FACULTY OF MEDICINE AND HEALTH SCIENCES

The effectiveness of vNOTES for hysterectomy in women with benign gynaecological disease

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Abbreviations

AE	Appendectomy
AH	Abdominal Hysterectomy
BMI	Body Mass Index
BSO	Bilateral Salpingo-Oophorectomy
CABG	Coronary Artery Bypass Graft
CCT	Controlled (non-randomised) Clinical Trials
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence Interval
CONSORT	CONsolidated Standards of Reporting Trials
COS	Core Outcome Set
CRD	Centre for Reviews and Dissemination
CROWN	CoRe Outcomes in Women's and Newborn health
CS	Caesarean Section
DIY	Do It Yourself
DUB	Dysfunctional Uterine Bleeding
DVT	Deep Venous Thrombosis
HALON	Hysterectomy by transabdominal Laparoscopy Or transvaginal NOTES
Hb	Haemoglobin
ICU	Intensive Care Unit
IDEAL	Idea; Development; Exploration; Assessment; Long-term study
IQR	InterQuartile Range
ITT	Intention To Treat

IV	Inverse Variance
LASH	Laparoscopic Supracervical Hysterectomy
LAVH	Laparoscopic Assisted Vaginal Hysterectomy
LH	Laparoscopic Hysterectomy
LLETZ	Large Loop Excision of Transformation Zone
LS	Laparoscopic Sterilisation
MD	Mean Difference
MH	Mantel-Haenszel
MP	Multiple Ports
NOS	Newcastle-Ottawa Scale
NOTES	Natural Orifice Transluminal Endoscopic Surgery
OBGYN	Obstetrics & Gynaecology
OR	Odds Ratio
PICO	Population Intervention Comparison Outcome
PID	Pelvic Inflammatory Disease
POP-Q	Pelvic Organ Prolapse Quantification
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM	Patient Reported Outcome Measures
PROSPERO	Prospective Register of systematic reviews
QoL	Quality of Life
RCT	Randomised controlled trials
RH	Robotic Hysterectomy
RR	Risk Ratio

RTVNH	Robotic Total Vaginal NOTES Hysterectomy
RVANH	Robotic Vaginally Assisted NOTES Hysterectomy
SAP	Statistical Analysis Plan
SD	Standard Deviation
SILS	Single-Incision Laparoscopic Surgery
SMD	Standardized Mean Differences
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SR	Systematic Review
SSFS	Short Sexual Functioning Scale
TAH	Total Abdominal Hysterectomy
TLH	Total Laparoscopic Hysterectomy
TVNH	Total Vaginal NOTES Hysterectomy
USO	Unilateral Salpingo-Oophorectomy
VANH	Vaginally Assisted NOTES Hysterectomy
VAS	Visual Analogue pain Scale
VH	Vaginal Hysterectomy
VNH	Vaginal NOTES Hysterectomy
vNOTES	transvaginal Natural Orifice Transluminal Endoscopic Surgery

Chapter 1

Introduction and outline of thesis

1.1 Introduction

1.2 Outline of thesis

1.1 Introduction

Hysterectomy is the surgical removal of the uterus. It is the most commonly performed major gynaecologic surgical procedure (1). It is performed for benign and malignant indications. The most common benign indications are: fibroids (30%), dysfunctional uterine bleeding (20%), endometriosis and/or adenomyosis (20%), genital prolapse (15%), chronic pelvic pain (10%) and endometrial hyperplasia (6%) (2).The most common malignant indications are endometrial cancer, cervical cancer and ovarian cancer.

The first reported elective hysterectomy was performed by Conrad Langenbeck in 1813 using a vaginal approach (3). The first elective abdominal (subtotal) hysterectomy was performed in 1863 by Charles Clay (3). These two techniques remained the gold standard in the 19th and 20th century. The first paradigm shift towards a less invasive hysterectomy technique came at the end of the 20th century after the introduction of laparoscopy in gynaecological surgery. This new approach enabled gynaecological surgeons to perform pelvic surgery through a number of small abdominal incisions using endoscopic instruments and a small camera, thereby avoiding larger abdominal incisions and reducing surgical trauma. Minimally invasive surgery improves cosmetic outcome, and also reduces surgical trauma, which in turn decreases the inflammatory and neuroendocrine responses, and leads to less postoperative pain and quicker recovery (5). Harry Reich performed the first laparoscopically assisted vaginal hysterectomy (LAVH) in 1989 and the first total laparoscopic hysterectomy (TLH) in 1993 (3). The advantages of laparoscopy over traditional laparotomy have been accepted worldwide for many years (4). To further reduce surgical morbidity, the evolutionary trend has been towards even less invasive techniques, such as single-incision laparoscopic surgery (SILS) and natural orifice transluminal endoscopic surgery (NOTES).

We performed a study to demonstrate the feasibility of TLH through a single small umbilical incision with the use of conventional, reusable laparoscopic instruments, and an inexpensive, self-constructed single-port device in 2013 and 2014 (6). During the same period we started performing research on NOTES. NOTES reaches the abdominal cavity by scar-free means; no incisions are made in the abdominal wall. NOTES can be performed via a variety of approaches, including stomach, oesophagus, bladder and rectum, but the majority of NOTES procedures have been performed transvaginally, as the vagina provides direct access to the peritoneal cavity (7). We performed a study demonstrating the feasibility and safety of adnexectomy by transvaginal NOTES (vNOTES) for adnexal masses up to 110mm in 2013 and 2014 (8). We demonstrated in 2015 that vNOTES can be a good approach for adhaesiolysis (9). We performed a study demonstrating the feasibility of a salpingectomy for ectopic

pregnancy via vNOTES in 2014 and 2015 (10). After our initial experience with vNOTES for adnexal surgery and hysterectomy, we believed that vNOTES offers a lot of advantages for patients over conventional laparoscopic surgery and SILS. Besides the obvious aesthetic advantages, we were under the impression that patients had less postoperative pain and recovered quicker from the surgery. The duration of the surgery also seemed shorter. We decided to stop our research into SILS and focus on vNOTES. In 2015 we published a new hysterectomy approach via Total Vaginal NOTES Hysterectomy (11).

Based on our experience with these preliminary studies on vNOTES, we started to believe that Natural Orifice Surgery may be the next paradigm shift towards a less invasive hysterectomy technique. There was however extremely little scientific evidence supporting our theory. We therefore initiated this thesis to conduct further research on hysterectomy via Natural Orifice Transluminal Endoscopic Surgery and to gather scientific evidence for this technique.

The focus of this thesis is to address hysterectomy via Natural Orifice Transluminal Endoscopic Surgery. The specific aims of the thesis can be summarized as follows:

1. To assess the use of an access port for vNOTES that had not been validated for this approach
2. To assess the feasibility of robotic NOTES hysterectomy
3. To assess the current evidence for hysterectomy via vNOTES
4. To study the efficacy and short term safety of vNOTES hysterectomy compared to TLH for benign gynaecological disease in women with non-prolapsed uteri

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1.2 Outline of This Thesis

Chapter 1 predefines the four research questions in the introduction of the present thesis:

1. To assess the use of an access port for vNOTES that had not been validated for this approach
2. To assess the feasibility of robotic NOTES hysterectomy
3. To assess the current evidence for hysterectomy via vNOTES
4. To study the efficacy and short term safety of vNOTES hysterectomy compared to TLH for benign gynaecological disease in women with non-prolapsed uteri

In **Chapter 2** we aim to investigate whether Gelpoint Advanced Access Platform and Gelpoint Mini Advanced Access Platform, two platforms developed for trans umbilical SILS and not validated for transvaginal use, are suitable ports for transvaginal NOTES hysterectomy and adnexectomy.

In **Chapter 3** we aim to investigate whether transvaginal robotic surgery is possible. If transvaginal robotic surgery is possible, we aim to develop two new hysterectomy techniques via transvaginal robotic NOTES and assess their feasibility: Robotic Vaginally Assisted NOTES Hysterectomy (RVANH) for parous patients and Robotic Total Vaginal NOTES Hysterectomy (RTVNH) for nulliparous patients.

In **Chapter 4** we aim to give an overview of the new hysterectomy techniques via NOTES.

In **Chapter 5** we aim to critically appraise studies comparing benefits and harms in women with benign disease without prolapse undergoing hysterectomy by NOTES versus laparoscopy. We will perform a systematic review and meta-analysis.

In **Chapter 6** we will set up a prospective, randomised controlled, single centre, single blinded, parallel group, non-inferiority efficacy study (HALON trial). The objective will be to compare vNOTES and the established TLH for the successful removal of a uterus for benign gynaecological pathology. The study population will be all women 18-70 years of age, regardless of parity with a benign indication for hysterectomy. First we will present the protocol of this trial.

Then we will present the results of the HALON trial. The primary outcome is the successful removal of a uterus with the intended approach without conversion to an alternative approach. The secondary outcomes are: the proportion of women discharged on the same day, postoperative pain scores and analgesics used, postoperative infection, peri- and postoperative complications, hospital readmissions, duration of the procedure, incidence of dyspareunia, sexual wellbeing and costs up to six weeks.

In **Chapter 7** (Discussion and conclusion) we aim to summarize the findings of the studies presented in this thesis. We also aim to answer the four research questions of this thesis. Finally, we will reflect on

the impact that this thesis can have on the clinical practice of hysterectomy: is there a place for this new hysterectomy technique at the moment and how can it evolve in the near and further future? Is there a point in further researching this new surgical technique and what would be the appropriate further study designs?

In **Chapter 8** we will present a brief summary of the thesis in English and in Flemish.

Appendices Publications

Presentations

Curriculum vitae

Chapter 2

GelPOINT (Applied Medical) is a suitable port for transvaginal NOTES procedures.

Jan Baekelandt, Dominique Cavens

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Gelpoint is a suitable port for transvaginal NOTES procedures

Abstract

The purpose of this study was to assess whether the Gelpoint advanced access platform and the Gelpoint mini advanced access platform (Applied Medical, Rancho Santa Margarita, CA, USA) are suitable ports for performing vNOTES (transvaginal Natural Orifice Transluminal Endoscopic Surgery) procedures.

