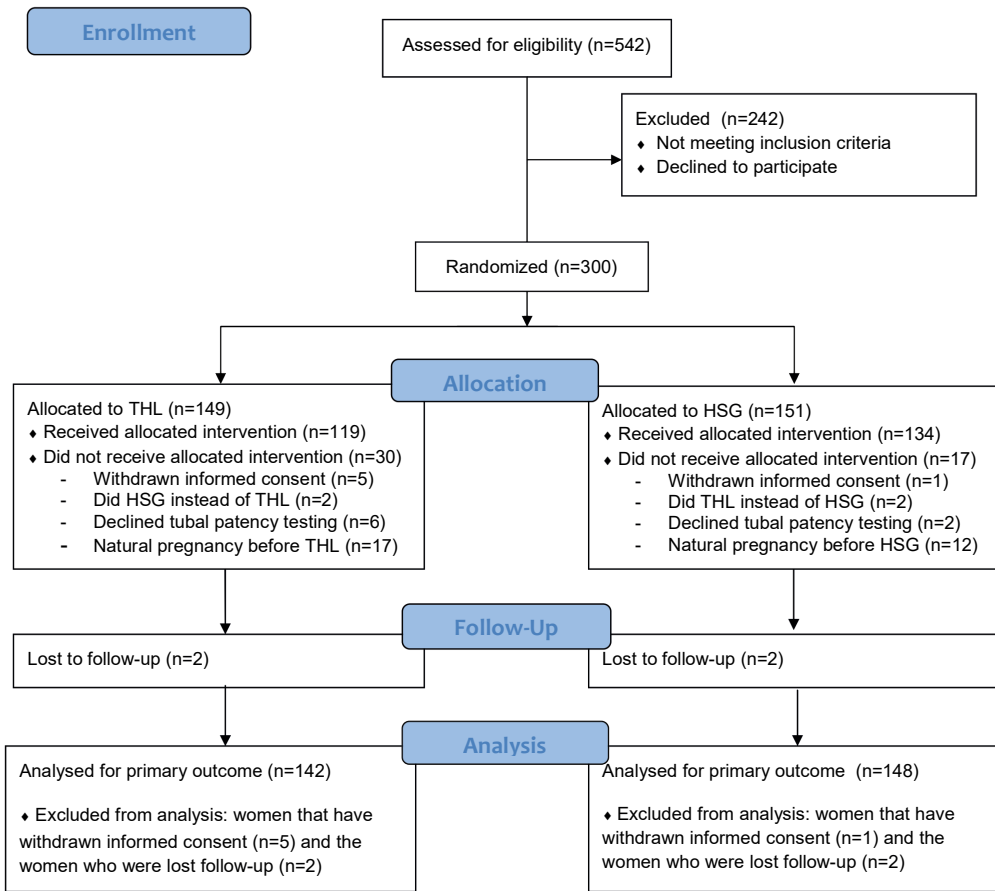


Figure 1: Follow-up per randomization

Unilateral tubal patency was found in 8 women (6.0%) and bilateral tubal occlusion in 3 women (2.2%). Intrauterine abnormalities were detected in 3 women (2.2%). For HSG, we used oil-based contrast in 45 women (33.6%) and water-based contrast in 89 women (66.4%). Two women underwent an additional hysteroscopy because of intrauterine abnormalities.

In the THL group, 4 women (2.8%) suffered complications versus one in the HSG group ($p = 0.204$). Two women had a bleeding of the vaginal wall that needed suturing, 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 hospitalization.

Table 2. Results of tubal evaluation

	THL (n,%) (n=119)	HSG (n,%) (n=134)	p-value
Results			
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			
Endometriosis	5 (4.2)	n.a.	n.a.
Adhesions	6 (5.0)	n.a.	n.a.
Intrauterine abnormalities	n.a.	3 (2.2)	n.a.

Primary outcome

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

Secondary outcomes

Figure 2 shows the cumulative incidence of conception leading to live birth for both groups. 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, versus 20 (13.5%) in the HSG group (RR = 0.84 (95% CI: 0.46 – 1.55), $p = 0.581$). In total, 12 (8.4%) of women in the THL group experienced multiple pregnancies compared to 19 (12.8%) in the HSG group ($p = 0.320$). Ectopic pregnancy was only diagnosed in the HSG group in 2 women (1.4%) and not at all in the THL-group ($p = 0.499$).

Table 3 shows subsequent treatment after fertility evaluation in the two groups. Expectant management was advised in 47.9% of women in the THL group versus 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 intra-uterine insemination with or without mild ovarian hyperstimulation (40.3% in the THL group versus 41.0% in the HSG group, $p = 0.909$). IVF or ICSI was scheduled in 1.7% in the THL group versus 2.2% in the HSG group ($p = 1.000$).

Fertility enhancing laparoscopic surgery was performed in 5 women (4.2%) in the THL group. This was carried out due to endometriosis in 3 patients, adhesions in one, and in another woman a bilateral tuboneostomy was performed because of hydrosalpinges. In



Figure 2: Kaplan Meier analysis assessing the difference between groups in time to conception leading to live birth

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
<i>followed by IUI</i>	29 (24.4)	32 (23.9)	1.000
Ovulation induction	7 (5.9)	8 (6.0)	1.000
IUI with and without MOH	48 (40.3)	55 (41.0)	0.909
<i>followed by IVF</i>	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
<i>followed by IUI</i>	1 (0.8)	4 (3.0)	0.374
<i>followed by IUI and IVF</i>	4 (3.4)	1 (0.7)	0.190

Abbreviations:
 IUI: intra-uterine insemination
 MOH: mild ovarian hyperstimulation
 IVF: in-vitro fertilization

the HSG group, 8 women (6.0%) underwent a therapeutic laparoscopy because of abnormalities. This was due to endometriosis in 5 women, endometriosis and adhesions in one woman, tuboneostomy and adhesiolysis in one woman and clipping a rudimentary horn of the uterus in one woman.

DISCUSSION

This multicenter randomized controlled trial showed that a strategy for tubal patency testing using THL was non-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.

Strengths and limitations

The main limitation of our study was the sample size. Due to lack of funding of this trial, only the 4 Dutch hospitals that already performed THL in their routine fertility work-up were able to participate in our trial. Therefore, the inclusion rate was lower than anticipated, compromising the statistical power, and the study was halted after three years. However, with 300 women included, this still is the largest study on this topic at the time of writing.

We performed our study in a selected 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 sub-fertile women with a high risk of tubal pathology.

THL and HSG are different procedures, each having advantages and disadvantages. We already showed that HSG and THL have a comparable diagnostic performance when used as a first-line diagnostic test in sub-fertile 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. Using 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.

However, it is still not certain if obtaining more information about pelvic abnormalities actually leads to a better fertility outcome. Previously we 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 to 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 gave a severe reduction in the chances of a natural conceived pregnancy (Verhoeve et al. 2011).

The disadvantage of THL is the higher rate of failed procedures and complications compared to HSG. Our study shows a failure rate of 6.7%, which is comparable to known literature when THL is performed by experienced gynecologists (Verhoeven et al. 2004, van Tetering et al. 2007). Recent studies show 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. 2015).

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 this trial, we used water-based contrast in two-third 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 unfortunately due to the small groups it was not feasible 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. Thus far there have been no studies on the effect of tubal flushing with an oil-based solution after THL.

In summary, we found that a strategy for tubal patency testing using THL was non-inferior to a strategy using HSG in case of conception leading to live birth at 24 months after randomization, in women with a low risk of tubal pathology. Based on these results, neither procedure is preferable to the other.

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CHAPTER 4

THE COST-EFFECTIVENESS OF TRANSVAGINAL HYDROLAPAROSCOPY VERSUS HYSTEOSALPINGOGRAPHY IN THE WORK-UP FOR SUBFERTILITY

M.A. van Kessel, C.T. Pham, R. Tros, G.J.E. Oosterhuis, W. K.H. Kuchenbecker, M.Y. Bongers,
B.W.J. Mol, C.A.M. Koks.

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ABSTRACT

Study question

Is a strategy starting with transvaginal hydrolaparoscopy (THL) cost-effective compared to a strategy starting with hysterosalpingography (HSG) in the work-up for subfertility?

Summary answer

A strategy starting with THL is cost-effective compared to a strategy starting with HSG in the work-up for subfertile women.

What is known already

Tubal pathology is a common cause of subfertility and tubal patency testing is one of the cornerstones of the fertility work-up. Both THL and HSG are safe procedures and can be used as a first-line tubal patency test.

Study design, size, duration

This economic evaluation was performed alongside a randomized clinical trial comparing THL and HSG in 300 subfertile women, between May 2013 and October 2016. For comparisons of THL and HSG, the unit costs were split into three main categories: costs of the diagnostic procedure, costs of fertility treatments, and the costs for pregnancy outcomes

Participants/materials, setting, methods

Subfertile women scheduled for tubal patency testing were eligible. Women were randomized to a strategy starting with THL or a strategy starting with HSG. The primary outcome of the study was conception leading to a live birth within 24 months after randomization. The mean costs and outcomes for each treatment group were compared. We used a non-parametric bootstrap resampling of 1000 re-samples to investigate the effect of uncertainty and we created a cost-effectiveness plane and cost-effectiveness acceptability curves.

Main results and the role of chance

We allocated 149 women to THL and 151 to HSG, and we were able to achieve complete follow-up of 142 versus 148 women, respectively. After the fertility work-up women were treated according to the Dutch guidelines and based on a previously published prognostic model. In the THL group, 83 women (58.4%) conceived of a live born child within 24 months after randomization compared to 82 women (55.4%) in the HSG group (difference 3.0% (95% CI: -8.3 – 14.4)). The mean total costs per woman were lower in the THL group, compared to the HSG group (THL group €4991 versus €5262 in the HSG

group, mean cost difference = -€271 (95% CI -€273 to -€269)). Although the costs of the diagnostic procedure itself were higher in the THL group, in the HSG group more women underwent diagnostic and therapeutic laparoscopies and also had higher costs for fertility treatments.

Limitations, reasons for caution

Our trial was conducted in women with a low risk of tubal pathology, therefore the results of our study are not generalizable to women with high risk of tubal pathology. Furthermore, this economic analysis was based on the Dutch healthcare system, and possibly our results are not generalizable to countries with different strategies or costs for fertility treatments.

Wider implications of the findings

After 2 years of follow-up we found a live birth rate of 58.4% in the THL group versus 55.4% in the HSG group and a lower mean cost per woman in the THL group, with a cost difference of -€271. The findings of our trial suggest that a strategy starting with THL is cost-effective compared to a strategy starting with HSG in the workup for subfertile women. However, the cost difference between the two diagnostic strategies is limited compared to the total cost per woman in our study and before implementing THL as a first-line strategy for tubal patency testing, more research on other fields such as patient preference and acceptance is necessary.

Key words: Hysterosalpingography, transvaginal hydrolaparoscopy, fertiloscopy, tubal patency test, fallopian tubes, cost-effectiveness

INTRODUCTION

Tubal pathology is a common cause of subfertility. Depending on the population and the duration of subfertility, tubal factors can be found in 15-30% of subfertile women (Evers 2012, Anyalechi et al. 2021), therefore the evaluation of tubal function is one of the cornerstones of fertility examination.

Hysterosalpingography (HSG) has been one of the most commonly used outpatient first-line tubal patency tests, although its sensitivity is low in women with a low risk of tubal pathology (Broeze et al. 2011). HSG was originally developed as a diagnostic instrument; however, recent studies show a possible therapeutic effect of tubal flushing with oil-based contrast (Dreyer et al. 2017, van Rijswijk et al. 2020). The gold standard in tubal patency testing, however, is laparoscopy with chromopertubation. Compared to HSG, laparoscopy gives more information about other pelvic pathology such as the presence of peritubal adhesions or endometriosis and tubo-ovarian contact.

Transvaginal hydrolaparoscopy (THL) is a technique developed by Gordts (Gordts 1998). In this procedure access to the pouch of Douglas is obtained by culdocentesis using the transvaginal route, after which hydroflotation is used for the exploration of the pelvis. The tubo-ovarian structures can be visualised with a small endoscope, in their natural position and without manipulation. This procedure can be performed in an outpatient department using local anaesthesia (Gordts 1998) and is well tolerated by the patient. Considering the fact that laparoscopic techniques for tubal testing give additional information about pelvic pathology, one could suppose that using a laparoscopic technique leads to an earlier detection of pelvic abnormalities and that it may influence the choice of subsequent fertility treatment.

However, there is insufficient evidence on which technique has the best diagnostic capacity for the subfertile couple and if there is a difference in cost-effectiveness between the different strategies.

Our recent randomized controlled trial (RCT) (THL-trial, NTR3462) showed no significant difference in live birth or time to conception between a strategy starting with THL or a strategy starting with HSG in 300 subfertile women with a low risk of tubal pathology (van Kessel et al. 2020). In this article we assess the costs and effects of both strategies in a cost-effectiveness analysis, which was performed alongside the THL trial.

MATERIALS AND METHODS

This economic evaluation was performed alongside the THL trial, a randomized clinical trial comparing THL and HSG in subfertile women. The study was performed according to Good Clinical Practice guidelines and the study protocol was approved by the Institutional Review Board of the Amsterdam Medical Center (AMC, Amsterdam, the Nether-

lands) and by the board of directors of the other participating hospitals. The trial was registered in the Dutch Trial Registry (NTR3462). In each of the participating centers, patient counseling, data collection and monitoring was performed by dedicated research nurses. All women provided written informed consent prior to randomization.

Study population

Women were eligible if they were undergoing a fertility work-up 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. Women were not eligible if they had a contraindication for THL (i.e. an immobile uterus or a retroverted uterus, evidence of endometriosis, masses or cysts in the pouch of Douglas, or ovarian cysts interfering with THL) if they had positive Chlamydia PCR, prior tubal testing or prior tubal surgery. Women with a known allergy to iodine or methylene blue were also not included.

Study design

Potential participants were recruited in four Dutch teaching hospitals (Amsterdam, Nieuwegein, Zwolle and Veldhoven) between 2013 and 2016. Eligible women were informed about the study by dedicated research nurses. After receiving their written informed consent, women were randomly allocated to a strategy starting with THL (experimental arm) or with HSG (control arm). Randomization was performed by the doctors or research nurses with the use of a secured online randomization program (ALEA, FormsVision) (Tros et al. 2019).

Interventions

In the THL group, the procedure was scheduled in the follicular phase of the menstrual cycle. THL was performed as described by Gordts (Gordts 1998). In two of the participating hospitals the Storz re-usable system was used (KARL STORZ, Tuttlingen, Germany) and in two hospitals the disposable Fertiloscope (Fertility Focus, Warwick UK). The procedure was performed in the out-patient department, using local anesthesia. An additional diagnostic laparoscopy was performed either if THL was inconclusive, or if in THL the pouch of Douglas was not reached.

In the HSG group, the procedure was scheduled in the follicular phase of the cycle. The procedure was performed in the radiology department. The contrast medium, either water-soluble contrast (Telebrix Hystero, Guerbet) or oil-soluble contrast (Lipiodol Ultra-Fluide, Guerbet), was used according to hospital-specific protocols. An additional diagnostic laparoscopy was performed when the HSG showed abnormalities or if HSG failed to show a reliable result. Furthermore, in women with a normal HSG, a diagnostic laparoscopy (DLS) was scheduled if a pregnancy did not occur after 6 to 12 months, to rule out pelvic abnormalities that were not noticed by HSG.

Additional treatment

After completion of the fertility work-up and tubal assessment, the prognostic model of Hunault was used for the prediction of a natural conception within 12 months (Hunault et al. 2004). When there was no tubal pathology, in general, expectant management was advised when the probability of natural conception within 12 months was >30%. In couples with a probability <30%, IUI with mild ovarian hyperstimulation (IUI-MOH) was advised. IUI-MOH was also advised when there was mild male subfertility (total motile sperm count 3-10 million), or after a period (6 months) of expectant management without natural conception.

When severe tubal pathology was diagnosed, or in case the couple did not conceive after 3-6 cycles of IUI, couples were counselled for IVF or ICSI. In women diagnosed with hydrosalpinges, endometriosis or severe adhesions, fertility enhancing laparoscopic surgery was scheduled.

Outcomes

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

Economic analysis

The economic evaluation was performed as a cost-effectiveness analysis from a health care perspective, focusing on direct medical costs. We compared the direct medical costs of THL and HSG, the cost of fertility treatments, and the medical costs related to pregnancy and delivery to assess the costs made to achieve a live birth until 24 months after randomization.

Data on resource use were collected from the individual case record forms. For each woman, we registered the type and number of interventions received until pregnancy occurred or until the end of the study period of 24 months. We registered all types of pregnancies and their outcomes.

The costs for each parameter were derived from previous publications (Verhoeve et al. 2013, Eijkemans et al. 2005, Tjon-Kon-Fat et al. 2011, Bouwmans et al. 2008, Lemmers et al. 2018, Lukassen et al. 2004, Mol et al. 2015). The costs for HSG, THL and fertility enhancing surgery were calculated. Since HSG was performed with oil-based contrast in 35% and water-based contrast medium in 65%, we averaged the cost of the contrast medium. The cost parameters and unit costs included in the economic evaluation (expressed in euros) are presented in Table I. All calculations were standardized to 2019 prices using consumer price index data (CBS the Netherlands). The unit costs were split into three main categories: costs of the diagnostic procedure, costs of fertility treatments, and the costs for pregnancy outcomes. The costs for fertility treatment were estimated from

the unit cost for IUI multiplied by the mean number of IUI cycles per woman in each treatment group, and the estimated unit cost for IVF/ICSI was multiplied by the mean number of ETs per woman in each treatment.

Table 1 Unit costs for diagnostic techniques, fertility treatments and pregnancy outcomes.

Cost item	Unit cost (Euros) indexed to 2019	Reference
Diagnostic technique		
HSG	289	Calculation
THL	425	Calculation
Diagnostic laparoscopy	1272	Verhoeve et al. 2013
Treatment		
Ovulation induction	61	Eijkemans et al. 2005
IUI with MOH	323	Tjon-Kon-Fat et al. 2015
IVF/ICSI	2754	Bouwman et al. 2008
Therapeutic laparoscopy	4084	Calculation
Pregnancy and delivery		
Miscarriage (curettage)	1565	Lemmers et al. 2018
Singleton live birth	3302	Lukassen et al. 2004
Twin live birth	17442	Lukassen et al. 2004
Ectopic pregnancy (tubectomy)	3420	Mol et al. 2015

MOH = mild ovarian hyperstimulation

HSG: hysterosalpingography

THL: transvaginal hydrolaparoscopy

Statistical analysis

Data were analyzed using the intention-to-treat principle. The mean costs and outcomes for each treatment group were compared. Costs were combined with effectiveness by calculating incremental cost-effectiveness ratios (ICER). The ICER per additional live birth was calculated by dividing the difference in total costs by the difference in outcome for the two strategies.

We used a non-parametric bootstrap resampling of 1000 re-samples to investigate the effect of uncertainty in our estimates. We generated a cost-effectiveness plane to visualize the uncertainty about the expected difference in costs and outcomes between the two diagnostic strategies. Furthermore we generated cost-effectiveness acceptability curves to indicate the probability that a diagnostic strategy with THL is cost-effective compared to a strategy with HSG, for a range of values of the maximum acceptable cost per live birth.

Statistical analysis were performed using SPSS version 26 (IBM statistics, Armonk, NY, USA) and Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

A value of $P < 0.05$ was considered to be significant.

RESULTS

Participants and trial outcomes

Between May 2013 and October 2016 we randomized 300 women, of which 149 were 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 can be found in Table II. At 24 months after randomization, two women in the THL-group and two women in the HSG-group were lost to follow-up (Fig. 1).

Table II Baseline characteristics of women in a study comparing the cost-effectiveness of transvaginal hydrolaparoscopy to hysterosalpingography.

Characteristic	THL (n=144)	HSG (n=150)
Female age (years, mean + SD)	31.6 (+/- 3.9)	31.9 (+/-4.0)
Median BMI (kg/m ² IQR)	23.4 (21.0 - 26.9)	23.3 (21.2 – 26.2)
Intoxications		
Smoking	27 (18.8%)	25 (16.7 %)
Alcohol	37 (25.7%)	44 (29.3%)
Drugs	1 (0.7%)	1 (0.7%)
Type of subfertility		
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	108 (75.0 %)	129 (86.0%)
Median VCM (IQR)	47.5 (17.25-98.5)	51.0 (22.0-118.0)
Positive Chlamydia serology	16 (11.1%)	16 (10.7%)

VCM: (volume x concentration x percentage progressively moving spermatozoa)

IQR: interquartile range

HSG: hysterosalpingography

THL: transvaginal hydrolaparoscopy

In both groups, the fertility treatment was started according to findings of the fertility examinations and based on the prognostic model of Hunault. During the follow-up period, the treatment modality was not fixed, but adjusted if needed. For example, if no conception occurred after 3-6 insemination treatments, the couple was counseled for

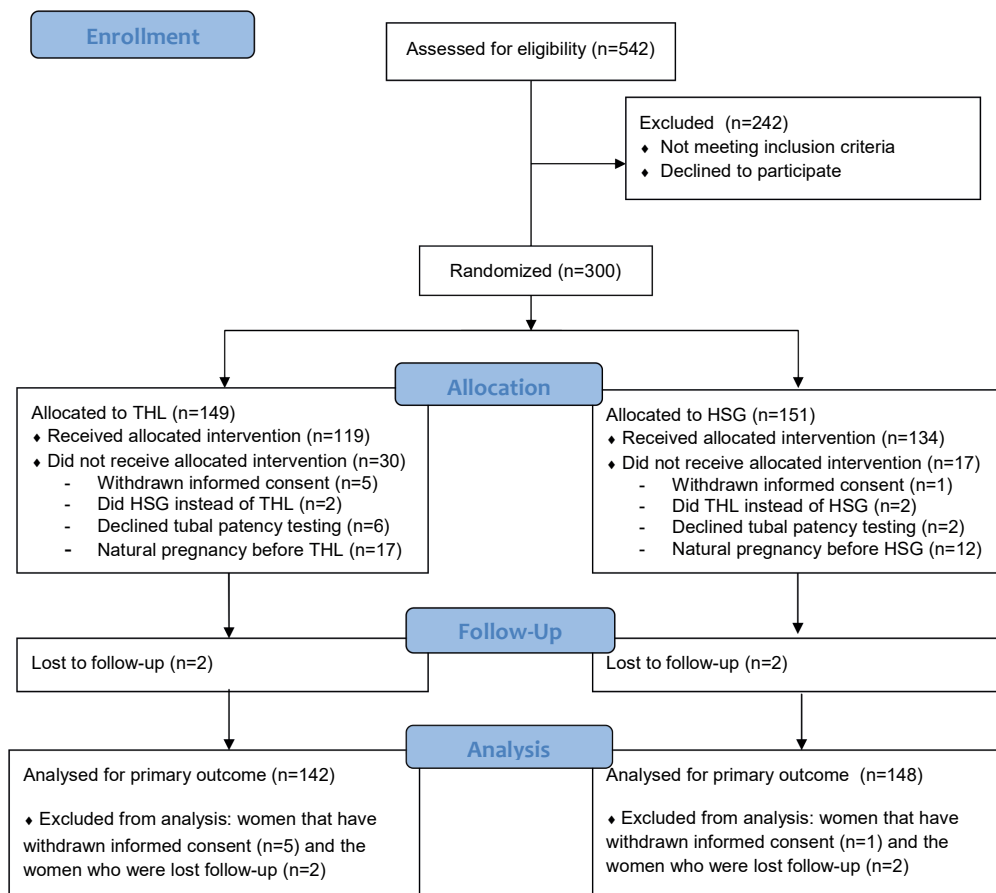


Figure 1 CONSORT flow diagram for a comparison of the cost-effectiveness of transvaginal hydrolaparoscopy versus hysterosalpingography in the work-up for subfertility.

HSG: hysterosalpingography
 THL: transvaginal hydrolaparoscopy

IVF treatment. Between randomization and the scheduled procedure, 17 and 12 women conceived naturally in the THL group and HSG group, respectively. In the THL-group 28 women were managed expectantly, nine women underwent ovulation induction, 59 women were treated with IUI and 21 women were treated with IUI followed by IVF treatment. Two women were referred directly for IVF treatment. Based on the findings at THL a diagnostic laparoscopy was performed in two women and fertility-enhancing surgery was performed in six women. All of the women that underwent fertility-enhancing surgery were subsequently treated with IUI and/or IVF. In the HSG group, 27 women were managed expectantly, eight women underwent ovulation induction, 60 women were treated with IUI and 26 women were treated with IUI followed by IVF

treatment. Three women were referred for IVF treatment. In the HSG group, 22 women underwent subsequent laparoscopy. In 11 women laparoscopy was scheduled because of an abnormal or inconclusive HSG (four women underwent diagnostic laparoscopy and seven women underwent laparoscopic fertility-enhancing surgery) and in another 11 women laparoscopy was scheduled for women with a normal HSG that did not conceive after 6-12 months (in six women only diagnostic laparoscopy was performed and in five women laparoscopic fertility-enhancing surgery was performed because of the presence of pelvic pathology such as endometriosis and adhesions with open tubes). After fertility enhancing surgery nine women were subsequently treated with IUI and/or IVF.

After 24 months of follow-up we found a live birth rate of 58.4% in the THL group versus 55.4% in the HSG group (difference 3.0% (95% CI: -8.3 – 14.4)). Multiple pregnancy and miscarriage rate were low and did not differ in both groups. Ectopic pregnancy did not occur in the THL group and it occurred in two women in the HSG group. No differences in time to conception ($p = 0.199$) and time to conception leading to live birth ($p = 0.308$) were found.

A comparison of the mean costs per woman by cost category for the two treatment groups is provided in Table III. The mean cost was lower in the THL group, compared to the HSG group (THL group €4991 versus €5262 in the HSG group, mean cost difference = -€271 (95% CI -€273 to -€269). Although the costs of the diagnostic procedure itself were higher in the THL group (€425 versus €289, difference -€135), the total mean cost per woman was higher in the HSG-group. In the HSG group more women underwent diagnostic and therapeutic laparoscopies and also had higher costs for fertility treatments such as IUI-MOH.

Table III Comparison of mean costs per woman for the two treatment groups.

	THL	HSG
Diagnostic technique		
HSG/THL and diagnostic laparoscopy	€380	€352
Fertility treatments		
OI, IUI-MOH IVF/ICSI and Therapeutic laparoscopy	€2106	€2345
Pregnancy outcomes		
Miscarriage, Ectopic pregnancy, Singleton and multiple livebirth	€2505	€2565
Total cost	€4991	€5262

OI= ovulation induction

MOH = mild ovarian hyperstimulation

HSG: hysterosalpingography

THL: transvaginal hydrolaparoscopy

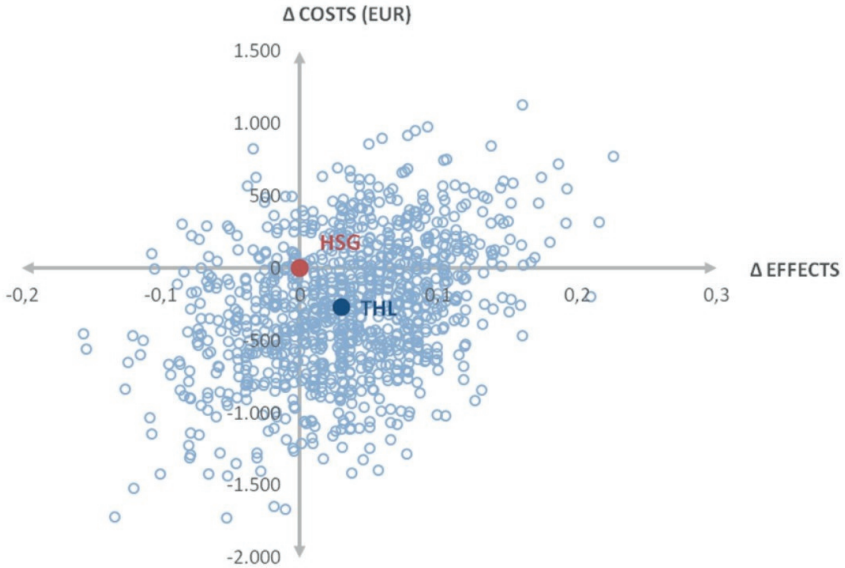


Figure 2 The cost-effectiveness plane representing the incremental costs and effects of a strategy with THL compared to HSG and the joint uncertainty around the ICER. The spread of the bootstrapped samples (n=1,000) across the horizontal plane indicates that there is greater uncertainty regarding the magnitude of effect than the difference in costs.