Between March and October 2015, 110 procedures by vNOTES using the aforementioned Gelpoint ports were performed by a single surgeon (BJ).

Patient and perioperative data were analysed. Seventy-seven patients underwent a Vaginally Assisted NOTES Hysterectomy (VANH), and 33 patients underwent vNOTES adnexal surgery, including 4 salpingectomies, 25 adnexectomies and 4 ovarian cystectomies. There were no conversions to standard laparoscopy or laparotomy, and all procedures were completed using a Gelpoint port. The mean operation time for VANH was 56 minutes and 25,5 minutes for adnexal surgery. There were no intraoperative complications and the postoperative pain scores were low.

The Gelpoint port is a suitable port for VANH, and the Gelpoint mini port is suitable for vNOTES adnexal procedures.

The main advantages of using Gelpoint port compared to self-constructed glove ports are shorter setup time, easier instrument transfer through the trocars, better ergonomics, and a less fragile port. The greatest disadvantage is the higher cost.

Introduction

The advantages of laparoscopy over traditional laparotomy have been accepted worldwide for many years (1). To further reduce surgical morbidity, the evolutionary trend has been towards even less invasive techniques, such as single-incision laparoscopic surgery (SILS) and natural orifice transluminal endoscopic surgery (NOTES). Minimally invasive surgery improves cosmetic outcome, and also reduces surgical injury, which in turn decreases the inflammatory and neuroendocrine responses, and leads to less postoperative pain and quicker recovery (2).

NOTES reaches the abdominal cavity without visible scars. To this end, numerous surgical procedures are performed via a natural body orifice. In recent years this technique has gained popularity among general surgeons, gynaecologists, urologists and gastroenterologists, and its feasibility and safety have been approved (3).

NOTES can be performed via a variety of approaches, including the stomach, oesophagus, bladder and rectum, but the majority of NOTES procedures have been performed transvaginally, as the vagina provides direct access to the peritoneal cavity (4). Operations performed in the abdomen through transvaginal Natural Orifice Transluminal Endoscopic Surgery are referred to as vNOTES operations. Culdotomy has been used widely for several surgical procedures (not only by gynaecologists but also by general surgeons for extraction of large specimens) and it has been approved as safe and easy to close (5).

In *hybrid NOTES* the surgical procedure is performed through a natural body orifice with transabdominal assistance. The term *pure NOTES* refers to procedures that involve only transluminal access.

Due to its potential benefits, including no visible scars, fewer port-related complications, and less painful and faster postoperative recovery, transvaginal pure NOTES for benign adnexal masses was included in our surgical repertoire in November 2013. After initial experience with vNOTES for adnexal surgery (6), vNOTES adhaesiolysis (7), vNOTES salpingectomy (8), vNOTES ovarian cystectomy, vNOTES myomectomy, Vaginally Assisted NOTES Hysterectomy (VANH) (9), and Total Vaginal NOTES Hysterectomy (TVNH) (9) were introduced in our daily surgical practice.

Initially all the procedures were performed using only conventional, reusable laparoscopic instruments and an inexpensive, self-constructed single port device (6,7,8,9). In March 2015 Gelpoint and Gelpoint mini ports were introduced to replace glove ports for vNOTES procedures in our department.

This study aims to demonstrate that the Gelpoint advanced access platform and Gelpoint mini advanced access platform (Applied Medical, Rancho Santa Margarita, CA, USA) provides a good alternative to the self-constructed glove port. Both platforms were developed for trans umbilical single site surgery, but can potentially offer benefits over a glove port when used transvaginally for vNOTES. The Gelpoint and Gelpoint mini consist of two parts: a wound protector, as used in a glove port; and a lid that clicks onto the wound protector and contains a gel cushion that can be perforated with trocars.

Materials and methods

Patients

Between March and October 2015 a total of 110 vNOTES hysterectomies, salpingectomies, adnexectomies and cystectomies were performed by a single surgeon (BJ) using the Gelpoint port for transvaginal access.

Each patient was selected based on a benign gynaecological disease diagnosis, and on the following criteria : no contraindication for general anaesthesia, pneumoperitoneum, or Trendelenburg position; no fixed uterus, strong pelvic adhesions, or nodularity in the Pouch of Douglas on clinical examination; no history of pelvic inflammatory disease; and no suspicion for malignancy. Obesity, a Body Mass Index (BMI) > 30 kg/m^2, and the absence of vaginal delivery, were not considered as exclusion criteria, whereas virginity and pregnancy were.

The following patient and perioperative data were collected and retrospectively analysed : patient age, BMI, parity, history of vaginal delivery, previous pelvic surgery, type of surgery, total operation time, serum haemoglobin (Hb) drop (change between the preoperative and postoperative Hb 1 day after surgery), perioperative complications, and postoperative pain score.

Duration of surgery was defined as the time from the placement of the Foley catheter to the completion of vaginal closure. Bowel, bladder, urethral or vascular injuries, and blood loss > 300 ml, were considered to be intraoperative complications. Short-term postoperative complications were considered to be urinary tract infection, postoperative ileus, vaginal vault bleeding or infection, or haematuria.

Postoperative pain was assessed using the visual analogue pain scale (scoring from 0 = no pain, to 10 = worst imaginable pain). The visual analogue pain scale score was evaluated at 6 and 24 hours postoperatively. All patients received the same intraoperative analgesia: intravenous paracetamol 1000mg and ketorolac trometamol 20mg. Postoperative pain was managed by paracetamol 1000mg, and ketorolac trometamol was administered on patient's demand.

Prophylactic intravenous antibiotic therapy, cefazolin 2g and metronidazole 500mg, was administered during surgery. No vaginal intercourse was allowed for 6 weeks after the procedure. Each patient was reassessed at the postoperative consultation 6 weeks after surgery.

Surgical Technique

Vaginally Assisted NOTES Hysterectomy

The patient was placed in lithotomy position in a vacuum mattress. The operation field was disinfected and draped. A Foley catheter was inserted into the bladder.

A circular incision was made around the cervix using a cold knife. The Pouch of Douglas and vesico-uterine peritoneum were opened using cold scissors. Both uterosacral ligaments were clamped, transected using cold scissors and tied off using a Vicryl-1 suture. A Gelpoint port was used as vNOTES port and inserted into the peritoneal cavity. Carbon dioxide was insufflated until a maximal

intraperitoneal pressure of 15mmHg. A laparoscope was inserted and the peritoneal cavity was inspected. The patient was then placed in Trendelenburg position. Three trocars are inserted into the Gelpoint lid. The laparoscope is inserted in the bottom central trocar and is held by the first assistant. The surgeon operates the endoscopic instruments through the two top trocars. (Figure 1)

The ureter was identified but not routinely dissected. The decision to dissect it was based on whether it could be identified transperitoneally. The uterine artery, the ovarian ligament, and the meso of the Fallopian tube, were coagulated using a bipolar grasper and then transected. In patients requiring an adnexectomy, the infundibulopelvic ligament was coagulated using a bipolar grasper and then transected. Haemostasis was checked and the peritoneal cavity was rinsed. The NOTES port and uterus were removed transvaginally and the pneumoperitoneum was deflated. In cases where the uterus was too large to extract in toto, it was manually morcellated so that it could be removed vaginally.

The colpotomy was closed using a running Vicryl-1 suture. A vaginal plug (betadine gauze 10cmx5m) was placed to compress the vaginal vault, and was removed after 3 hours together with the Foley catheter.

Adnexal Surgery

The patient was placed in lithotomy position in a vacuum mattress. The operation field was disinfected and draped. A Foley catheter was inserted into the bladder.

A 2.5 cm posterior colpotomy was made using a cold knife and the pouch of Douglas was opened using cold scissors. A Gelpoint mini port was used as vNOTES port and was inserted into the Pouch of Douglas. Carbon dioxide was insufflated until a maximal intraperitoneal pressure of 15mmHg was reached. An optic was inserted and the peritoneal cavity was inspected. The patient was then placed in Trendelenburg position. Three trocars are inserted into the Gelpoint lid. The laparoscope is inserted in the bottom central trocar and is held by the first assistant. The surgeon operates the endoscopic instruments through the two top trocars. (Figure 2)

Salpingo-oophorectomy

The ureter was identified, but not routinely dissected. It was only dissected if it could not be identified transperitoneally. The proximal end of the Fallopian tube was coagulated at its uterine origin using a reusable bipolar grasper, and was transected using cold scissors. The ovarian and infundibulopelvic ligaments were coagulated and transected. The adnexa was resected. If necessary, the same procedure

was repeated for the contralateral adnexa. The peritoneal cavity was rinsed and haemostasis was checked.

Small and benign adnexa were removed directly through the wound protector part of the Gelpoint mini port. Large adnexa or adnexa that were macroscopically suspicious, were placed in an endobag (Memobag, Teleflex). The purse string of the endobag was pulled through the wound protector and the purse string was released. The content of the cyst was aspirated to reduce the volume of the adnexa. The endobag was removed with the adnexa inside it.

Salpingectomy

After applying medial traction to the Fallopian tube, the mesosalpinx was coagulated and transected using a standard bipolar forceps and cold scissors.

This process was repeated from distally to proximally until the insertion of the Fallopian tube into the uterus. The Fallopian tube was then transected at its origin. The Fallopian tube was removed through the wound protector part of the Gelpoint mini.

Ovarian cystectomy

The ovarian cortex was incised using cold scissors. An ovarian cystectomy was performed. Ovarian haemostasis was obtained using a bipolar forceps. The ovarian cyst was removed as described above for salpingo-oophorectomy.

The Gelpoint mini port was then removed.

The colpotomy was closed using three interrupted figure-of-eight Vicryl 2/0 sutures. A vaginal plug (betadine gauze 10cmx5m) was placed to compress the vaginal vault, and was removed after 3 hours together with the Foley catheter.