HSG: hysterosalpingography
 THL: transvaginal hydrolaparoscopy

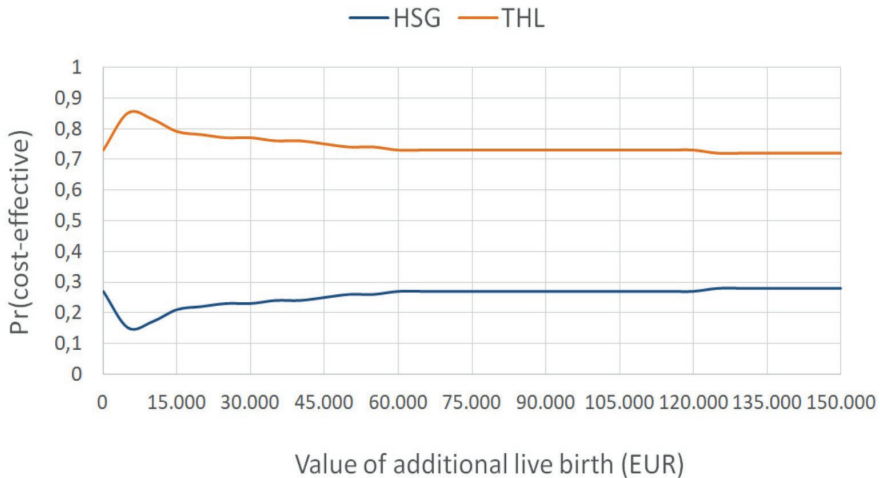


Figure 3 Cost-effectiveness acceptability curves for live birth, showing the probability that THL is cost-effective compared to HSG over a range of values for the maximum acceptable value for added livebirth, for example, if the maximum acceptable ratio is 5,000 EUR per additional live birth, the probability that THL is cost-effective compared with HSG is 0.83

THL: transvaginal hydrolaparoscopy
 HSG: hysterosalpingography

The spread of the bootstrap samples across the south and north-eastern quadrants indicates that there is uncertainty regarding the effectiveness of THL over HSG and less uncertainty regarding the cost difference between THL and HSG (Fig. 2). The base case outcome is that a strategy starting with THL costs less and is more effective than a strategy starting with HSG, making THL the dominant strategy.

The cost effectiveness acceptability curve (CEAC) shows that if, for example, the maximum acceptable ratio is 5,000 EUR per additional live birth, the probability that THL is cost-effective compared with HSG is 0.83 (Fig. 3). Alternatively, this can be interpreted as there being a 83% chance that the potential additional cost of having a THL, compared with having an HSG, is less than 5,000 EUR per additional live birth.

DISCUSSION

We performed an economic evaluation alongside a RCT including subfertile women scheduled for tubal patency testing during fertility work-up, and randomized for THL or HSG in women with a low risk of tubal pathology. After 2 years of follow-up we found a live birth rate of 58.4% in the THL group versus 55.4% in the HSG group (difference 3.0% (95% CI: -8.3 – 14.4)). Total mean costs per woman were also lower in the THL group (mean cost difference = -€271 (95% CI -€273 to -€269)). This leads to a strategy with THL being the dominant strategy.

Strengths and limitations

An important strength is that this study was based on a large multicenter RCT comparing a strategy starting with THL with a strategy starting with HSG. The follow-up lasted for 24 months after randomization and few women were lost to follow-up. Although few studies have mentioned the costs of THL, a comparison of the costs and effect of HSG and THL has not been made before.

During the 2-year follow-up period the treatment of the couple was managed according to the Dutch guidelines of fertility management. This means that there was not one fixed treatment modality, but that one couple could have different forms of treatment during the follow-up period. This also reflects daily practice in fertility treatment.

One of the limitations of this study is that HSG was performed according to local hospital protocol, which means that oil-based contrast medium was used in two hospitals (35% of participating women) and water-based contrast medium in the other two hospitals (65% of participating women). During the randomization period of our trial there was no robust evidence yet of the benefits of tubal flushing with oil-based contrast medium.

Therefore it is not possible to evaluate if there is any additional effect of tubal flushing in this RCT.

Second, in the THL group we found more women with anovulatory cycles compared to the HSG group. However, the assignment to either the strategy with THL or HSG was by means of randomization and the costs of ovulation induction in the two groups were comparable, therefore we do not think that this would lead to a meaningful difference in the costs of fertility treatments between the two groups. Moreover, this trial was conducted specifically in women with a low risk of tubal pathology. Women with a high suspicion of tubal or pelvic pathology, for example because of visible hydrosalpinges, deep-infiltrating endometriosis or a mass in the pouch of Douglas, would benefit by scheduling a laparoscopic procedure to visualize the pelvic cavity and to perform operative laparoscopy directly if needed (den Hartog et al. 2008, Practice Committee of the American Society for Reproductive Medicine 2021, National Institute for Health and Care Excellence [NICE] 2013). The results of our study are, therefore, not generalizable to women with high risk of tubal pathology.

Third, this trial was conducted in the Netherlands, using price calculations of the Dutch healthcare system and the currency in Euro's. The cost difference in our study between a strategy starting with THL and a strategy starting with HSG was €271, with the THL group having higher costs for the diagnostic procedure and the HSG group having higher costs because of treatments and additional laparoscopies. The cost difference between the two diagnostic strategies is limited compared to the total cost per woman in our study. Our findings might not be generalizable to other countries, for example if other diagnostic and treatment strategies are used to manage the subfertile couple. Also a large variation in costs of fertility treatments worldwide (Salam 2017) has to be taken into account.

Furthermore, in the Netherlands, fertility treatments including ART are reimbursed by the healthcare system, if the woman meets specific criteria. In other countries where fertility treatments are not reimbursed by the healthcare insurance, the medical costs that the couple needs to pay out of their pocket are important in the decision-making process and this could lead to different choices for fertility treatment.

Our cost-effectiveness analysis is performed using a health care perspective, and we focused on direct medical costs during treatment. During follow-up we did not monitor indirect costs such as productivity loss due to absence from work, transportation etc. From a societal perspective these costs have to be taken into account. It could be expected that costs from a societal perspective would be higher for the strategy starting with HSG because in that group women underwent more treatments, more cycles and also more laparoscopies during the follow-up period.

THL was introduced as a new technique for tubal patency testing over 20 years ago. The technique is used in different clinics as a first-line tubal patency test, but HSG still is the most commonly used test worldwide. In our RCT, we compared the cost and effects of a strategy of tubal patency testing with THL with a strategy of tubal patency testing with HSG. We found that the two diagnostic procedures have comparable performance in safety, pain and acceptability (Tros et al. 2019) and that live birth rates with the two diagnostic strategies were not statistically different. This cost-effectiveness analysis showed that THL is cost-effective compared to HSG in the subfertility work-up. From this point of view THL could be proposed as a feasible first-line tubal patency test. The preference of the subfertile couple, however, still needs to be taken into account, in both clinical decision making as well as in guideline development. In order to examine the preferences of subfertile women on different aspects of the procedures of tubal patency testing, we are currently conducting a discrete choice experiment.

In conclusion, after 2 years of follow-up we found a live birth rate of 58.4% in the THL group versus 55.4% in the HSG group (difference 3.0% (95% CI: -8.3 – 14.4)). Although the cost of the diagnostic procedure was higher in the THL group, the total mean costs per woman were higher in the HSG group. The main drivers for the higher cost in the HSG group were the additional laparoscopies and costs of fertility treatments. The findings of our trial suggest that a strategy starting with THL is cost-effective compared to a strategy starting with HSG in the workup for subfertile women.

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CHAPTER 5

FERTILITY-RELATED QUALITY OF LIFE IN SUBFERTILE WOMEN UNDERGOING TUBAL TESTING WITH TRANSVAGINAL HYDROLAPAROSCOPY OR HYSTEOSALPINGOGRAPHY

M.A. van Kessel, M. Paulussen, R. Tros, M.Y. Bongers, B.W.J. Mol, C.A.M. Koks

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ABSTRACT

Objective

Both subfertility and its management can have significant impact on quality of life (QoL). Tubal patency testing as part of the fertility work-up, is considered to cause more physical complaints and stress than other tests. Pain scores for HSG are higher than for THL, but acceptability of the procedures was found to be comparable. Fertility-related QoL has not yet been studied in women undergoing tubal patency testing.

Study design

We performed a standardized questionnaire study alongside a previously reported randomized controlled trial comparing THL and HSG in subfertile women, in which 24-month live birth rates occurred in 58.5% versus 55.4%, respectively. We randomly assigned 300 subfertile women to THL or HSG between May 2013 and October 2016. Women were eligible if they were undergoing a fertility work-up with an indication for evaluation of tubal patency. Fertility-related QoL was measured six weeks after the procedure with the validated FertiQoL questionnaire. The scores for the Core scale and subscales between THL and HSG were compared using Mann-Whitney-U test and multiple linear regression analysis.

Results

The questionnaire was completed by 84 women in the THL group (56%) and 96 women in the HSG group (64%). Core scores were 74.6 ± 12.8 for THL and 73.4 ± 12.4 for HSG ($p=0.39$). Scores for the Emotional domain were 64.5 ± 19.0 for THL versus 66.0 ± 16.3 ($p=0.67$) for HSG. Scores for the 'Mind-body' domain for THL were 76.9 ± 15.6 versus 74.1 ± 18.0 for HSG ($p=0.42$), while scores for the Relational domain were 79.2 ± 12.9 for THL and 76.9 ± 15.6 for HSG ($p=0.21$). Scores for the Social domain for THL were 77.9 ± 15.1 versus 76.7 ± 14.1 , ($p=0.42$). The multiple linear regression analysis showed only a statistical significant positive effect of older age on the score for the Emotional domain ($p=0.015$).

Conclusion

In a preselected group of women with low risk for tubal pathology we did not find differences in fertility-related QoL between tubal patency testing with THL versus HSG.

Keywords: Transvaginal hydrolaparoscopy, Hysterosalpingography, Tubal patency test, Subfertility, Quality of Life, FertiQoL

INTRODUCTION

One out of eight couples trying to conceive experience fertility problems. It is known that subfertility as well as subfertility treatments can have a significant impact on quality of life (QoL) (Verhaak et al. 2007; Cosineau and Domar 2007; Greil et al. 2011; Mathiessen et al. 2011). In the work-up for subfertility, diagnostic procedures for tubal patency testing are known to cause more physical complaints and stress than other examinations (Eimers et al. 1997). Women experience the procedure as an important step in the whole treatment of their subfertility, and written information combined with the opportunity to discuss the procedure with their healthcare professional can reduce stress and anxiety (Williams et al. 2010).

In the work-up for subfertility, various strategies for tubal patency testing are possible. Two common diagnostic procedures are hysterosalpingography (HSG) and transvaginal hydrolaparoscopy (THL). In the Netherlands HSG is traditionally performed as a first line tubal patency test. In HSG a catheter is inserted in the uterus through the cervical canal and a contrast medium instilled through the catheter with fluoroscopic images taking intermittently to evaluate the uterine cavity and the patency of the tubes. It doesn't give information about the presence of other pelvic abnormalities such as endometriosis or peritubal adhesions and its sensitivity is significantly lower in low-risk than in high-risk women (Broeze et al. 2011). THL on the other hand 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 a diagnostic laparoscopy.

The diagnostic accuracy of THL compared to HSG has been validated in several studies. The agreement on tubal patency testing between the two procedures is good, however THL is superior in diagnosing endometriosis and peritubal adhesions (Shibahara et al. 2001, Cicinelli et al. 2001, Tros et al. 2019), whereas HSG can show intrauterine abnormalities which THL cannot detect (Tros et al. 2019).

The diagnostic accuracy of THL compared to diagnostic laparoscopy is considered to be good, with sensitivity between 70 and 100% and specificity up to 100% (Dechaud et al. 2001, Darai et al. 2000, Casa et al. 2002, Watrelot et al. 2003).

In a randomized controlled trial comparing THL and HSG as a first line diagnostic strategy for tubal pathology in subfertile women, we found that THL and HSG are comparable in diagnosing tubal pathology (Tros et al. 2019). Furthermore, we found significantly higher pain scores for HSG compared to THL on a 10 point visual analogue scale (painscore 4.7 (SD: 2.5) for THL versus 5.4 (SD: 2.5) for HSG ($p=0.038$). 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 (Tros et al. 2019). We previously reported that the primary outcome, conception leading to live birth in 24 months, occurred in 58.5% in THL-group versus 55.4% in HSG group. We did not find a statistical difference in live birth rates or time to live birth (van Kessel et al. 2021).

Considering the burden of subfertility examinations and treatment, it is important to take QoL into account when evaluating diagnostic or therapeutic strategies in fertility management. In this study we evaluate fertility related QoL in infertile women undergoing either THL or HSG as a diagnostic procedure for tubal patency evaluation.

MATERIAL AND METHODS

This QoL-evaluation was performed alongside the THL-trial, a randomized controlled clinical trial comparing HSG and THL in subfertile women at low risk of tubal disease (van Kessel et al. 2021, Tros et al. 2019). The study was performed according to Good Clinical Practice (GCP) guidelines and the study protocol was approved by the Institutional Review Board of the Amsterdam Medical Center (AMC, Amsterdam, the Netherlands), and by the boards of directors of the participating hospitals. The trial was registered in the Dutch Trial Registration (NTR3462). In each of the participating centers, patient counseling, data collection and monitoring were performed by dedicated research nurses. All women provided written informed consent prior to randomization.

Study Population

Women were eligible 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 one year of unprotected intercourse. Women were not eligible if they had a contraindication for THL or HSG.

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 written informed consent, women were randomly allocated to a strategy starting with THL (experimental arm) or with HSG (control arm). Six weeks after the randomized procedure, women were sent a questionnaire which consisted of questions about the general characteristics, absence of work and quality of life. For the measurement of QoL we used the Dutch version of the validated FertiQoL questionnaire, a specifically designed questionnaire to measure QoL in the subfertile

population. It consists of 36 items scored on a five-point scale, addressing five key domains in fertility problems. In the fertiQoL questionnaire a high score indicates a more favorable QoL (Boivin 2011).

INTERVENTIONS

In women allocated to THL, the procedure was scheduled in the follicular phase of the menstrual cycle. THL was performed as described by Gordts (Gordts et al. 1998). In two of the participating hospitals we used the Storz re-usable system (KARL STORZ, Tuttlingen, Germany) and in two hospitals the disposable Fertiloscope (Fertility Focus, Warwick UK) was used. The procedure was performed in an out-patient department, using local anesthesia. Antibiotics were not given. An additional hysteroscopy was only performed in case of suspected uterine anomaly or intrauterine pathology on ultrasound. In women allocated to THL an additional diagnostic laparoscopy was performed either if THL was inconclusive, or if in THL the pouch of Douglas was not reached.

In women allocated to HSG, the HSG procedure was scheduled in the follicular phase of the cycle. The procedure was performed in the radiology department. The contrast medium (either water-soluble contrast (Telebrix Hystero, Guerbet) or oil-soluble contrast (Lipiodol Ultra-Fluide, Guerbet) was used according to hospital specific protocols). Antibiotics were not given. In women allocated to HSG an additional diagnostic laparoscopy was performed when the HSG showed abnormalities or if HSG failed to show a reliable result. Furthermore, in women with a normal HSG, a DLS was scheduled if a pregnancy did not occur after 6 to 12 months, to rule out pelvic abnormalities that were not noticed by HSG.

Additional treatment

After the completion of the fertility work-up and tubal assessment, the prognostic model of Hunault was used for the prediction of a natural conception within 12 months (Hunault 2004), and treatment of the couple was advised according to the Dutch guidelines.

Statistical analysis.

Baseline characteristics of the participating women, stratified by allocation, were described using mean and standard deviation for continuous variables and count and percentage for categorical variables. The FertiQoL scores were grouped by the randomized intervention (HSG or THL) and analyzed according to the intention to treat principle. Means and sample variances were computed. Tests for normality of distri-

bution were performed. Since FertiQol scores were not normally distributed, between-group comparisons were performed using the Mann-Whitney U test. We performed multiple linear regression analysis.

We used IBM SPSS version 26.0. P-values of 0.05 or lower were considered to indicate statistical significance.

RESULTS

Between May 2013 and October 2016, we randomly allocated 300 women to THL (n=149) and HSG (n=151). These women were sent the questionnaire 6 weeks after the procedure. Of these 300 women, 180 women (60%) completed the questionnaire (THL n=84 and HSG n= 96). One woman in the THL group was excluded because of pregnancy before tubal patency investigation. Out of these 179 women, 3 did not complete the full questionnaire (THL n=1, HSG n=2).

Table 1 : Baseline characteristics

Baseline characteristics	HSG n=96	THL n=84
Mean age (+/-SD)	31.8 (+/-3.7)	31.7 (+/-4.0)
Mean duration of subfertility, months (+/-SD)	25.6 (+/-11.8)	24.1 (+/-14.8)
Primary subfertility (%)	81 (84.4%)	57 (68.7%)
Mean BMI (+/-SD)	24.0 (+/-4.3)	23.7 (+/-5.0)
Ovulatory cycles	79 (82.3%)	62 (73.8%)
Level of education		
<i>Primary school</i>	0 (0%)	1 (1.2%)
<i>Secondary school</i>	15 (15.6%)	6 (7.2%)
<i>College</i>	30 (31.3%)	22 (26.2%)
<i>University</i>	35 (36.5%)	33 (39.3%)
<i>Research university</i>	14 (14.6%)	15 (17.8%)
<i>Other/unknown</i>	2 (2.1%)	7 (4.8%)

Abbreviations:

BMI: Body mass index, kg/m².

Baseline characteristics were comparable and are presented in table 1. Total scores as

Table 2: FertiQol scores: total scores and subscale scores

FertiQol	HSG n=94	THL n=83	p-value
Core Mean score (SD)	73.4 (12.4)	74.6 (12.8)	0.39
Emotional Mean score (SD)	66.0 (16.3)	64.5 (19.0)	0.67
Mind body Mean score (SD)	74.1 (18.0)	76.9 (15.6)	0.42
Relational Mean score (SD)	76.9 (13.1)	79.2 (12.9)	0.21
Social Mean score (SD)	76.7 (14.1)	77.9 (15.1)	0.42

Table 3: Association between FertiQoL scores and patient characteristics (multivariable analysis)

Variables	Core		Emotional		Mind/body		Social		Relational	
	Beta (95%CI)	p-value	Beta (95%CI)	p-value	Beta (95%CI)	p-value	Beta (95%CI)	p-value	Beta (95%CI)	p-value
Age	0.48 (-0.05-1.01)	0.08	0.90 (0.18-1.62)	0.02	0.59 (-0.13-1.30)	0.12	0.30 (-0.32-0.92)	0.34	0.14 (0.41-0.69)	0.61
Type of subfertility										
*Primary	Ref		Ref		Ref		Ref		Ref	
*Secondary	-1.89 (-6.66-2.88)	0.44	-2.39 (-8.9-4.13)	0.47	-1.34 (-7.77-5.09)	0.68	-1.96 (-7.57-3.65)	0.49	-2.13 (-7.09-2.83)	0.40
Duration of subfertility										
	0.01 (0.15-0.16)	0.93	0.10 (-0.11-0.31)	0.33	0.02 (-0.19-0.22)	0.88	0.01 (-0.17-0.19)	0.89	-0.08 (-0.24-0.09)	0.36
BMI										
	-0.27 (-0.73-0.19)	0.25	-0.32 (0.94-1.31)	0.32	-0.32 (-0.91-0.32)	0.34	-0.24 (-0.77-0.30)	0.39	-0.23 (-0.71-0.24)	0.31

well as subscale scores on the FertiQoL questionnaire were computed according to the scoring system, and presented in table 2. Missing items were taken into account for by using the formula $25/k$ in which k stands for the items being filled in for each subscale or total scores.

Mean fertiQoL scores were 74.6 ± 12.8 for THL and 73.4 ± 12.4 for HSG ($p=0.39$). Scores for the Emotional domain were 64.5 ± 19.0 for THL versus 66.0 ± 16.3 for HSG ($p=0.67$). Scores for the 'Mind-body' domain for THL were 76.9 ± 15.6 versus 74.1 ± 18.0 for HSG ($p=0.42$), scores for the Relational domain were 79.2 ± 12.9 for THL and 76.9 ± 15.6 for HSG ($p=0.21$). Scores for the Social domain were 77.9 ± 15.1 for THL versus 76.7 ± 14.1 for HSG, ($p=0.42$).

The influence of age, type of subfertility, duration of subfertility and BMI has been measured by multiple linear regression analysis and is shown in table 3. We did not find an association for the type of subfertility, BMI or duration of subfertility on FertiQoL scores. Older age was related to a higher FertiQoL score, but only in the emotional domain ($p=0.015$).

DISCUSSION

We previously reported no difference in live birth rates between tubal assessment with THL and HSG. The current secondary analysis of this RCT reports no differences in fertility-related QoL for subfertile women undergoing HSG or THL, six weeks after the procedure. In the multivariate analysis older age was related to a higher FertiQoL score, but only in the emotional domain.

Strengths and weaknesses

Our study is performed alongside a RCT with a sample size of 300 women. To our knowledge fertility related QoL is not yet studied in women undergoing tubal patency testing.

Although comparing QoL after two different diagnostic strategies might be something that is infrequently done, we do have the opinion that QoL is an important factor in the comparison. The two procedures are known to have a significant difference in pain scores, in their chance of complications, in the amount of information they give and in the impact that their outcomes have on the subsequent fertility treatment.

The response rate of our study was 60%. Although this is considered an acceptable rate within questionnaire research, this could lead to a possible selection bias and therefore to higher or lower scores on the FertiQoL. Hansen et al. examined the impact of non-responders on health and lifestyle outcomes and found that non-responders more often reported to be in fair or bad health and that there was a trend to lower mental health in the non-responder group (Hansen et al. 2014). As we don't have information about the non-responders in our group, it is not possible to determine the direction of the non-responder bias in our study.

Furthermore, our study population is a heterogeneous population; we included subfertile women with an indication for tubal patency testing, in a population having a low risk of tubal pathology. Possibly more factors influencing FertiQoL scores could be indicated, other than tubal diagnostic testing. Because of the design of this study impact of these other factors could not be ruled out. Nevertheless we think that our study population reflects the clinical practice of fertility care.

Comparison to other literature

In our study, scores on the FertiQoL questionnaire were comparable to previous cohorts performed in the general subfertile population and the population of women treated for PCOS or unexplained fertility (Aarts et al. 2011, Huppelschoten et al. 2013, Santoro et al. 2016). A possible explanation is that although undergoing a tubal patency test can be stressful, it does not have a clinically relevant impact on fertility related QoL 6 weeks after the procedure. Also, the fact that women have been given extensive information about the two procedures before enrolling in our RCT, could possibly have led to the procedure having less effect on their quality of life (Handelzalts et al. 2016; Guvenc et al. 2020). Similar to other studies we found an association between older age and a higher fertility related quality of life (Cusatis et al. 2019; Santoro et al. 2016)

Consequences and impact on daily practice

The burden of fertility examinations and fertility treatment is well known and an important factor for the clinician to take into account when taking care of the subfertile couple. Considering the fact that invasive tubal patency testing is perceived more stressful than the other tests in the fertility workup, it is important for the healthcare provider to be sensitive to the need of emotional support. Between tubal patency testing with HSG or THL we did not find a difference in quality of life 6 weeks after the procedure.

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CHAPTER 6

ASSESSING SUBFERTILE WOMEN'S PREFERENCES FOR HYSTEOSALPINGOGRAPHY OR TRANSVAGINAL HYDROLAPAROSCOPY IN THE FERTILITY WORK-UP: A LABELED DISCRETE CHOICE EXPERIMENT

M.A. van Kessel, M.M.V. Paulussen, M.Y. Bongers, B.W.J. Mol, C.A.M. Koks, B.A.B. Essers

Manuscript in preparation

ABSTRACT

Objective

To investigate women's preferences for hysterosalpingography or transvaginal hydro-laparoscopy for diagnosing tubal pathology

Study design

Labeled discrete choice experiment (DCE)

Setting

Single center DCE

Population

57 subfertile women with an indication for tubal patency testing

Methods

We defined attributes based on literature review, structured patient interviews and expert focus group meeting. This resulted in five final attributes: the chance of having a "false negative" test, complication rate, failure rate, subsequent management after a failed procedure and the waiting time for the procedure. We collected baseline characteristics. In the DCE women were asked to choose between choice sets with hypothetical scenarios of two tubal patency tests with different levels of the attributes. Data were analysed by using multinomial logistic regression.

Results

The questionnaire was returned by 54 out of 57 women. For THL women preferred a lower chance of a false negative result, a lower failure rate and a shorter waiting time. If a THL is not conclusive or if there is a failure to reach the pouch of Douglas, women prefer to have a conventional laparoscopy over expectant management. Women choosing HSG preferred a lower chance of a false negative result, a shorter waiting time and a lower chance of complications.

Conclusion

The chance of a false negative result, failure rates, the chance of complications and waiting time are attributes that impact women's preference for tubal patency testing strategy.

INTRODUCTION

Approximately one in six couples trying to conceive is subfertile, meaning that no natural conception occurs after 12 months of unprotected intercourse (Taylor 2003). Facing subfertility can be perceived as highly stressful (Cosineau and Domar 2007) and can lead to relational problems and problems in the sexual relationship (Nelson et al. 2008).

Fertility examinations have the purpose to examine the cause of subfertility and to determine which fertility treatment is best for the couple. Tubal patency testing is one of the cornerstones of the fertility examinations. Tuboperitoneal factors as an explanation of subfertility are found in 15-30% of the couples, depending on the population and the duration of subfertility (Anyalechi et al. 2021). Tubal patency testing is usually reserved as a last step in the fertility evaluation, because these diagnostic tests are more invasive than the other tests in the fertility workup and the burden to the woman is higher. Over the past decades, various methods of tubal patency testing have been developed and there is a large practice variation in tubal patency testing (Roest et al. 2018). Until now conventional diagnostic laparoscopy is still considered the gold standard for tubal patency testing. Our experience is that women who undergo a fertility workup, are often not informed about the different techniques for tubal patency testing.

Traditionally HSG is performed as a first-line tubal patency test. HSG is radiological diagnostic procedure, in which the patency of the fallopian tubes is evaluated by fluoroscopic images while a radio-opaque contrast medium is instilled through a catheter in the uterus. HSG can demonstrate if the tubes are patent and if the uterine cavity has abnormalities. It does not give reliable information about the presence of other pelvic pathology such as endometriosis or adhesions, which can also be a cause of subfertility. The procedure can either be performed with water-based contrast medium or oil-based contrast medium. The incidence of complications such as intravasation of contrast and PID is low (Roest et al. 2020). The exposure to radiation is around 3.6 mGY (Suliman et al. 2008). In a meta-analysis containing data of 4521 women, 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). Although HSG has been originally developed as a diagnostic instrument; there is evidence of a fertility enhancing effect of tubal flushing with oil-based contrast compared to water-based contrast medium (Dreyer et al. 2017).