Results

One hundred and ten procedures were successfully performed via vNOTES using the Gelpoint port (Applied Medical, Rancho Santa Margarita, CA, USA) in combination with conventional reusable laparoscopic instruments. This included 77 hysterectomies, 25 adnexectomies, 4 salpingectomies and 4 ovarian cystectomies. No conversion to standard laparoscopy or laparotomy was necessary. There were no intraoperative complications. The short term postoperative complications were limited to 7 patients with cystitis.

Table 1 presents an overview of the patient and perioperative data. Mean operation time for a hysterectomy was 56 mins, and 25,5 mins for adnexal surgery . The mean drop in Hb level was 1,5 g/dl for the hysterectomies. These data were not available for the adnexal surgery, as most patients were treated on an outpatient basis. Most patients scored a low postoperative pain score with a mean score of 1,8 24hours after surgery for the hysterectomies and 1,6 for the adnexal surgery. Uterine weight ranged from 25 to 642 g, with a mean of 155,9 g. The mean size of the adnexal mass was 45,5 mm, with the largest cyst measuring 110 mm.

Each patient was examined 6 weeks after surgery. There was no vaginal wound infection nor dehiscence, and no patient complained of pain during pelvic examination. All patients were in good health.

Discussion

In this study, 110 operations were successfully performed via vNOTES using a Gelpoint port as the access port. There were no conversions to a different port type. In addition, there were no conversions to laparotomy or conventional laparoscopy, and no technical problems occurred. The procedures were completed within reasonable operating time and there were no intra-operative complications. Postoperatively there were only minor complications : 7 patients presented with cystitis. Overall, patients scored low pain scores at 6 and 24h postoperatively.

To the best of our knowledge, this comprises the first report on the use of the Gelpoint port for vNOTES.

Multiple techniques exist for performing a hysterectomy. A classical vaginal hysterectomy is a total hysterectomy performed entirely through vaginal access under direct vision using conventional surgical instruments. A VANH is a total hysterectomy where first the caudal part of the uterus is dissected vaginally under direct vision (as in a classical vaginal hysterectomy), and thereafter the rest of the hysterectomy is performed via transvaginal NOTES using an endoscopic camera and endoscopic instruments.

Over the last few years, the use of robotic and laparoscopic techniques has increased, while traditional vaginal and abdominal hysterectomies have been performed less frequently (10).

According to the Cochrane Database the preferred technique to perform a hysterectomy is via conventional vaginal surgery. When a vaginal hysterectomy is not possible, a laparoscopic hysterectomy may avoid the need for an abdominal hysterectomy (11). Making use of the advantages

of endoscopic surgery, vNOTES hysterectomy broadens the indications for vaginal hysterectomy and helps overcome its limitations, while the NOTES approach avoids abdominal wall wounds and trocar related complications (9). A study on vNOTES appendectomies also reported shorter hospitalization, quicker recovery, less analgesic requirement, and better cosmetic satisfaction (13).

One could argue that some of the hysterectomies in this case series could have been performed by conventional vaginal hysterectomy in the hands of a skilled vaginal surgeon. In our experience, the vNOTES approach broadens the indications for vaginal hysterectomy. In a period of six months before the introduction of vNOTES hysterectomy in our department, 80% of benign hysterectomies were performed laparoscopically, 19% vaginally and 1% per laparotomy. In a six month period after the introduction of vNOTES hysterectomy, 88% of benign hysterectomies were performed transvaginally (65% vNOTES and 23% conventional vaginal hysterectomy), 10% laparoscopically and 2% per laparotomy.

When compared with a conventional vaginal hysterectomy, the vNOTES approach facilitates the removal of Fallopian tubes, which is routinely performed in all hysterectomies in our department. It also facilitates adnexectomy during hysterectomy, when indicated. The improved visualization facilitates haemostasis and the resection of larger uteri.

When compared to single incision laparoscopic surgery (SILS), comparable technical difficulties appear related to instrument collision, limited triangulation, and reduced traction of tissue (14,15). Due to the colpotomy providing a more flexible entry compared to the infra-umbilical fascia opening, these difficulties are found to be less restricting when compared to SILS (6).

One could argue the possibility of pelvic infection after vaginal surgery, however none of the 110 patients presented with this complication after the vNOTES procedures. Previous studies have shown that this complication is unlikely to happen, especially when prophylactic antibiotics are administered (16,17). In addition, there is no evidence to suggest a difference in prevalence of dyspareunia between conventional compared to endoscopic transvaginal surgery, and studies show the absence of dyspareunia in mid- and long-term follow-up (16–18). As was the case for our study protocol, sexual abstinence should be recommended for 6-8 weeks as is the recommendation for conventional transvaginal surgery (18).

Some contra-indications should be considered before performing vNOTES. In case of massive haemoperitoneum, the endoscopic view will get disturbed (19). When Pouch of Douglas adhesions can be expected, a thorough pelvic examination should be performed prior to surgery, and in the case of unexpected Pouch of Douglas obliteration, conversion to transabdominal laparoscopy should be

considered. Another contra-indication for vNOTES is virginity. On the other hand, nulliparity or the absence of vaginal delivery should not be seen as contra-indications to perform vNOTES, and neither should be obesity. If a good Trendelenburg position can be achieved, the bowel and mesenterium can be lifted out of the pelvis and will not impair visualization.

The major limitation of vNOTES is the inability to overview the pelvic area, in particular the vesico-uterine pouch, and thus lesions such as bladder endometriosis or anterior uterine wall myomas can be missed. Innovations in endoscopes will help overcome this limitation and provide the ability to explore the entire abdominal cavity via vNOTES (19).

The Gelpoint advanced access platform was successfully used in 77 VANH procedures and the Gelpoint mini advanced access platform was successfully used in 33 vNOTES adnexal procedures. Both were used in thin as well as in obese patients (BMI 17,9-36,7) and provided a good CO_2 seal for pneumoperitoneum.

The Gelpoint port offers several advantages over a self-constructed glove port. These include a shorter setup time (as there is no need to construct a glove port), easier instrument transfer through the trocars, better ergonomics, and a less fragile port, reducing the risk of accidental puncture and CO_2 leak.

The greatest disadvantage is the higher cost. There is also a limitation to 4 trocars compared to 5 when using the glove port. In this study, all procedures were performed without difficulty using only 3 trocars, as easier port transfer reduces the need for a larger number of ports.

Conclusion

The feasibility and potential benefits of VANH and vNOTES adnexal surgeries have previously been demonstrated (6,8,9,17).

In this study, 110 vNOTES procedures were successfully performed using Gelpoint ports, demonstrating that the Gelpoint advanced access platform and Gelpoint mini advanced access platform are suitable for VANH and vNOTES adnexal surgery respectively.

Both ports can be used in slim as well as in obese patients and provide a good CO_2 seal, and good access to the peritoneal cavity.

The main advantages of Gelpoint ports over a self-constructed glove port are shorter setup time, easier instrument transfer through the trocars, better ergonomics, and a less fragile port. These advantages

need to be weighed against the higher cost of the port. We found the limitation to 4 trocars compared to 5 in a glove port, not to be as disadvantageous as the easier port transfers with Gelpoint ports reduced the need for more than 3 trocars.

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Table 1 : Overview of patient and perioperative characteristics

	HYSTERECTOMY (n= 77)		ADNEXAL SURGERY (n= 33)	
Data	Mean	Range	Mean	Range
Age (years)	51	34 - 73	51	22 – 82
BMI (kg/m^2)	25,4	18,4 – 36,7	23,8	17,9 – 33,6
Total operating time (min)	56	40 – 120	25,5	20 – 120
Serum hemoglobine drop (g/dl)	1,5	-0,6 – 4,2		
Postoperative pain score				
6h	2,3	1 – 6	1,8	0 – 5
24h	1,8	1 - 7	1,6	1 – 2
Weight of uterus (g)	155,9	25 – 642		
Size of adnexal mass (mm)			45,5	15 – 110

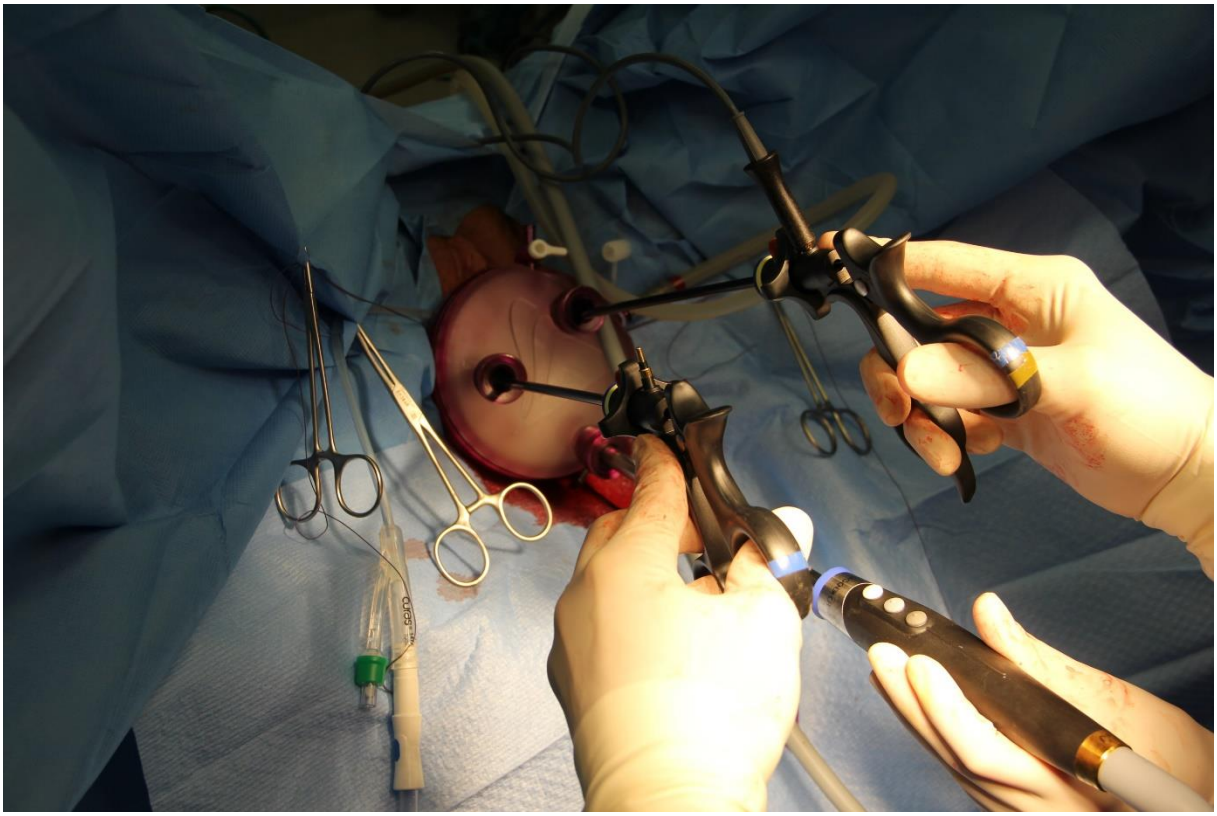

FIG. 1. GelPOINT setup for transvaginal natural orifice transluminal endoscopic surgery.