THL on the other hand, is a more recently developed technique for tubal patency testing (Gordts 1998). It is an out-patient procedure, where access to the pouch of Douglas is obtained through the posterior vaginal vault, by a Veress needle system. After instillation

of warm saline the pelvic cavity can be explored for abnormalities such as endometriosis and adhesions and the patency of the tubes can be tested with methylene blue. The procedure is well tolerated in an outpatient setting under local anesthesia. THL has a failure rate of 2-6%, which means the inability to enter the pouch of Douglas during the procedure (Tros et al. 2020). Perforation of the bowel can occur, and this complication is usually treated conservatively with antibiotics (Verhoeve et al. 2012, Gordts et al. 2021). Until now there has been no publications on the therapeutic effect of tubal flushing at THL with oil based medium, although a recent publication shows that tubal flushing at THL with an oil based medium is feasible (Roest et al. 2022).

The diagnostic accuracy of THL compared to HSG has been validated in some studies. The agreement on tubal patency testing between the two procedures is good (Cicinelli et al. 2001) however, THL is superior in diagnosing endometriosis and peritubal adhesions (Shibahara et al. 2001). Because women with endometriosis and adhesions have a reduced chance of a non-IVF conception (van Kessel et al. 2018) this leads to the assumption that women with open tubes but the presence of endometriosis or adhesions would benefit from early detection and early start of fertility treatment.

We recently compared the cost and effects of a strategy of tubal patency testing with THL with a strategy of tubal patency testing with HSG, in women with a low risk of having tubal pathology. We did not find a significant difference in live birth rate and in the time to conception leading to a live birth using THL as a first line test for tubal patency compared to using HSG (van Kessel et al. 2021). We found lower pain scores with THL compared to HSG, and we found the two procedures to be comparable in terms of tolerability and complication rate (Tros et al. 2019). A cost-effectiveness analysis showed that THL is cost-effective compared to HSG in the subfertility work-up, although the cost difference compared to the total cost is relatively small (van Kessel et al. 2022).

Until now, limited research has been performed to study the values and preferences of subfertile women in the diagnostic work-up. This study aims to investigate what characteristics of THL or HSG are preferred by women, by performing a labeled discrete choice experiment (DCE).

MATERIALS AND METHODS

Methods

We conducted a labeled DCE in the fertility department of Máxima MC, Veldhoven, the Netherlands. Enrollment took place between September 2021 and August 2022. We

asked women in the work-up for subfertility with an indication for evaluation of tubal patency to participate. Subfertility was defined as the inability to conceive after at least one year of unprotected intercourse. Women were informed of the study by their gynecologist, fertility doctor or a dedicated research nurse. After providing written informed consent women received an email, with a link to the online questionnaire. Data were treated anonymously. The study was performed according to Good Clinical Practice (GCP) guidelines and the study protocol was approved by the Institutional Review Board of the Máxima MC.

DCE design

To identify and select attributes and levels for the DCE, a literature review was performed. The objective of the literature review was to identify which factors could be important for women with subfertility when choosing between the two techniques of tubal patency testing. The results of the literature review were discussed within an expert focus group with gynecologists specialized in infertility. Based on this focus group meeting, a list of possible attributes for the DCE was formulated. Subsequently we developed a script for structured patient interviews in order to gain insight into the patient perspective on the list of attributes. These interviews were held by telephone by one researcher (MP). Women were asked to comment on the attributes that were derived from literature and to rank the attributes from most important to least important. Also they were asked if there were any other aspects that they missed in our list of attributes. The patient interviews were recorded and transcribed and appraised by three researchers (BE, MvK, CK). This resulted in five final attributes: the chance of having a “false negative” test, complication rate, failure rate, subsequent management after a failed procedure and the waiting time for the procedure. A range of possible attribute levels were derived from literature (Campo et al. 1999, Darai et al. 2001, Dechaud et al. 2001, Shaaban et al. 2013, Foroozanfard et al. 2013, Tanahatoc et al. 2003, Kissler et al. 2011, Verhoeve et al. 2004, Tros et al. 2020, Shibahara et al. 2007, Stumpf and March 1980, Roest et al. 2020) and discussed with the expert focus group. The final list of attributes and their levels are illustrated in TABLE I.

We conducted a DCE with a labeled design with 12 hypothetical choice sets of treatment A (THL) and treatment B (HSG) with 5 attributes. Because THL and HSG have different characteristics that are specific for the test and not variable (the procedure itself with the information that the test can give, and also the evidence of a fertility enhancing effect of tubal flushing with oil-based contrast with HSG), we chose to do a labeled design. The first part of the questionnaire consisted of general questions regarding baseline characteristics, age, duration of subfertility and previous pregnancies. The second part of the questionnaire consisted of information about the DCE. To become familiar with

Table i attributes and levels

	THL	HSG
False negative rate	0 %	15%
	7 %	20%
	18 %	35%
Complication rate	1% chance of mild complications among which rectum perforation and infection	1% chance of mild complications among which intravasation of contrast medium and infection
	3% chance of mild complications among which a rectum perforation and infection	5% chance of mild complications among which intravasation of contrast medium and infection
Failure rate	2%	1%
	4%	
	6%	
Policy after failure	Expectant management Laparoscopy Other diagnostic test (HSG)	Expectant management Laparoscopy
Waiting time	2 weeks	2 weeks
	4 weeks	4 weeks
	6 weeks	
	8 weeks	

the concept of a DCE, a simple DCE question for choosing a phone was included. Subsequently, the actual DCE was presented with 12 choice sets. Each choice set consisted of two hypothetical procedures for tubal patency testing, labeled THL and HSG. The women were asked to choose their preferred treatment of choice for each of the 12 choice sets (Figure 1).

Figure 1 An example of a choice set

	THL	HSG
False negative rate	18%	15%
Complication rate	1% chance of mild complications among which rectal perforation and infection	5% chance of mild complications among which intravasation of contrast and infection
Failure rate	6%	1%
Management after failure	Other diagnostic test (HSG)	Expectant management
Waiting time	6 weeks	4 weeks
I would choose	<input type="checkbox"/> THL	<input type="checkbox"/> HSG

Design

The software Ngene was used to generate a fractional factorial efficient labeled design. Based on five attributes with corresponding levels as shown in Table 1, 24 choice sets were created with two blocks, each consisting of 12 choice sets. A forced choice design (without an opt-out option) was chosen, assuming that women always choose to have tubal patency testing. First a pilot among ten women was conducted to assess if the questionnaire was well understood and to examine if the regression model performed well. No modifications were necessary. The results of the pilot were subsequently used to update the final design.

Sample size

Using the rule of thumb by Orme & Johnson (Orme et al. 1998, Johnson et al. 2003), we calculated a minimum sample size for the DCE. This formula is defined as $500 \times \frac{\text{maximum number of attribute levels (4)}}{\text{the number of choice sets (12)}} \times \text{the number of alternatives (2)}$ which indicates that our study would need a minimum of 83 respondents.

Statistical analysis

For the demographic data we used SPSS version 26 (Armonk, New York, USA). We calculated means and standard deviations for continuous parameters and number and percentage for dichotomous or nominal data. Data analysis was performed using multinomial logit regression with Nlogit software version 6 (Econometric Software, Inc. Plainview, NY USA). The attribute "subsequent management after a failed procedure" was dummy coded while the other attributes were coded as continuous variables. The a-priori expectations were that women would prefer a lower level of false negatives, failure rate, complication and waiting time which is expressed by a negative sign in the regression coefficient. Subsequent management was expected to be positive compared to no further action and thus a positive sign was assumed. In addition, we performed a simulation analysis based on the results of the multinomial regression model. A p-value of <0.05 was considered as statistically significant.

RESULTS

Participants

Out of the 57 women that were informed about the study and gave written informed consent to participate in the study, 54 completed the online questionnaire (94.7%). The baseline characteristics of the women that participated are presented in TABLE II.

Table II Baseline characteristics

Characteristic	n=54
Mean female age in years (+ SD)	31.7 (+/- 3.8)
Type of subfertility (%)	
*primary (%)	79.6%
*secondary (%)	20.4%
Duration of subfertility in months, median (IQR)	24 (16-30)

Abbreviations:

SD: standard deviation

IQR: interquartile range

Findings

Results of the multinomial logit regression model show that when women choose for THL a lower chance of a false negative result, a low failure rate and a lower waiting time all are preferred. The chance of having complications did not have significant impact on their preferences. Furthermore if THL is not conclusive women prefer to have a conventional laparoscopy compared to expectant management.

For women choosing HSG a lower chance of a false negative result, a shorter waiting time and a lower chance of complications were preferred. The subsequent strategy (diagnostic laparoscopy) for a failed or inconclusive HSG did not have a significant impact.

Furthermore our regression analysis shows that women made their choices based on the different attributes in the discrete choice experiment and not based on the label of the design because the constant was not statistically significant. In this study, women preferred THL in 71% of the choice sets and HSG in 29% of the choice sets. The results of our multinomial logit regression are shown in TABLE III.

Table III Attribute coefficients and relative importance

	Coefficient significance		CI (95%)	
THL				
Lower chance of having false negative test	-0.09457	>0.01	-0.12120	-0.06795
Lower chance of complications	-0.12057	NS	-0.31503	0.07388
Lower failure rate	-0.17187	>0.01	-0.29330	-0.05044
Management after failed test				
*laparoscopy	0.48994	>0.05	0.02307	0.95681
*HSG	0.34842	NS	-0.13148	0.82832
Waiting time	-0.11153	>0.01	-0.19552	-0.02755
HSG				
Lower chance of having false negative test	-0.06021	>0.01	-0.08640	-0.03403
Lower chance of complications	-0.14542	>0.01	-0.24541	-0.04542
Management after failed test				
*laparoscopy	0.14457	NS	-0.25838	0.54752
Waiting time	-0.25280	>0.05	-0.45649	-0.04911
Constant	-0.63852	NS	-1.88375	0.60671

DISCUSSION

Main findings

In this DCE we found that subfertile women preferred for THL a lower chance of a false negative result, a low failure rate and a shorter waiting time. If a THL is not conclusive or there is a failure to reach the pouch of Douglas, women prefer to have a conventional laparoscopy over expectant management. Women choosing HSG, preferred a lower chance of a false negative result, a shorter waiting time and a lower chance of complications.

Strengths and limitations

To our knowledge, this is the first study that has used a DCE to quantify women's preferences about tubal patency testing in the fertility work-up.

Other studies comparing THL and HSG as different techniques of tubal patency testing have been focused mainly on the clinical outcomes and feasibility of the tests, on pain scores and tolerability of the procedures, on quality of life and on cost-effectiveness. We do believe that the preference of the subfertile woman is an important outcome measure and should be taken into account when comparing these diagnostic strategies. We developed our DCE and selected our attributes based on literature study, patient interviews and an expert focus group meeting. This extensive preparation gives a set of attributes that can be used to reliably measure patient preferences. We did not reach our intended sample size of 83 women, because the inclusion of women in the study went slower than anticipated. Our analysis with 54 women, showed significant outcomes in terms of preference on specific attributes, but it is possible that we would have found stronger associations when we would have reached the intended sample size.

Furthermore, we chose to compare only two techniques of tubal patency testing, THL and HSG but there are more different diagnostic techniques available for tubal patency testing. Comparing more than 2 different techniques in a labeled model would be complex and difficult to interpret.

Interpretation

In our structured patient interviews and in the subsequent DCE we found that women find it important that the test enables them to be informed about the cause of their subfertility. Compared to conventional laparoscopy, the "gold standard" of tubal patency testing, both THL and HSG have a chance of giving a "false negative result". This means that there is tuboperitoneal pathology, but the THL or HSG did not detect it. Because HSG is a radiological procedure that gives information about the patency of the tubes, while THL is an endoscopic procedure that gives information about tubal patency and also about other pelvic pathology, the risk of having a "false negative result" is higher

for women that undergo a HSG. In the structured interviews most women stated that this attribute was important to them, but due to the sample size of our study, it was not possible to calculate the relative importance of this attributes compared to the other ones.

Other aspects that we assumed to be important, based on literature review at the start of our study, such as pain and tolerability of the procedure and the use of X-rays for HSG, were considered not important during the patient interviews and therefore not included as an attribute.

Both in the interviews and in the DCE, patients prefer a shorter waiting time for a scheduled procedure. THL and HSG are usually scheduled in the follicular phase of the cycle; HSG in the radiology department and THL in an outpatient procedure room. In our experience the mean waiting times for THL have been longer than for HSG in our hospital, which can influence patient preference.

We chose to perform a labeled DCE because THL and HSG are different types of procedures and the specific characteristics of the techniques (the information that they give and the possibility of tubal flushing) cannot be formulated into an attribute. However, we found in the regression analysis, that women in the DCE based their choice on the different attribute levels of the DCE and did not specifically make their choice for the label of THL and HSG.

There have been many studies using a DCE to examine patient preference in fertility treatments, but for the fertility work-up patient preference has not been measured yet. Due to the sample size of our study it is not possible to conclude which attribute women value most important and which test they would prefer. However, our results are relevant for different stakeholders, i.e. subfertile couples, fertility care professionals and policymakers, because they provide more insight in the perspective of the subfertile women about the aspects of tubal patency testing in the fertility work-up and they enable informed decision making. Further research is needed to compare our findings to the other forms of tubal patency testing in the fertility work-up.

Conclusion

We found that subfertile women when choosing THL preferred a lower chance of a false negative result, a lower failure rate and a shorter waiting time. If a THL is not conclusive or failure to reach the pouch of Douglas, women prefer to have a conventional laparoscopy over expectant management. Women choosing HSG preferred a lower chance of a false negative result, a shorter waiting time and a lower chance of complications.