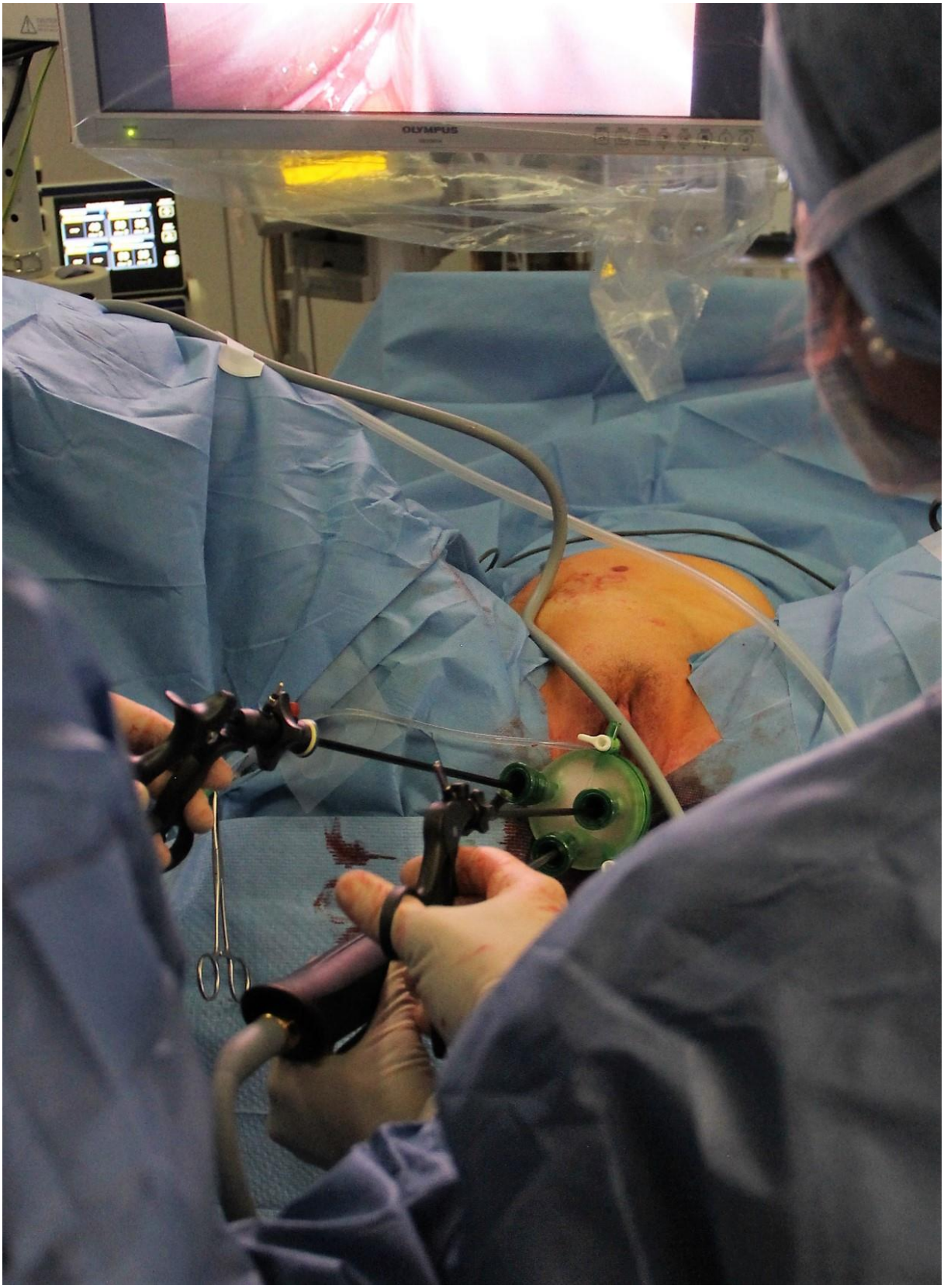

FIG. 2. GelPOINT mini-setup for transvaginal natural orifice transluminal endoscopic surgery.

Chapter 3

3.1 Robotic vaginally assisted NOTES hysterectomy: the first case series demonstrating a new surgical technique.

Jan Baekelandt

Gynecological Surgery 2015;13:57-62

3.2 Robotic Vaginal NOTES Hysterectomy: Two new surgical techniques.

Jan Baekelandt

Journal of Gynecologic Surgery 2016;32(5):270-277

3.1 Robotic Vaginally Assisted NOTES Hysterectomy: The First Case Series Demonstrating A New Surgical Technique

Abstract:

Objective: The objective of this case series is to demonstrate a new hysterectomy technique via transvaginal Natural Orifice Transluminal Endoscopic Surgery (NOTES) using robotic surgery.

Setting: Previous experience with the Da Vinci Xi (Intuitive Surgery) for gynaecological oncology, and with NOTES for adnexal surgery and hysterectomy, led to the decision to combine the advantages of these techniques, namely to reduce the invasiveness of robotic surgery and improve the ergonomics of NOTES.

Intervention: A robotic Vaginally Assisted NOTES Hysterectomy (VANH) was performed in five patients with a myomatous uterus. The circumcision of the cervix, the opening of the anterior and posterior peritoneum, and the transection of both sacro-uterine ligaments was performed by classical vaginal surgery. A NOTES port was constructed by assembling a surgical glove, a wound protector, 4 Da Vinci 8mm trocars and 1 reusable 5mm trocar. The ring of the wound protector was then inserted transvaginally into the peritoneal cavity to create a pneumoperitoneum. The hysterectomy was performed via transvaginal NOTES using the surgical robot. Subsequently a bilateral adnexectomy was performed in the same way. Once the hysterectomy and bilateral adnexectomy were completed, the robot and glove port were removed. When the uterus was too large to extract in toto, it was manually morcellated so that it could be removed vaginally. The colpotomy was closed as in classical vaginal surgery.

Conclusion: This is the first case report demonstrating that vaginal robotic surgery is possible and that it can be used to perform a hysterectomy. Robotic Vaginally Assisted NOTES Hysterectomy (RVANH) makes use of the advantages of robotic surgery to broaden the indications for vaginal hysterectomy and can help overcome its limitations, while the NOTES approach avoids abdominal wall wounds and trocar related complications. Further developments in robotic technology will help overcome the problem of robotic arm collision. Robotic hysterectomy via vaginal access is a novel approach that requires further validation. The extra cost and set up time of RVANH will also need to be assessed in comparison to the advantages it provides over a vaginally assisted NOTES hysterectomy or total laparoscopic hysterectomy.

Background:

Aiming to minimise surgical morbidity, the evolution from laparotomy to laparoscopy has now extended into the area of even less invasive surgery such as robotics, single incision laparoscopic surgery (SILS), and natural orifice transluminal endoscopy (NOTES). Minimally invasive surgery not only improves cosmetic outcome, but also reduces surgical injury. This in turn decreases the inflammatory and neuroendocrine response resulting in less post-operative pain and quicker recovery [1, 2].

NOTES attempts to reach the abdominal cavity by scar-free means, i.e. numerous surgical procedures are performed via a natural body orifice. This technique has gained popularity amongst general surgeons, gynaecologists, urologists and gastroenterologists over the past few years and its feasibility and safety have been approved [3].

NOTES can be performed via a variety of approaches including stomach, oesophagus, bladder, and rectum, but the majority of NOTES procedures have been performed transvaginally [4]. The vagina can easily be decontaminated and provides direct access. Culdotomy has been used widely for several surgical procedures (not only by gynaecologists but also by general surgeons for extraction of large specimens) and it has been approved as safe and easy to close [5].

In *hybrid* NOTES the surgical procedure is performed through a natural body orifice with trans abdominal assistance. The term *pure* NOTES refers to procedures that involve only transluminal access.

Hysterectomy via NOTES, after performing an anterior and posterior colpotomy and transection of sacro-uterine ligament via classical open vaginal surgery, has been described [6,7]. We refer to this technique as vaginally assisted NOTES hysterectomy (VANH) as the first part of this procedure is performed by conventional vaginal surgery and in the second part of the procedure, the hysterectomy is performed via NOTES. Previous experience with the Da Vinci Xi (Intuitive Surgery) for gynaecological oncology, and with NOTES for adnexal surgery and hysterectomy, led to the decision to combine the advantages of these techniques, namely to reduce the invasiveness of robotic surgery and improve the ergonomics of NOTES.

Material and Methods

Patients

A single surgeon (BJ) performed 5 robotic VANH to evaluate the feasibility of the technique. All patients were selected for hysterectomy due to myomatous uterus. Patients were selected based on the

following criteria: no contraindication for general anaesthesia, pneumoperitoneum or Trendelenburg position; no fixed uterus, strong pelvic adhesions or nodularity in the Pouch of Douglas on clinical examination; no history of pelvic inflammatory disease; no suspicion for malignancy. Obesity (BMI > 30) was not considered to be an exclusion criteria.

The following patient and perioperative data were collected and retrospectively analysed: patient age, body mass index (BMI), parity, mode of delivery, previous surgery, type of surgery, operating time, serum haemoglobin (Hb) drop (change between the preoperative Hb and postoperative Hb one day after surgery), peri-operative complications, postoperative pain score, hospitalization time, and weight of the uterus. The duration of surgery was defined as the time form the placement of the Foley catheter to the end of vaginal closure. It was measured in three stages: vaginal time, docking time and console time. Vaginal time was the time when the surgeon was operating by classical vaginal surgery: from placement of the Foley catheter until the sacro-uterine ligaments were ligated and after undocking the robot until the end of vaginal closure. Docking time was the time for docking and undocking the robot. Console time was the time when the surgeon was operating at the robotic console.

Bowel, bladder, ureteral or vascular injuries, as well as blood loss > 300 ml were considered as intraoperative complications. Short-term postoperative complications were identified to be urinary tract infection, postoperative ileus, vaginal vault bleeding or infection, or haematuria.

Postoperative pain was assessed using the visual analogue pain scale (VAS) (scoring from 0 = no pain, to 10 = worst imaginable pain). The VAS score was evaluated at 6 and 24 hours postoperatively. All patients received the same intraoperative analgesia: intravenous paracetamol 1000 mg and ketorolac trometamol 20 mg. Postoperative pain was managed by paracetamol 1000 mg and ketorolac trometamol was administered on patient's demand.

Prophylactic intravenous antibiotic therapy, cefazolin 2 g and metronidazole 500 mg, was administrated during surgery.

No vaginal intercourse was allowed for 6 weeks after the procedure. Each patient was re-assessed at the post-operative consultation 6 weeks after surgery.

Surgical technique (video)

A robotic VANH was performed. The patient was placed in lithotomy position as for a classical vaginal hysterectomy. The circumcision of the cervix, the opening of the anterior and posterior peritoneum, and the transection of both sacro-uterine ligaments was performed by classical vaginal surgery. A

NOTES port was constructed by assembling a surgical glove, a wound protector, 4 Da Vinci 8mm trocars and 1 reusable 5mm trocar (Fig.1). The ring of the wound protector was then inserted transvaginally into the peritoneal cavity to create a pneumoperitoneum (Fig.2). A Da Vinci Xi surgical robot was side docked between the legs of the patient (Fig. 3). Three arms were connected to the trocars in the glove port. The fourth arm was not used. Using a 30° optic, a fenestrated bipolar grasper, and a vessel sealer, the hysterectomy was performed via transvaginal NOTES using the surgical robot. Subsequently a bilateral adnexectomy was performed in the same way. Once the hysterectomy and bilateral adnexectomy were completed, the robot and glove port were removed. When the uterus was too large to extract in toto, it was manually morcellated so that it could be removed vaginally (Fig.4). The colpotomy was closed as in classical vaginal surgery. No abdominal incisions were made.

Results

Five robotic VANH's were successfully performed without perioperative complications. No conversion to standard multi incision laparoscopy or laparotomy was necessary.

Table 1 presents an overview of patient and perioperative data. Individual patient details are presented in Table 2. Mean vaginal time was 18.2 minutes, mean docking time was 17.8 minutes, and mean console time was 33.6 minutes. Three patients had had previous surgery. There were no intraoperative complications. One patient had a postoperative superficial thrombophlebitis in her leg. The mean drop in haemoglobin level was 1.2 g/dl. Most patients scored a low postoperative pain score (range 2-3) 6 and 24 hours after surgery. All uteri were benign upon pathological examination (specimen weight 70- 575g). All patients had previous vaginal deliveries and one patient had had a previous Caesarean section.

Each patient was examined six weeks after surgery. There was no vaginal wound infection nor dehiscence, and none of the patients complained of pain during pelvic examination. All patients were in good health and were back at work.

Discussion

These first five cases of robotic VANH were performed successfully. The procedures were completed within a reasonable operation time and without major complications. No conversion to laparotomy, transabdominal robotic surgery or standard laparoscopy was necessary. The duration of

hospitalisation was similar to the hospitalisation time for a laparoscopic or vaginal hysterectomy in our department.

To the best our knowledge this is the first report on RVANH (Robotic Vaginally Assisted NOTES Hysterectomy) and on the use of a Da Vinci surgical robot via vaginal access. As the Da Vinci Xi surgical robot is designed for multiport access, we experienced significantly more robotic arm collision during these transvaginal NOTES procedures than we normally experience during multiport transabdominal procedures. Particularly in the second more obese patient with the larger uterus, the arms had to be repositioned more frequently during the final stage of the hysterectomy. Having longer robotic instruments would have better facilitated this part of the procedure. Overall the arm collision problem was smaller than we had anticipated.

Conventional transvaginal surgery has significant advantages compared to laparoscopic surgery, such as the absence of abdominal scarring and faster recovery from surgery [8]. It is the preferential approach to hysterectomy [9]. Most medium sized uteri (mean uterine weight in this case series was 329 gram) can be removed vaginally by an experienced vaginal surgeon. By performing transvaginal NOTES, the technical drawbacks of transvaginal surgery, including limited visualisation to attempt good haemostasis and difficulty in performing adnexectomy in case of adhesions between the adnexa and the uterus, can be overcome. Additionally, NOTES eliminates the risk of trocar related complications and induces less post-operative pain [10]. It has been demonstrated that very large uteri can be removed via VANH, and that ligating the uterine vessels transvaginally before dissecting the rest of the uterus, results in less blood loss compared to a transabdominal laparoscopic approach where there is more manipulation before occlusion of the feeding vessels [6,7].

When comparing RVANH with our previous experience of VANH performed with conventional laparoscopic instruments, we found the vessel sealer to be very useful. It permitted us to perform the entire robotic part of the procedure using just two instruments: a vessel sealer and a fenestrated bipolar grasper. We have tried using different non-articulating and articulating sealing devices in VANH but always found the handles too bulky, causing collision between the surgeon's hands and the assistant's hands holding the camera. Therefore we mostly use a bipolar grasper and cold scissors during VANH, which requires more port transfers, as one always needs to change instruments between coagulating and transecting. Using the Da Vinci robot and the vessel sealer solves this problem of hand collision and need for frequent instrument changes. The other advantages of robotic surgery over laparoscopic surgery also apply to vaginal robotic surgery: better ergonomics, camera control,…

One could argue the possibility of pelvic infection after vaginal surgery, however no patient presented with this complication after the RVANH procedure. Previous studies have also shown that post-

operative pelvic infection is unlikely, especially when prophylactic antibiotics are administered [7, 11]. As the vaginal vault is closed in the same way as in a classical vaginal hysterectomy, no differences in incidence of dyspareunia are to be expected. Sexual abstinence should be recommended for six to eight weeks, as is the recommendation for conventional transvaginal surgery [7].

As previously mentioned by Lee et al [12], the major limitation of transvaginal NOTES is the inability to overview the pelvic area, in particular the vesico-uterine pouch, and thus lesions such as bladder endometriosis can be missed. Innovation of endoscopes is desirable to overcome this limitation and to have the ability with NOTES to explore the entire abdominal cavity.

Further technical innovations in surgical robots will also help overcome the problem of robotic arm collision and will therefore reduce the time of surgery. As with all robotic surgery the cost of a RVANH hysterectomy will need to be assessed in comparison to the advantages it provides over a VANH or a total laparoscopic hysterectomy.

Conclusion

These are five case series demonstrating that vaginal robotic surgery is possible and that it can be used to perform a hysterectomy. RVANH makes use of the advantages of robotic surgery to broaden the indications for vaginal hysterectomy and can help overcome its limitations, while the NOTES approach avoids abdominal wall wounds and trocar related complications. Further developments in robotic technology will help overcome the problem of robotic arm collision. Robotic hysterectomy via vaginal access is a novel approach that requires further validation. The extra cost and set up time of RVANH will also need to be assessed in comparison to the advantages it provides over a VANH or total laparoscopic hysterectomy.

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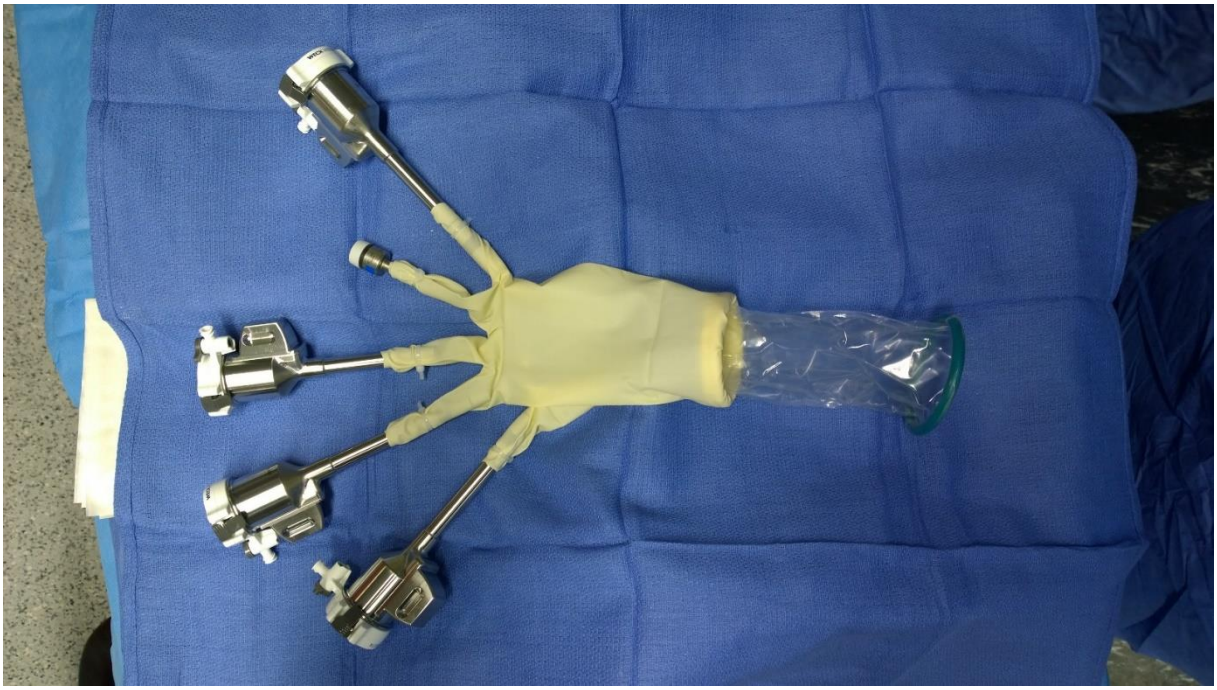