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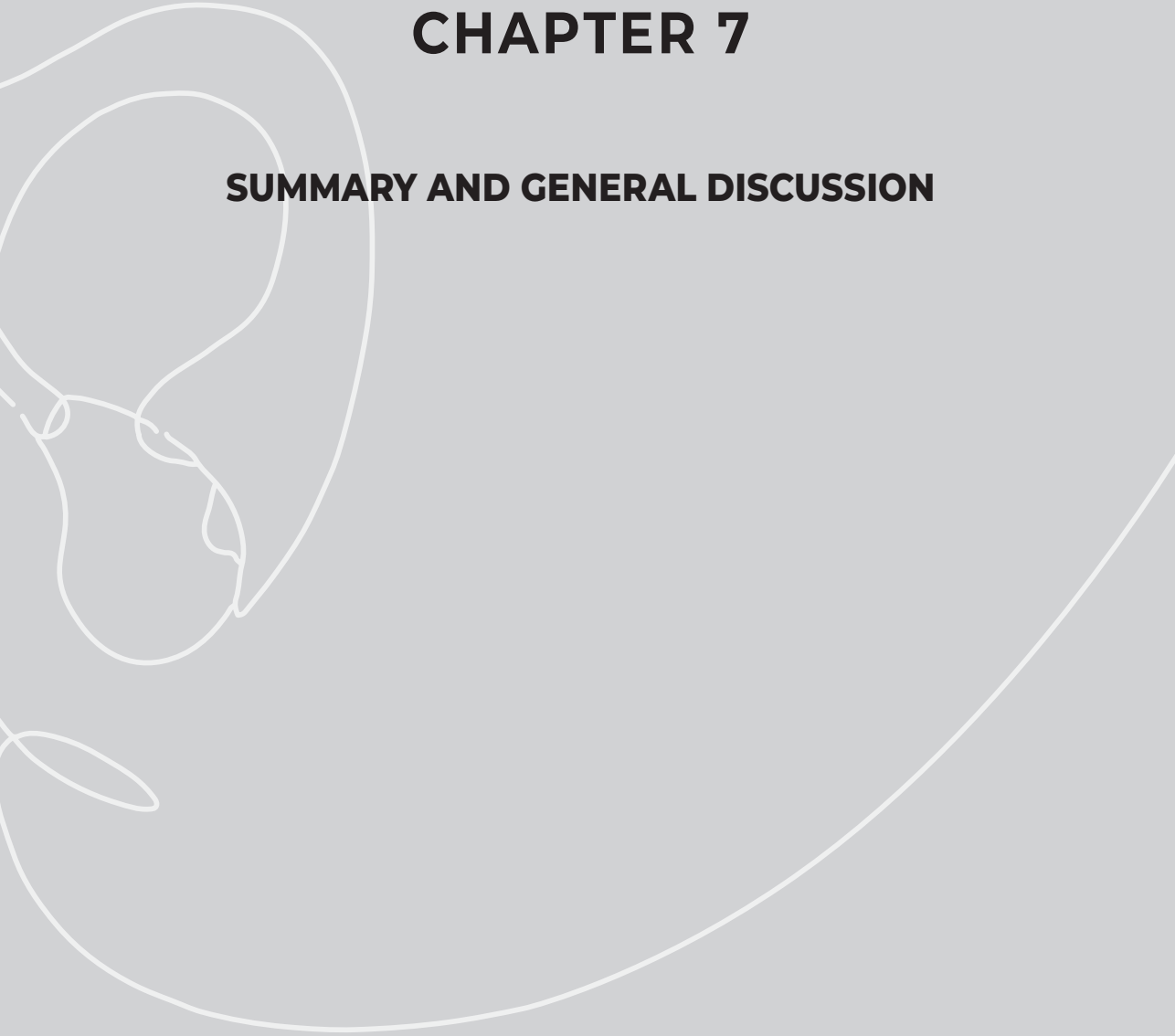
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CHAPTER 7

SUMMARY AND GENERAL DISCUSSION



SUMMARY AND GENERAL DISCUSSION

Subfertility, defined as the non-occurrence of pregnancy after 12 months of unprotected intercourse, affects approximately one in six couples that are trying to conceive. In the work-up for subfertility there are different diagnostic procedures to determine the cause of subfertility and to determine the subsequent treatment if needed.

This thesis focuses on two different methods of tubal patency testing in the work-up for subfertile women: THL and HSG. Both are established diagnostic procedures for tubal patency. They have different characteristics, such as invasiveness of the procedure, pain during the procedure, and different ways of visualization either via radiological images of the uterine cavity and tubes versus direct visualization of the tubes, fimbrial ends and ovaries with an endoscope.

We investigated the prognostic value of THL in a retrospective cohort of women that underwent THL as a first-line tubal patency test. We compared both diagnostic procedures in a randomised controlled trial. We investigated if a diagnostic strategy starting with THL was non-inferior to HSG in the workup for subfertility. Alongside this trial we investigated the cost-effectiveness of the two procedures. Furthermore we explored fertility-related quality of life in women undergoing these procedures and we assessed which characteristics of the diagnostic procedures for tubal patency testing are most important for women that are undergoing a fertility work-up.

SUMMARY

In a multicenter retrospective cohort we studied 1,033 women that underwent THL as their first-line tubal patency test in their subfertility work-up. In **CHAPTER 2** we describe the findings of their THL-procedures and the subsequent pregnancy rates. The primary outcome measure was intrauterine pregnancy, either after natural conception, ovulation induction or after treatment with controlled ovarian stimulation and intrauterine insemination (non-IVF conceptions). Cumulative intrauterine pregnancy rates were calculated using Kaplan–Meier analysis and fecundity rate ratios (FRR) were established. THL showed bilateral patent tubes in 83%, one-sided tubal occlusion in 12.4% and bilateral tubal occlusion in 4.6% of women. 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).

We conclude that both bilateral tubal occlusion and the combination of endometriosis and adhesions strongly reduce the chance of a non-IVF pregnancy, while women with either adhesions or endometriosis have a limited reduction of their fertility chances. One-sided tubal occlusion did not have impact on non-IVF conception.

In **CHAPTER 3** we describe the results of our multicenter randomised controlled trial comparing THL and HSG as a first-line tubal patency test in subfertile women. Subfertile women scheduled for tubal patency testing were eligible. Women with a positive Chlamydia PCR, prior tubal testing or tubal surgery, a retroverted uterus, masses or cysts in the pouch of Douglas, and allergies to iodine or methylene blue were excluded. The primary outcome was conception leading to live birth within 24 months after randomisation. We allocated 149 women to a strategy with THL and 151 to a strategy with HSG. We were able to achieve complete follow-up in 142 versus 148 women. After the fertility work-up women were treated according to the Dutch guidelines and based on the prognostic model of Hunault. 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 and multiple pregnancies were not statistically different in the two groups. Ectopic pregnancy was only found in the HSG group (2 women) and not in the THL group. We conclude that in a preselected group of subfertile women with a low risk of tubal pathology, use of a strategy with THL was not inferior to a strategy with HSG for predicting conception leading to live birth.

In **CHAPTER 4** we evaluate the cost-effectiveness of a diagnostic strategy starting with THL with a strategy starting with HSG in the subfertility work-up. We performed an economic evaluation of our multicentre randomised controlled trial comparing THL and HSG in 300 subfertile women. The mean costs and outcomes for each treatment group were compared. We used a non-parametric bootstrap resampling of 1,000 re-samples to investigate the effect of uncertainty and we created a cost-effectiveness plane and cost-effectiveness acceptability curves. The mean costs per woman were lower in the THL group, compared to the HSG group (THL group €4991 versus €5262 in the HSG group, mean cost difference = -€271 (95% CI -€273 to -€269)). Although the costs of the diagnostic procedure itself were higher in the THL group, the total costs were higher in the HSG group, because more women underwent diagnostic and therapeutic laparoscopies and also had higher costs for fertility treatments. The findings of our trial suggest that a strategy starting with THL is more cost-effective compared to a strategy starting with HSG in the workup for subfertile women.

We asked the women participating in the THL-trial to score their fertility-related QoL on the validated FertiQoL questionnaire six weeks after the procedure. In **CHAPTER 5** we describe the findings of this study. The scores for the Core scale and subscales between THL and HSG were compared using Mann-Whitney-U test and multiple linear regression analysis. The questionnaire was completed by 84 women in the THL group and 96 women in the HSG group. We found scores on the different domains of the FertiQoL questionnaire comparable between the two groups. The multiple linear regression analysis showed only a statistical significant positive effect of older age on the score for the Emotional domain.

We investigated in women with an indication for tubal patency testing, what their preferences are for characteristics of the diagnostic procedures HSG and THL. In **CHAPTER 6** we present the results of our discrete choice experiment (DCE). We defined attributes based on literature review, structured patient interviews and expert focusgroup meetings. We designed a labeled DCE, in which women were asked to choose between choice sets with hypothetical scenarios of two tubal patency tests with different levels of the attributes. Data were analysed by using multinomial logistic regression. We found that for THL women preferred a lower chance of a false negative result, a lower failure rate and a shorter waiting time. If a THL is not conclusive or failure to reach the pouch of Douglas, women prefer to have a conventional laparoscopy over expectant management. Women choosing HSG preferred a lower chance of a false negative result, a shorter waiting time and a lower chance of complications.

DISCUSSION

The aims of this thesis were to evaluate different aspects of THL and HSG in the fertility work-up. We evaluated the prognostic capacity of THL and compared live birth and time to conception after a strategy with THL or HSG in a randomised trial. Furthermore, we evaluated cost-effectiveness of the two strategies, quality of life of subfertile women undergoing tubal patency testing with either strategy and women's preferences on different aspects of the tubal patency test. Here, the findings from the different studies of this thesis will be discussed in light of the available literature and the implications for further research and clinical practice will be pointed out.

Tubal patency testing: prognostic capacity

The prognostic capacity to predict the occurrence of a non-IVF pregnancy is the most important aspect of the tubal patency test in the fertility work-up. The test has to distinguish between two categories: women who can still conceive using at least one

of their Fallopian tubes and women who have a strongly reduced chance of a natural conception, thus emphasizing the need for IVF or tubal surgery.

The Chlamydia Antibody Test (CAT) is considered to be a screening tool to evaluate which women are at a higher risk of having tubal pathology due to a previous infection with Chlamydia Trachomatis. It is a non-invasive test and easy to perform during the fertility work-up, but it only gives a risk estimate and does not detect tubal pathology by imaging or visualization of the tubes and pelvic anatomy. In a meta-analysis the sensitivity of CAT was 0.53 with a specificity of 0.72, for any tubal pathology (Broeze et al. 2012). Women with a positive CAT have a higher risk of tubal obstruction at HSG and laparoscopy and compared to women with a negative CAT their chance of having a natural conceived pregnancy is 57% lower (Keltz et al. 2013). And even if a woman with a positive CAT has open tubes at tubal patency testing with HSG or laparoscopy, her chances of having a natural conception are lower compared to a woman with a negative CAT, with an adjusted Fecundity Rate Ratio (FRR) of 0.66 for CAT-positive women (Coppus et al. 2011). Steiner et al. found comparable results, with a reduced probability of a natural conception of 35% (Steiner et al. 2015).

Whereas CAT is considered a screening instrument, HSG is in many hospitals the next step in the diagnostic work-up. Previous studies have shown that women with bilateral occlusion or hydrosalpinx at their HSG have a strongly reduced chance of a natural conception. In these studies unilateral tubal occlusion at HSG led to an adjusted FRR of 0.80 (Mol et al. 1999) and 0.81 (Verhoeve et al. 2011) and bilateral tubal occlusion led to a FRR of 0.49 (Mol et al. 1999) and 0.28 (Verhoeve et al. 2011).

Diagnostic laparoscopy with chromopertubation has always been considered the gold standard or reference standard for tubal patency testing. In a Canadian cohort Mol et al. found adjusted FRRs of 0.51 and 0.15 for unilateral and bilateral tubal occlusion at laparoscopy as well as FRR of 0.60 for peritubal adhesions and FRR of 0.52 for mild endometriosis, whereas there were no pregnancies among couples with endometriosis grade III/IV (Mol et al. 1999). In a Dutch prospective cohort study Verhoeve et al. found FRRs of 0.85 for unilateral and 0.24 for bilateral tubal pathology.

For THL in our retrospective cohort, we found that the FRRs for unilateral and bilateral tubal occlusion were comparable to those of diagnostic laparoscopy, but we also found that women with the combination of endometriosis and adhesions had a strongly reduced chance of non-IVF conception with a FRR of 0.42. We conclude that in the fertility work-up from a prognostic point of view, THL gives information about the patency of the fallopian tubes and also about the presence or absence of tuboperitoneal pathology and that THL has a comparable predictive capacity for non-IVF conception compared to the gold standard diagnostic laparoscopy.

The role of endometriosis and adhesions in subfertility

One of the major differences between THL and HSG is that THL allows direct visualization of the fallopian tubes and can observe the presence of peritubal disease, whereas HSG does not. Especially in the case of women with endometriosis or extensive adhesions but with open tubes, it could be an advantage to perform a THL, because HSG would probably not detect this form of tubal pathology. It raises the question about the role of peritubal disease in subfertile women and if there is a need to actively search for it. If during the fertility work-up there is evidence of endometriosis or adhesions, would it change the subsequent treatment plan for the couple?

It is known that amongst women with unexplained subfertility half of them will have a form of pelvic pathology at diagnostic laparoscopy in the form of either adhesions or endometriosis (Tanahatoo et al. 2005, den Hartog et al. 2008). In a study of 495 couples with unexplained subfertility and a normal HSG, laparoscopy before the start of IUI showed in 25% of women pelvic pathology that led to a change in the treatment plan (Tanahatoo et al. 2003). In our retrospective cohort of women that underwent THL as their first-line tubal patency test, we included only women with a low risk of tubal pathology. In women with the suspicion of endometriosis, a palpable mass in the pouch of Douglas, a fixed retroverted uterus or with ovarian cysts needing treatment, THL is not a feasible procedure. In these women a diagnostic laparoscopy was planned instead of a THL. Nevertheless, we found in our retrospective cohort tuboperitoneal disease such as endometriosis and/or adhesions in almost 20% of women.

There is evidence that laparoscopic treatment for pelvic pathology enhances the chance of a natural conception. A recent Cochrane review suggests that in subfertile women with mild or moderate endometriosis, laparoscopic treatment of the endometriosis increases ongoing intrauterine pregnancy rates compared to diagnostic laparoscopy only (OR 1.89; 95%CI 1.25 to 2.86) (Bafort et al. 2020) and a meta analysis of RCT's and non-RCT's showed that live birth rate was significantly increased after laparoscopic surgery for mild and moderate endometriosis compared to diagnostic laparoscopy only (RR 1.52; 95%CI 1.26 to 1.84) (Jin and Ruiz Beguerie, 2014).