Fig. 1 A NOTES port was constructed by assembling a surgical glove, a wound protector, 4 Da Vinci 8mm trocars and 1 reusable 5mm trocar

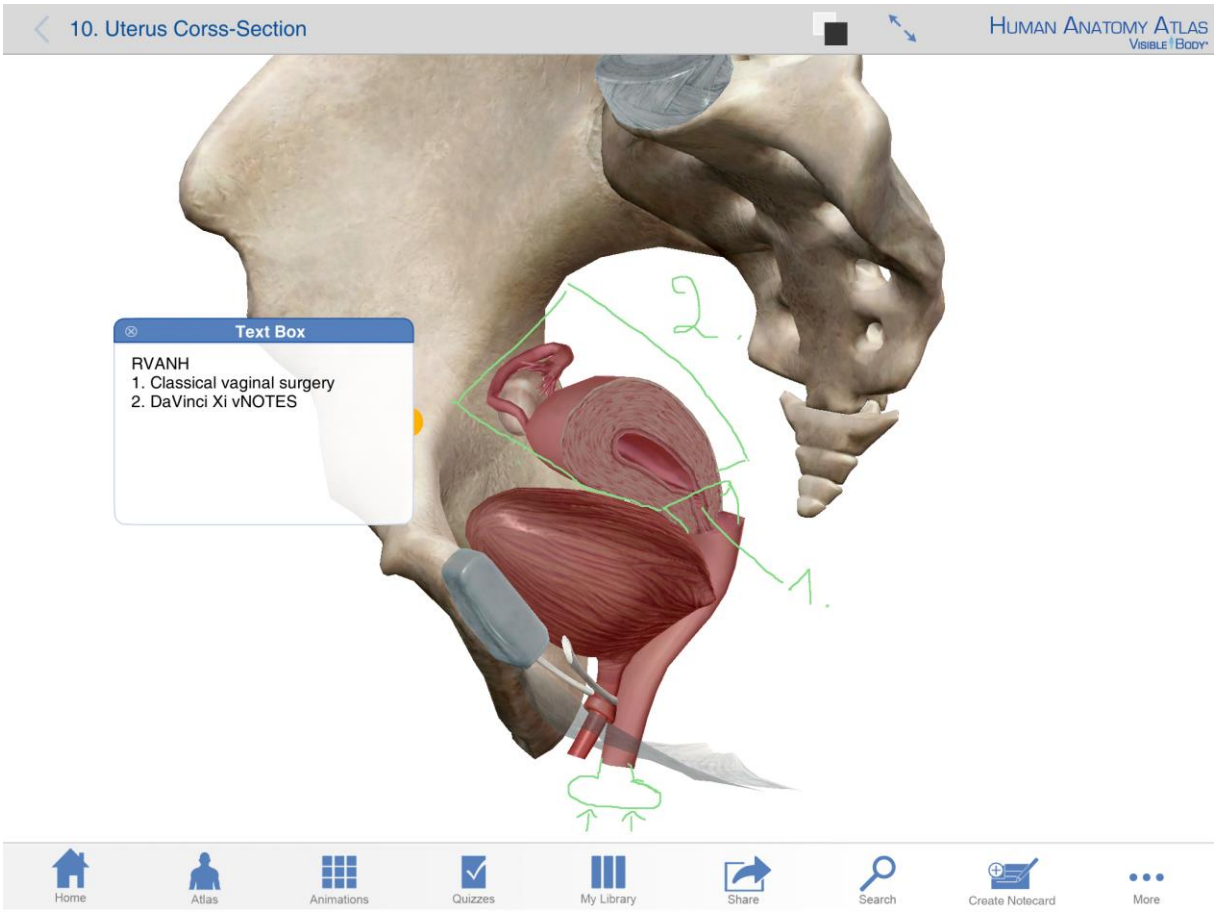

Fig.2 Both sacro-uterine ligaments are transected by classical vaginal surgery (1.). The ring of the glove

port is placed transvaginally into the peritoneal cavity (position indicated by 1.) The rest of the procedure is performed by Da Vinci Xi (2.)

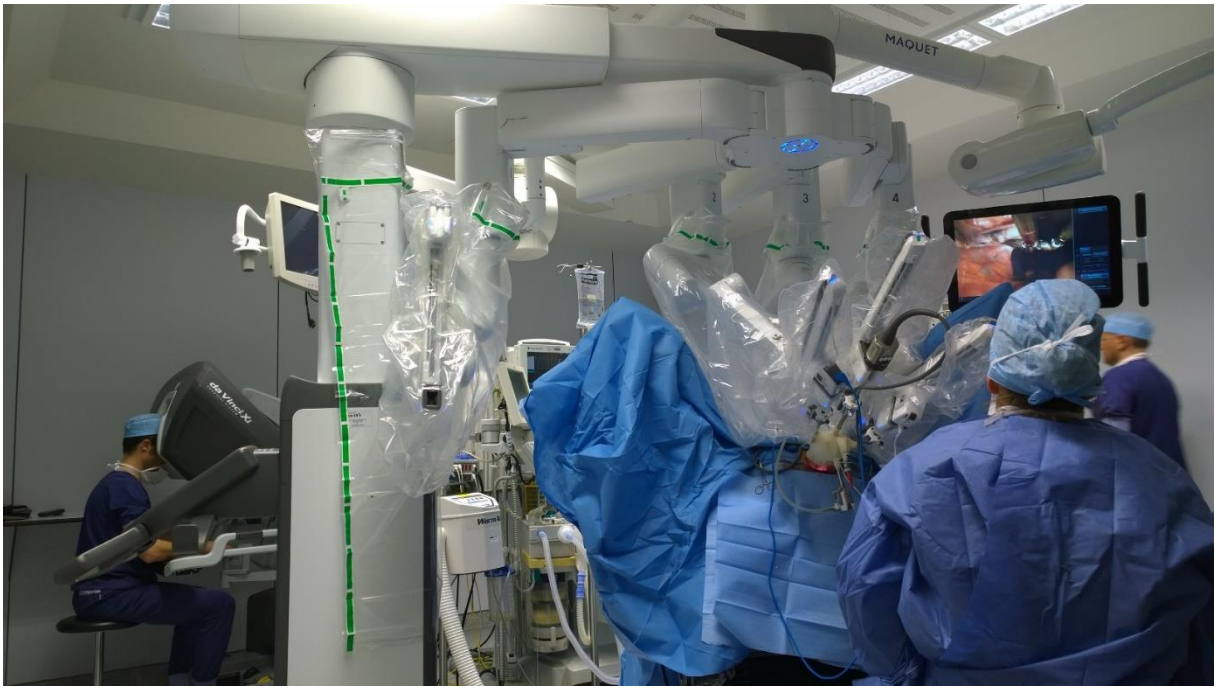

Fig. 3 The Da Vinci Xi surgical robot is side docked between the legs of the patient

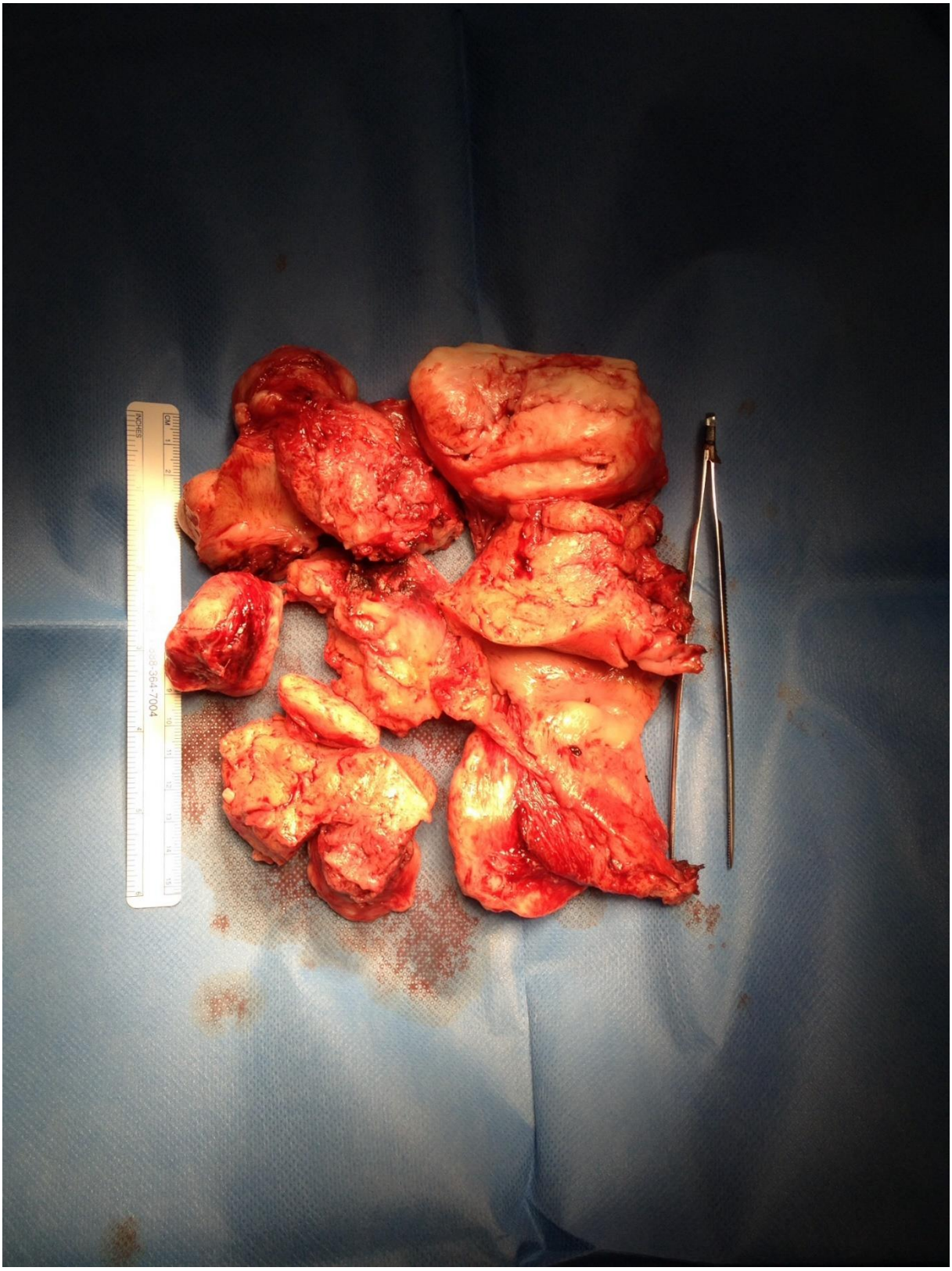

Fig. 4 The uterus was manually morcellated so that it could be removed vaginally

Data	Mean	Range
Age (years)	53.2	46-60
BMI (kg/m^2)	24.3	21.2-30.5
Operating time (min)		
Vaginal time	18,2	15-26
Docking time	17,8	15-20
Console time	33,6	12-65
Serum hemoglobin drop (g/dl)	1.2	0.5-2.6
Postoperative pain score		
6h	2.4	2-3
24h	2	2
Uterine weight (g)	329	70-575

Table 1 Overview of patient and perioperative characteristics

Patient no.	Age (years)	BMI (kg/m^2)	Parity	Delivery mode	Previous surgery	Type of surgery	Operating time (min)			Serum hemoglobin drop (g/dl)	Peri-operative complications	Postoperative pain score		Hospitalisation (days)	Weight Uterus (grams)
							Vaginal	Docking	Console			6h	24h		
1	52	23.7	1	NVD	Laparotomy for spinal surgery Abdominoplasty	RVANH+BSO	15	20	45	0.6	/	3	2	2	363
2	54	30.5	2	NVD	/	RVANH+BSO	20	20	65	0.8	Superficial thrombophlebitis	3	2	3	575
3	60	22.7	2	NVD	Appendectomy Laparotomy for ovarian torsion	RVANH	15	19	12	2.6	/	2	2	3	70
4	54	23.4	3	NVD	/	RVANH	15	15	26	0.5	/	2	2	3	506
5	46	21.2	4	CS x1	LLETZ	RVANH	26	15	20	1.6	/	2	2	2	132

NVD = Normal Vaginal Delivery; CS = caesarean section; LLETZ = Large Loop Excision of Transformation Zone; RVANH = Robotic Vaginally Assisted NOTES Hysterectomy; BSO = bilateral salpingo-oophorectomy

Table 2 Patient and perioperative characteristics of consecutive patients

3.2 Robotic Vaginal NOTES Hysterectomy: Two New Surgical Techniques

Abstract:

Objective: To compare two new hysterectomy techniques by robotic vaginal NOTES, and to demonstrate that a transvaginal robotic hysterectomy can be performed in nulliparous patients by Natural Orifice Transluminal Endoscopic Surgery (NOTES).

Design: Case series.

Method: Previous experience with Total Vaginal NOTES Hysterectomy (TVNH) and with transvaginal robotic surgery for Robotic Vaginally Assisted NOTES Hysterectomy (RVANH), led to the decision to combine these techniques to perform Robotic Total Vaginal NOTES Hysterectomy (RTVNH) in nulliparous patients. Twenty patients were included in this study. In 10 nulliparous patients a RTVNH was performed. A glove port was inserted into the vagina to create a pneumovagina. A Da Vinci Xi surgical robot was side docked between the legs of the patient. The hysterectomy was performed via transvaginal NOTES using the surgical robot. Once the hysterectomy was completed, the robot and glove port were removed. The colpotomy was closed as in classical vaginal surgery. The data of these patients were compared to that of 10 parous patients who underwent a RVANH.

Results: All procedures were completed without conversion to transabdominal laparoscopy or laparotomy. The mean patient data and results for RTVNH/RVANH were: age 49/63; BMI 26.4/27.8; total operating time: 118/90 minutes; Hb drop: 1.2/1.3 g/dl; uterus weight: 149/213 grams; pain score day 1: 2/2, and day 2: 2/2. One complication occurred in the RVANH group: a superficial thrombophlebitis.

Conclusion: This case series confirms that robotic transvaginal surgery is feasible and can be used to perform a total hysterectomy. RTVNH enabled hysterectomies to be performed without any abdominal incisions in nulliparous patients, who had been determined as unsuitable candidates for classical vaginal hysterectomy. RTVNH and RVANH are novel techniques and require further validation. Further developments in robotic technology will help overcome the practical problem of arm collision, and will increase the time efficiency of the procedure.

Introduction:

Surgical evolution from laparotomy to laparoscopy, with the aim of reduced morbidity, has now further broadened to include less invasive surgery, such as robotics, single incision laparoscopic surgery (SILS), and natural orifice transluminal endoscopy (NOTES). As well as improving cosmetic outcome, minimally invasive surgery also reduces surgical injury. The result is decreased inflammatory and neuroendocrine response, leading to low post-operative pain scores and faster recovery [1, 2].

The goal of NOTES is to reach the abdominal cavity by scar-free means, thus surgical procedures are performed via a natural body orifice. In recent years these techniques have gained popularity amongst general surgeons, gynaecologists, urologists and gastroenterologists, and their feasibility and safety have now been accepted[3].

The stomach, oesophagus, bladder, and rectum all provide adequate NOTES access points, but the majority of NOTES procedures have been performed transvaginally [4]. The vagina provides direct access to the peritoneal cavity and can easily be decontaminated. Not only gynaecologists but also general surgeons make extensive use of culdotomy for several surgical procedures, for extraction of large specimens, and it has been approved as safe and easy to close [5].

In *hybrid* NOTES the surgical procedure is performed through a natural body orifice with trans abdominal assistance. The term *pure* NOTES refers to procedures that involve only transluminal access.

Hysterectomy via NOTES, after performing an anterior and posterior colpotomy and transection of the uterosacral ligaments via classical open vaginal surgery, has been described [6,7]. We refer to this technique as vaginally assisted NOTES hysterectomy (VANH) as the first part of this procedure is performed by conventional vaginal surgery and in the second part of the procedure, the hysterectomy is performed via NOTES (Table 1.).

In a Total Vaginal NOTES Hysterectomy (TVNH), the entire hysterectomy is performed via transvaginal NOTES [8]. In VANH the circumcision of the cervix, the anterior and posterior colpotomy, and the ligation of the uterosacral ligaments are performed by classical vaginal surgery, whereas in TVNH this part of the procedure is also performed using endoscopic instruments via NOTES approach. This enables the surgeon to easier perform the anterior and posterior colpotomy in patients without descensus, who have not delivered vaginally, and in patients with previous caesarean sections [8].

The first case report on transvaginal robotic surgery was presented at the 7th Annual SERGS Meeting on Robotic Gynaecological Surgery in June 2015 [9]. From the first case series of 5 patients, a new technique of Robotic Vaginally assisted NOTES hysterectomy (RVANH) was published [10]. RVANH makes use of the advantages of robotic surgery to broaden the indications for vaginal hysterectomy and can help overcome its limitations, while the NOTES approach avoids abdominal wall wounds and trocar related complications [10].

Previous experience with TVNH and with transvaginal robotic surgery for RVANH led to the decision to combine these techniques to perform Robotic Total Vaginal NOTES Hysterectomy (RTVNH) in nulliparous patients.

Materials and methods

Patients

A single surgeon (BJ) performed 20 robotic transvaginal NOTES (vNOTES) hysterectomies: 10 RTVNH on nulliparous patients, who had been determined as unsuitable candidates for classical vaginal hysterectomy, and 10 RVANH on parous patients. In the RTVNH group, 7 patients were operated for a myomatous uterus, two for cervical dysplasia and 1 for Stage IA endometrial cancer. In the RVANH group, 5 patients were operated for Stage IA endometrial cancer and 5 patients for a myomatous uterus.

Patient selection criteria included: no contraindication for general anaesthesia, pneumoperitoneum or Trendelenburg position; no fixed uterus, strong pelvic adhesions, or nodularity in the Pouch of Douglas on clinical examination; no history of pelvic inflammatory disease. Obesity (BMI > 30) was not considered to be an exclusion criteria.

The following patient and perioperative data were collected and analysed: patient age, body mass index (BMI), parity, mode of delivery, previous surgery, type of surgery, operating time, serum haemoglobin (Hb) drop (change between the preoperative Hb and postoperative Hb one day after surgery), perioperative complications, postoperative pain score, hospitalization time, and weight of the uterus. The time from the placement of the Foley catheter to the completion of vaginal closure was taken as the duration of surgery. Intraoperative complications included: bowel, bladder, ureteric or vascular injuries, as well as blood loss > 300 ml. Short-term postoperative complications included postoperative ileus, vaginal vault bleeding or infection, urinary tract infection or haematuria.