However, most studies on the effect of adhesiolysis and fertility enhancing surgery on pregnancy rates were conducted in the nineties of the previous century, before the widespread introduction of IVF. Saravelos and Cooke found no difference in pregnancy outcome after open microsurgical versus laparoscopic adhesiolysis (Saravelos and Cooke 1995) and a significant higher cumulative pregnancy rate was found after adhesiolysis versus expectant management (Tulandi et al. 1990). Considering adhesiolysis and fertility enhancing surgery, it is important to realize that not all women with adhesions would benefit from fertility enhancing surgery. Women with a good prognosis for natural

conception after tubal surgery have limited filmy adnexal adhesions, mildly dilated tubes with thin walls, and the preservation of the mucosal folds in the endosalpinx, whereas women with poor prognosis have extensive dense peritubal adhesions, largely dilated tubes with thick fibrotic walls, and/or sparse or absent luminal mucosa (practice committee ASRM 2021).

Comparing IVF and fertility enhancing surgery is complex. When counseling a couple about these treatment options, several factors need to be taken into account, such as their age, ovarian reserve, medical history, extensiveness of the disease and the presence of other factors that reduce fertility. The advantage of IVF is, that it is a less invasive treatment compared to laparoscopic surgery, it will have a higher chance of pregnancy per cycle and treatment with IVF most likely lead to a shorter time to pregnancy. On the other hand, fertility enhancing surgery has a lower chance of pregnancy per cycle, but it has a long-lasting effect and allows the possibility of having subsequent pregnancies. Data on the results of tubal surgery and IVF are not directly comparable because surgical success is reported as pregnancy rate per patient, whereas IVF success rates are documented per cycle. As a result, there are no adequate trials comparing the pregnancy rates after tubal surgery vs. after IVF (Chua et al. 2017).

Data on cost-effectiveness of fertility enhancing surgery are not conclusive. In a retrospective cohort of couples with tubal pathology as their only explanation for subfertility, it was found that the costs of tubal surgery per woman were lower, but that the costs per live birth were comparable for either IVF and tubal surgery (Granberg et al. 2003). However, Philips et al through decision analytic modeling concluded that IVF is the most cost-effective treatment option for severe tubal factors and endometriosis, while fertility enhancing surgery is more cost-effective in the case of mild or moderate disease (Philips et al. 2000).

The role of tubal flushing at tubal patency testing

In the past years there has been more evidence of the fertility-enhancing effect of tubal flushing with oil-based contrast medium at HSG. The mechanism of tubal flushing seems to be multifactorial, but the most important explanation is that debris is flushed out from the fallopian tubes, therefore unblocking undamaged tubes. Also enhancement of ciliary activity and immunobiological actions on the endometrium or peritoneum are possible mechanisms. (Wang et al. 2020) Dreyer et al. found in a large Dutch RCT that there was a significantly higher rate of ongoing pregnancies within 6 months after randomisation among infertile women who underwent hysterosalpingography with oil-based contrast medium than among women who underwent this procedure with the use of water-based contrast medium. Also the subsequent live-birth rate was significantly higher. (Dreyer et al. 2017, van Rijswijk et al. 2020). A recent post-hoc analysis of

the H2Oil study found that in women suffering severe pain during the HSG procedure, the treatment effect of oil-based contrast compared to water-based contrast was significantly higher (van Welie et al. 2020). The effect of tubal flushing has been extensively studied in HSG, but there is not much evidence about the effect of tubal flushing at other forms of tubal patency testing. Ah Fadhli et al. showed in a RCT no difference in pregnancy rate between tubal flushing with oil-based contrast versus saline during diagnostic laparoscopy with chromopertubation (Al Fahdli et al. 2006). In THL methylene blue dye is used, which is an aqueous solution. The feasibility of tubal flushing with an oil-based contrast medium during THL has been tested (Roest et al. 2022); and in a pilot study the feasibility of tubal flushing at THL has been evaluated, but the results on pregnancy and life birth rate have not been published yet.

Patient preference

Tubal patency testing is an important part of the fertility work-up, and the result of the tubal patency test plays an important role in the subsequent treatment strategy. There are many different strategies for tubal patency testing and there is a large practice variation in the Netherlands (Roest et al. 2018) and worldwide (Helmerhorst et al. 1995). We have the opinion that in fertility care shared decision making is important, and studies about the preferences of the patients can be of value to the clinician. Also for healthcare policy makers patient preference studies are of importance.

Patient preference for tubal patency testing in the fertility work-up has not been studied before. In our DCE we found that for THL a lower chance of a false negative result, a low failure rate and a lower waiting time was preferred, but the chance of having complications did not have significant impact on their preferences. For women choosing HSG a lower chance of a false negative result, a shorter waiting time and a lower chance of complications were preferred. Furthermore for women choosing THL the preferred strategy after a failed or inconclusive procedure is conventional laparoscopy, whereas for a failed HSG the subsequent strategy did not play a significant impact. Due to a smaller sample size than anticipated it is not possible to measure the relative importance of the attributes.

It is known from preference studies on fertility treatments, that women are willing to trade-off specific preferences for a higher or lower level on another attribute. Bayram studied preferences for ovulation induction and found that preferences for either ovulation induction with rFSH versus laparoscopic elektrocoagulation of the ovary for women that are clomiphene resistant were significantly impacted by both the safety and the effectiveness of the procedure (Bayram et al. 2005) and Weiss found that half of anovulatory women treated with ovulation induction with or without intrauterine insemination based their preference on the lowest burden and half of them on a higher effectiveness (Weiss et al 2017). Van Empel et al. showed in a DCE amongst subfertile

woman and fertility physicians, that patients and physicians put considerable value on pregnancy rates. Patients however assigned more value to patient centeredness than physicians and were willing to trade-off a higher pregnancy rate for patient-centeredness (van Empel et al. 2011).

Implications for clinical practice

Based on the findings of this thesis we have the following implications for clinical practice:

- Women that during fertility work-up were found with either the combination of endometriosis and adhesions or bilateral tubal occlusion at THL have a significantly lower chance of a non-IVF conception. They benefit from early referral for IVF or fertility enhancing surgery.
- A diagnostic strategy starting with THL in the subfertility work-up does not lead to less live births compared to a diagnostic strategy starting with HSG, in women with low risk of tubal pathology.
- A diagnostic strategy starting with THL is cost-effective compared to the strategy with HSG in the work-up for subfertility. The direct costs of the diagnostic procedure of THL are higher than for HSG, but the total costs of the strategy with HSG are higher. The cost-difference compared to the total costs however is minimal.
- There is no difference in fertility related quality of life 6 weeks after the procedure between a tubal patency testing strategy with THL or a strategy with HSG.
- We found that subfertile women that are presented with a hypothetical choice set with attributes about tubal patency testing, value a lower chance of a false negative test, a lower risk of failure of the procedure, a lower complication rate and a shorter waiting time.
- National and international guidelines should implement THL as a possible option for tubal patency testing during the fertility work-up.

Implications for further research

THL and HSG are two different diagnostic procedures, each having their different characteristics and advantages. In 300 subfertile women we did not find a statistical significant difference in live birth or time to pregnancy with a diagnostic strategy based on THL or HSG.

THL gives more information about pelvic pathology such as endometriosis and adhesions. In our cohort study we found that women with endometriosis and adhesions had a reduced chance of a non-IVF pregnancy. If one would perform THL as a first-line patency test in the fertility work-up, these abnormalities will be found in an early stage of fertility treatment. Since their chances of natural pregnancy are reduced they would

benefit from either fertility enhancing surgery or IVF treatment. More research is needed to evaluate which of these treatments is most cost-effective.

THL has been developed in 1998 and it has been used as a first-line tubal patency test in several clinics both in the Netherlands and internationally. However, the procedure has not gained major popularity worldwide, and the practice variation of tubal patency testing is still wide. Possible barriers for the uptake of the procedure by gynecologists, is that the transvaginal technique for endoscopic surgery is not part of the standard gynecological curriculum and THL has a learning curve of 50 procedures (Tros et al. 2016). It would be valuable to analyse what factors influence the acceptance of THL and other techniques for tubal patency testing.

Operative THL is mainly described in relation to ovarian drilling for anovulatory women (Fernandez et al. 2001, Gordts et al. 2009). Literature shows that ovarian drilling with THL compared to conventional laparoscopy gives less postoperative adhesions (Giampaolino et al. 2016). It is however possible to perform minimal adhesiolysis and coagulation of endometriotic spots during THL (Gordts et al. 2021). There has been no studies published yet about the feasibility of these procedures, nor has cost-effectiveness been studied. Another next step in research would be to evaluate the feasibility and effect of tubal flushing during THL, since it has not been studied before. During THL the tubal patency is evaluated with methylene blue, which is an aqueous solution. Further research is needed to evaluate if women undergoing THL would have an additional benefit from tubal flushing with an oil-based contrast medium, after patency of at least one tube is proven with THL.

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CHAPTER 8

NEDERLANDSE SAMENVATTING



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Ongeveer een op de zes paren is verminderd vruchtbaar. Dit wil zeggen dat er na 12 maanden onbeschermd seksueel contact geen zwangerschap is ontstaan. In het oriënterend fertiliteitsonderzoek worden er verschillende onderzoeken verricht om de oorzaak van de verminderde vruchtbaarheid te achterhalen en daarmee te onderzoeken of het paar in aanmerking komt voor fertiliteitsbehandeling.

Dit proefschrift richt zich op twee verschillende vormen van tubadiagnostiek in het oriënterend fertiliteitsonderzoek, namelijk transvaginale hydrolaparoscopie (THL) en hysterosalpingografie (HSG). Beide vormen van tubadiagnostiek worden op dit moment al binnen het oriënterend fertiliteitsonderzoek uitgevoerd. THL en HSG zijn als diagnostisch onderzoek op meerdere vlakken verschillend, bijvoorbeeld in de mate van invasiviteit, in de mate van pijn tijdens de ingreep en in de informatie die ze geven. HSG is een radiologische procedure waarbij de doorgankelijkheid van de tubae wordt beoordeeld door middel van contrastvloeistof en doorlichtingsonderzoek, terwijl THL een procedure is waarbij het kleine bekken en de doorgankelijkheid van de tubae voor methyleenblauw door middel endoscopie worden beoordeeld.

We onderzochten de prognostische waarde van THL in een retrospectief cohort van vrouwen die THL ondergingen als tubadiagnostiek binnen het oriënterend fertiliteitsonderzoek. We vergeleken het gebruik van THL en HSG in een gerandomiseerde studie en we onderzochten of een strategie met THL in vergelijking met een strategie met HSG non-inferieur is met betrekking tot het aantal levend geboren kinderen na 24 maanden follow-up. We onderzochten daarnaast de kosteneffectiviteit van beide strategieën en de fertiliteitsgerelateerde kwaliteit van leven na de procedure. Ook onderzochten we welke aspecten van de bovengenoemde diagnostische strategieën belangrijk zijn voor vrouwen die het oriënterend fertiliteitsonderzoek ondergaan.

SAMENVATTING

In onze retrospectieve multicenter cohort studie werden 1033 vrouwen onderzocht die THL ondergingen als tubadiagnostiek binnen het oriënterend fertiliteitsonderzoek. In **HOOFDSTUK 2** beschrijven we de bevindingen van hun THL-procedures en de zwangerschapsuitkomsten na 36 maanden follow-up. De primaire uitkomstmaat was een intrauteriene zwangerschap ontstaan na natuurlijke conceptie, ovulatie inductie of na behandeling met intrauteriene inseminatie met milde ovariële hyperstimulatie (niet-IVF

conceptie). Door middel van Kaplan-Meier curves werd de tijd tot zwangerschap vergeleken voor vrouwen zonder afwijkingen, vrouwen met enkelzijdige tubapathologie en vrouwen met dubbelzijdige tubapathologie bij THL. Met behulp van multivariabele Cox regressie analyse werd de associatie tussen tubapathologie en het optreden van zwangerschap onderzocht, uitgedrukt in Fertiliteit Ratios's (FR's). Bij 83% van de vrouwen waren bij THL beide eileiders doorgankelijk, er was sprake van enkelzijdige tubapathologie bij 12,4% van de vrouwen en dubbelzijdige tubapathologie in 4.6% van de vrouwen. Cumulatieve intrauteriene zwangerschapspercentages waren 52% voor vrouwen met beiderzijds doorgankelijke tubae, 44% voor enkelzijdige tubapathologie (FR 1.04; 95% betrouwbaarheids interval [BI], 0.78 tot 1.39) en 7% voor vrouwen met dubbelzijdige tubapathologie (FR 0.13; 95% BI, 0.04 tot 0.43). Bij 6.4% van de vrouwen werd endometriose vastgesteld, zij hadden een FR van 0.73 (95% BI, 0.49 tot 1.09); bij 9,1% van de vrouwen werden adhesies vastgesteld wat leidde tot een FR van 0.68 (95% BI, 0.46 tot 1.02) en 3,9% van de vrouwen hadden zowel endometriose als adhesies bij THL, dit gaf een FR van 0.42 (95% BI, 0.20 tot 0.84). Concluderend kan worden gesteld dat vrouwen bij wie bij THL dubbelzijdige tubapathologie wordt vastgesteld of de combinatie van endometriose met adhesies, de kans op een niet-IVF conceptie sterk gereduceerd is. Vrouwen met enkel adhesies of endometriose hebben een matig, niet significant gereduceerde kans op een niet-IVF conceptie. Enkelzijdige tubapathologie had geen invloed op niet-IVF conceptie.

In **HOOFDSTUK 3** beschrijven we de resultaten van onze gerandomiseerde multicenter studie waarin we THL vergeleken met HSG als primaire vorm van tubadiagnostiek binnen het oriënterend fertiliteitsonderzoek. Subfertiele vrouwen met een indicatie voor tubadiagnostiek konden worden geïncludeerd. Exclusie criteria waren een positieve Chlamydia PCR, eerdere tubadiagnostiek of tubachirurgie, een uterus in RVF, ovariele cysten of afwijkingen in het cavum Douglasi, of overgevoeligheid voor methyleenblauw of jodium. De primaire uitkomstmaat was een conceptie leidend tot een levendgeboren kind binnen 24 maanden na de randomisatie. We randomiseerden 149 vrouwen voor een strategie met THL en 151 vrouwen voor een strategie met HSG. Van 142 vrouwen in de THL groep en 148 vrouwen in de HSG groep was volledige follow-up beschikbaar. Na het oriënterend fertiliteitsonderzoek werden vrouwen behandeld volgens de Nederlandse richtlijnen voor subfertiliteit en gebaseerd op het prognostisch model van Hunault. Het aantal doorgaande zwangerschappen leidend tot een levendgeboren kind was 83 in de THL groep (58,5%) en 82 in de HSG groep (55,4%) (verschil 3.0%, 95% betrouwbaarheidsinterval -8.3 tot 14.4) gebaseerd op de intention to treat analyse. De tijd tot conceptie was niet significant verschillend tussen beide groepen. Miskramen en meerlingzwangerschappen waren niet verschillend in beide groepen. Buitenbaarmoederlijke zwanger-

schap werd tweemaal gezien in de HSG-groep en niet in de THL groep. Onze conclusie is dat voor subfertiele vrouwen met een laag risico op tubapathologie, het gebruik van THL niet inferieur is aan het gebruik van HSG in het oriënterend fertiliteitsonderzoek.

In **HOOFDSTUK 4** evalueerden we de kosteneffectiviteit van een diagnostische strategie met THL met een diagnostische strategie met HSG in het oriënterend fertiliteitsonderzoek. We voerden een economische analyse uit parallel aan onze gerandomiseerde studie. De directe medische kosten en uitkomsten voor beide diagnostische strategieën werden vergeleken en door middel van bootstrap resampling werd het effect van onzekerheid in de uitkomsten geëvalueerd. We creëerden een kosteneffectiviteitsvlak en kosteneffectiviteit-acceptatie curve. De gemiddelde kosten waren lager in de THL-groep vergeleken met de HSG-groep (THL groep €4991 versus €5262 voor de HSG groep, gemiddelde kostenverschil = -€271 (95% BI -€273 to -€269)). Hoewel de berekende kosten voor de diagnostische procedure van THL hoger zijn dan die van HSG, zijn de totale medische kosten hoger in de HSG groep. In de HSG groep ondergingen meer vrouwen een diagnostische of therapeutische laparoscopie en ook waren we in deze groep hogere kosten voor fertiliteitsbehandelingen. Ons onderzoek liet zien dat een strategie met THL in het oriënterend fertiliteitsonderzoek kosteneffectief is ten opzichte van een strategie met HSG.

De fertiliteitsgerelateerde kwaliteit van leven van de vrouwen die deelnamen aan onze gerandomiseerde studie hebben we gemeten door middel van de gevalideerde FertiQoL vragenlijst zes weken na de procedure. In **HOOFDSTUK 5** beschrijven de bevindingen van dit onderzoek. De scores van de verschillende onderdelen van de FertiQoL vragenlijst werden vergeleken met een Mann-Whitney-U test en door middel van multiple lineaire regressie analyse. De vragenlijst werd ingevuld door 84 vrouwen in de THL groep en 96 vrouwen in de HSG groep. De scores op de verschillende onderdelen van de FertiQoL vragenlijst waren vergelijkbaar tussen de twee groepen. De multilineaire regressie analyse liet alleen een positief effect zien van een hogere leeftijd op de score in het emotionele domein.

We onderzochten tevens bij vrouwen die het oriënterend fertiliteitsonderzoek ondergaan wat hun voorkeuren zijn voor bepaalde aspecten van de THL en HSG. In **HOOFDSTUK 6** beschrijven we de resultaten van ons "discrete choice experiment" (DCE). Gebaseerd op literatuuronderzoek, gestructureerde patiënten interviews en een expert meeting werden attributen vastgesteld en de niveaus van de verschillende attributen werden bepaald door middel van literatuur onderzoek. We ontwikkelden een gelabeld DCE model waarin vrouwen werden gevraagd om te kiezen tussen keuzesets met hypothetische scenario's van twee procedures voor tubadiagnostiek met verschillende

levels van deze attributen. Voor THL vonden we dat vrouwen een voorkeur hebben voor een lagere kans op een fout-negatieve uitslag, een lagere kans op niet-slagen van de procedure en een kortere wachttijd. Als de THL niet gelukt is, hebben vrouwen een voorkeur voor conventionele laparoscopie ten opzichte van een expectatief beleid. Voor HSG hebben vrouwen een voorkeur voor een lagere kans op een fout-negatief resultaat, een kortere wachttijd en een lagere complicatiekans.



CHAPTER 9

IMPACT PARAGRAPH

IMPACT PARAGRAPH

Subfertility

Approximately one in six couples experience difficulties to conceive. A couple is subfertile if no pregnancy occurs after one year of unprotected intercourse. Possible explanations for subfertility are ovulatory dysfunction, sperm problems or pathology of the uterus or the fallopian tubes. Subfertility is called unexplained if after thorough examination no explanation for the subfertility is found. Tubal factors are found in 15-30% of subfertile couples. This thesis focuses on two different forms of diagnostic tests for tubal patency in the fertility work-up: transvaginal hydrolaparoscopy (THL) and hysterosalpingography (HSG).

THL and HSG

THL is an outpatient procedure under local anesthesia, where the pelvic organs are visualized with a small endoscope introduced in the pouch of Douglas through the fornix posterior of the vagina. The patency of the tubes is tested by chromopertubation with a methylene blue dye. HSG is a radiological diagnostic procedure, in which the patency of the tubes is visualized by a radio-opaque contrast medium. HSG is one of the most commonly used first-line tubal patency test in Dutch hospitals, although it has a low sensitivity and specificity in women with a low risk of tubal pathology. The gold standard for testing tubal patency is conventional diagnostic laparoscopy with chromopertubation, which is a more invasive procedure that requires general anesthesia and admission in the hospital.

One of the most important differences between THL and HSG is that THL is an endoscopic technique, with direct visualization of the pelvis and the tubes. The procedure gives not only information about the patency of the tubes but also about the presence of other pelvic pathology such as endometriosis and adhesions. HSG on the other hand is a radiological diagnostic procedure that demonstrates the patency of the tubes and the shape of the uterus, but does not allow to evaluate if there is other pelvic pathology.

Research questions and findings

Our main question for this thesis was if THL can be used as a first-line diagnostic strategy in the work-up of the subfertile couple. More specifically our research questions were to determine the prognostic capacity of THL to predict a non-IVF conception and to evaluate if a strategy with THL compared to a strategy with HSG in the work-up for subfertile couples is comparable in case of live births and time to pregnancy. Furthermore we wanted to evaluate if the two strategies are cost-effective and if there is a difference in quality of life after the two procedures. Moreover we wanted to examine women's preferences for different aspects of the tubal patency tests. Our most interesting findings indicate that:

1. THL can be used as a first-line diagnostic test in subfertile women. If a woman is found to have unilateral tubal occlusion at THL, her chances of non-IVF conception are comparable to those of a woman with 2 open tubes. If a woman is diagnosed with bilateral tubal occlusion, or if she has the combination of endometriosis and adhesions, her chances to have a non-IVF conception are significantly reduced.
2. In a randomised study with 300 subfertile women we found that THL was not inferior to HSG in terms of conception leading to live birth. After a follow-up period of 24 months we found a live birth rate of 58.5% in the THL-group versus 55.4% in the HSG-group (not significant) and no difference in time to conception leading to live birth. There was also no difference in miscarriages and twin-pregnancies.
3. We found that a strategy with THL is cost-effective to a strategy with HSG in the fertility work-up. The mean costs per woman for the diagnostic tests, fertility treatments and pregnancy were €4991 for the women in the THL-group, compared to €5262 in the HSG-group. The procedure of THL itself costs more than a HSG, but the women in the HSG group underwent more often a diagnostic or therapeutic laparoscopy and also had higher costs for their subsequent fertility treatments.
4. We found that there was no difference in fertility related quality of life between women that underwent THL or HSG 6 weeks after the procedure.
5. In our discrete choice experiment (DCE) we examined the preferences of subfertile women for different aspects of the tubal patency tests. We found that subfertile women when choosing THL preferred a lower chance of a false negative result, a lower failure rate and a shorter waiting time. If THL is not conclusive women prefer a conventional laparoscopy over an expectant management. Women choosing HSG preferred a lower chance of a false negative result, a shorter waiting time and a lower chance of complications.

RELEVANCE OF OUR FINDINGS

Societal relevance

In the Netherlands and also worldwide there is a large practice variation in the strategy and timing of tubal patency testing in the subfertility work-up. In this light the results of our research are relevant for both clinicians and patients, and for healthcare policy makers. For the clinician our research shows that THL could be used as an alternative to HSG in the fertility work-up. It is a feasible procedure with a low complication rate, and its'

prognostic capacity to predict non-IVF conception is comparable to the gold standard conventional laparoscopy. THL is cost-effective compared to HSG in the fertility work-up. Healthcare policy makers and guideline developers should evaluate THL as part of the possible strategies for tubal patency testing, and it should be included in guidelines for the fertility work-up.

In this research project, women's experience and opinion play an important part. It is well known that tubal patency testing in the fertility work-up can be stressful. We found that women undergoing THL in an outpatient setting had lower pain-scores than women undergoing HSG, but both procedures were evaluated as equally acceptable. Also there was no difference in fertility related quality of life between the two procedures. In our discrete choice experiment we found that a low chance of a false negative result, a low failure rate, a low chance of complications and a short waiting time. Knowing what is important for the subfertile woman, is necessary for shared decision making and therefore important for all stakeholders involved in fertility care.

Scientific relevance

Our research contributes to the field of knowledge about tubal patency testing in the subfertility work-up. Because there are various diagnostic techniques for testing tubal patency, our work needs to be seen in a bigger scope of research on tubal patency testing and fertility treatments. We compared THL and HSG as a first-line test in the fertility work-up. Although THL has been studied previously, a comparison with the most commonly used technique of tubal patency testing, HSG, has not been made previously in terms of fertility outcomes, cost-effectiveness, quality of life and the preference of subfertile women. Besides scientific publications, our main findings were also presented at conferences of both international fertility and gynecological endoscopic societies.

Further research

We found that if THL is used as a first-line patency in the subfertility work-up, women with mild endometriosis or adhesions but with open tubes, are diagnosed in an early stage of their fertility treatment. The chances of a natural conceived pregnancy are reduced in these women and more research is needed to evaluate if these women would benefit most from fertility enhancing surgery or from IVF treatment.

THL as a tubal patency test has been developed more than 25 years ago, but the technique has not been implemented in many hospitals. The practice variation on tubal patency testing is wide. Possible barriers for the uptake of the procedure by gynecologists, is that the transvaginal technique for endoscopic surgery is not part of the standard gynecological curriculum and that the learning curve needs to be taken into account. It

would be valuable to analyze what factors influence the acceptance of THL and other techniques for tubal patency testing.

Other aspects about THL that need to be investigated are the feasibility and cost-effectiveness of therapeutic procedures during THL, such as adhesiolysis and coagulation of endometriosis and to evaluate if there is an effect of tubal flushing during THL. There is evidence that tubal flushing with oil-based contrast medium compared to a water-based contrast medium at HSG leads to a higher percentage of live births after the procedure. The methylene blue dye to test the tubes at THL is water-based and it is yet still unknown if it would be feasible and effective to perform a tubal flushing with oil-based contrast medium after the procedure.



APPENDICES

LIST OF CO-AUTHORS AND AFFILIATIONS

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DANKWOORD

ABOUT THE AUTHOR

LIST OF CO-AUTHORS AND AFFILIATIONS

M.Y. Bongers, GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, the Netherlands and Department of Obstetrics and Gynaecology, Maxima Medical Center, Veldhoven, the Netherlands_

B.A.B. Essers, Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, Maastricht, the Netherlands

C.A.M. Koks, Department of Obstetrics and Gynaecology, Maxima Medical Center, Veldhoven, the Netherlands_

W.K.H. Kuchenbecker, Department of Obstetrics and Gynaecology, Isala, 8000 GK Zwolle, the Netherlands_

S.M.J. van Kuijk, Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre, Maastricht, the Netherlands

B.W.J. Mol, Monash University, Department of Obstetrics and Gynaecology, Clayton, Australia and Department of Obstetrics and Gynaecology, Aberdeen University, United Kingdom

G.J.E. Oosterhuis, Department of Obstetrics and Gynaecology, St. Antonius Hospital, Nieuwegein, the Netherlands_

M.M.V. Paulussen, Department of Obstetrics and Gynaecology, Maxima Medical Center, Veldhoven, the Netherlands_

C.T. Pham, Flinders Health and Medical Research Institute, Flinders University, South Australia, Australia

R. Tros, Department of Obstetrics and Gynaecology, Amsterdam UMC, Amsterdam, the Netherlands

M.M.A. Vernooij, Department of Obstetrics and Gynecology, St. Antonius Hospital, Nieuwegein, the Netherlands_

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ABOUT THE AUTHOR

Maria Anna (Mianne) van Kessel was born on December 25th of 1982 in Schiedam, the Netherlands. She grew up in Schiedam and graduated from secondary school Groen van Prinsterer in Vlaardingen in 2001. After two years of traveling she started Medical School in 2003 at UMC St Radboud in Nijmegen and she obtained her medical degree in 2010.

After her graduation in 2010 she started working as a medical doctor in the department of Obstetrics and Gynecology in Medisch Spectrum Twente in Enschede. Alongside the clinical work she started with the PhD project leading to this thesis in 2012, supervised by Prof. Dr. Ben Willem Mol, Prof. Dr. Marlies Y. Bongers and Dr. Carolien A.M. Koks.

She did her residencies in Obstetrics and Gynecology in Isala klinieken Zwolle, in UMCG Groningen and in Medisch Spectrum Twente, Enschede and she registered as a Gynecologist in 2019. She is working as a Gynecologist in the Dr. Horacio E. Oduber Hospitaal in Aruba, since December 2019.

Mianne lives together with her partner Zurieck Tramm and their son Victor (2018) in Aruba.