The visual analogue pain scale (VAS) (scoring from 0 = no pain, to 10 = worst imaginable pain) was used postoperatively to assess pain. It was evaluated at 6 and 24 hours postoperatively. Intravenous paracetamol 1000 mg and ketorolac trometamol 20 mg were administered intraoperatively to all patients. Postoperatively, pain was managed by paracetamol 1000 mg, and ketorolac trometamol was administered on patient's demand.

Prophylactic intravenous antibiotic therapy, cefazolin 2 g and metronidazole 500 mg, was administrated during surgery.

No vaginal intercourse was allowed for 6 weeks after the procedure. Each patient was re-assessed at the post-operative consultation 6 weeks after surgery.

Surgical technique (view video on www.inotess.com)

A robotic TVNH was performed in 10 nulliparous patients . A NOTES port was constructed by assembling a surgical glove, a wound protector, 4 Da Vinci 8mm trocars and 1 reusable 5mm trocar. The ring of the wound protector was then inserted into the vagina to create a pneumovagina. A Da Vinci Xi surgical robot was side docked between the legs of the patient. Three arms were connected to the trocars in the glove port. The fourth arm was not used. Using a 30° optic, a fenestrated bipolar grasper, and monopolar scissors, the hysterectomy was performed via transvaginal NOTES using the surgical robot (Figure 1.). The Fallopian tubes were removed with the uterus after bipolar cauterization and transection of the ovarian ligament. When indicated, the ovaries were removed as well by bipolar cauterization and transection of the infundibulopelvic ligament. Once the hysterectomy was completed, the robot and glove port were removed. When the uterus was too large to extract in toto, it was manually morcellated so that it could be removed vaginally. The colpotomy was closed as in classical vaginal surgery. No abdominal incisions were made.

A robotic VANH was performed in 10 parous patients. The patient was placed in lithotomy position as for a classical vaginal hysterectomy. The circumcision of the cervix, the opening of the anterior and posterior peritoneum, and the transection of both uterosacral ligaments, was performed by classical vaginal surgery. A NOTES port was constructed by assembling a surgical glove, a wound protector, 4 Da Vinci 8mm trocars and 1 reusable 5mm trocar. The ring of the wound protector was then inserted transvaginally into the peritoneal cavity to

create a pneumoperitoneum. A Da Vinci Xi surgical robot was side docked between the legs of the patient. Three arms were connected to the trocars in the glove port. The fourth arm was not used. Using a 30° optic, a fenestrated bipolar grasper, and a vessel sealer, the hysterectomy was performed via transvaginal NOTES using the surgical robot. The Fallopian tubes were removed with the uterus after transection of the ovarian ligament by vessel sealer. When indicated, the ovaries were removed as well after transection of the infundibulopelvic ligament by vessel sealer. Once the hysterectomy was completed, the robot and glove port were removed. When the uterus was too large to extract in toto, it was manually morcellated so that it could be removed vaginally. The colpotomy was closed as in classical vaginal surgery. No abdominal incisions were made.

Results

Twenty robotic vNOTES hysterectomies were successfully performed. No conversion to standard multi incision laparoscopy or laparotomy was necessary.

Table 2 presents an overview of patient and perioperative data. Individual patient details are presented in Table 3.

In the RTVNH group the mean age was 49 (range 40-73), mean BMI was 26.4 (range 20.5-40.2), mean procedure time was 118 minutes (range 75-165), mean Hb drop 1.2 (range 0.7-2.5), mean VAS score on day 1 was 2 (range 1-3), and on day 2 was 2 (range 1-2), and the mean uterus weight 149 grams (range 21-518). No complications occurred.

In the RVANH group the mean age was 63 (range 46-84), mean BMI was 27.8 (range 21.2-37.9), mean procedure time was 90 minutes (range 56-120), mean Hb drop 1.3 (range 0.5-2.6), mean VAS score on day 1 was 2 (range 2-3), and on day 2 was 2 (range 1-2), and the mean uterus weight 213 grams (range 70-575). One patient developed a superficial thrombophlebitis postoperatively.

Each patient was examined six weeks after surgery. There was no vaginal wound infection nor dehiscence, and none of the patients complained of pain during pelvic examination. All patients were in good health and back at work.

Discussion

These twenty cases of robotic vNOTES Hysterectomy were performed successfully. The procedures were completed within a reasonable operation time and without major complications. No conversion to laparotomy, transabdominal robotic surgery or standard laparoscopy was necessary. The duration of hospitalization was similar to that for a laparoscopic or vaginal hysterectomy in our department.

To the best our knowledge this is the first report on RTVNH. As the Da Vinci Xi surgical robot is designed for multiport access, we experienced significantly more robotic arm collision during these transvaginal NOTES procedures than we normally experience during multiport transabdominal procedures. Particularly in final stage of the hysterectomy, the arms had to be repositioned more frequently. Having longer robotic instruments and narrower robotic arms would have better facilitated this part of the procedure. Overall the arm collision problem was similar in the RTVNH and RVANH groups, and was smaller than we had anticipated.

When compared to laparoscopic surgery, conventional transvaginal surgery has significant advantages, such as the absence of abdominal scarring and faster recovery from surgery [11]. It is the preferential approach to hysterectomy [12]. Vaginal hysterectomy can be safely performed for large uteri [13] and in nulliparous women [14]. The risk of complications however is higher in nulliparous women [14]. The accessibility of the vaginal passage, disease confined to the uterus, and the surgeons experience are the major determining factors for the choice of route of hysterectomies [15]. Over the last years, the incidence of robotic hysterectomy and laparoscopic hysterectomy has increased and the incidence of vaginal and abdominal hysterectomy has decreased [16]. Enlarged uteri, undescensus, or restricted vaginal space in nulliparous women provide certain challenges for conventional vaginal hysterectomy techniques [7]. The technical drawbacks of transvaginal surgery, which include limited visualization to attempt good haemostasis and difficulty in performing adnexectomy in case of adhesions between the adnexa and the uterus, can be overcome by performing transvaginal NOTES [8,10]. In addition, the risk of trocar related complications is eliminated by NOTES and post-operative pain is reduced [17]. It has been demonstrated that very large uteri can be removed via VANH, and that ligating the uterine vessels transvaginally before dissecting the rest of the uterus, results in less blood loss compared to a transabdominal laparoscopic approach, where there is more manipulation before occlusion of the feeding vessels [6,7].

RTVNH and RVANH are two novel techniques requiring further validation. When comparing both patient groups that mainly differed in parity, the results were similar. The operating time for RTVNH was longer than for RVANH, which is also the case when comparing TVNH with VANH in our experience. RTVNH enabled us to perform hysterectomies without any abdominal incisions in nulliparous patients and women without previous vaginal delivery, who were assessed not to be candidates for a classical vaginal hysterectomy. However, from previous experience, we can conclude that this could also have been achieved by TVNH.

The major advantages of robotic surgery over laparoscopic surgery are: better ergonomics, better camera control and articulated wrist motion. When comparing RTVNH and RVANH with our previous experience with VANH and TVNH, we can confirm these advantages. However, the total operating time is significantly longer in RTVNH and RVANH, when compared with our experience with VANH and TVNH. Further technical innovations in surgical robots will help overcome the problem of robotic arm collision and will therefore reduce the time of surgery. The inability, during vNOTES, to overview the pelvic area, in particular the vesico-uterine pouch, is a major limitation that could lead to lesions such as bladder endometriosis being missed. Innovation of endoscopes is desirable to overcome this limitation and to have the ability with NOTES to explore the entire abdominal cavity [18]. As with all robotic surgery the cost of a RTVNH will need to be assessed in comparison to the advantages it provides over a TVNH or a total laparoscopic hysterectomy.

Pelvic infection after vaginal surgery could present a possible argument against RTVNH or RVANH, however no patient in this study presented such a complication. Previous studies have also shown that post-operative pelvic infection is unlikely, especially when prophylactic antibiotics are administered [7, 19]. To prevent ureteric damage, the uterus is pushed cranially and medially with a robotic fenestrated grasper. Closure of the vaginal vault follows the same technique as in a classical vaginal hysterectomy, thus no differences in incidence of dyspareunia are to be expected. Sexual abstinence should be recommended for six to eight weeks, as is the recommendation for conventional transvaginal surgery [7].

We follow the principles of the IDEAL paradigm for our surgical research [20]. It states the importance of scientific reporting on procedures in stage 1. This study describes two procedures in stage 1 according to IDEAL principles. Therefore the number of patients is small and the type of patients is highly selected. The output is descriptive. The intervention is a procedure inception and the outcome is proof of concept. It is important to stress that the results of a stage 1 study can never demonstrate superiority of a new surgical technique over

an existing technique. Conventional transvaginal surgery remains the preferential approach to hysterectomy and nulliparity is not a contraindication for a conventional vaginal hysterectomy. It is important to continue researching robotic vNOTES surgery as it potentially combines both the advantages of robotic surgery and of NOTES surgery. The NOTES approach offers better visualization and better access to remove the Fallopian tubes (and ovaries). It uses the advantages of endoscopic surgery to broaden the indications for a vaginal hysterectomy and helps overcome its limitation. Robotics adds improved ergonomics, better camera control and articulated wrist motion. Patients in IDEAL stage 1 are always highly selected, therefore the uterus sizes in this study were small. Now that proof of concept has been demonstrated, further IDEAL stage 2 studies need to demonstrate the advantages of RVANH and RTVNH for removing larger uteri.

Conclusion

This case series confirms that robotic transvaginal surgery is feasible and that it can be used to perform a total hysterectomy. RTVNH is feasible and enabled us to perform hysterectomies without any abdominal incisions in nulliparous patients, who were assessed not to be candidates for a classical vaginal hysterectomy. RTVNH and RVANH make use of the advantages of robotic surgery to broaden the indications for vaginal hysterectomy and can help overcome its limitations, while the NOTES approach avoids abdominal wall wounds and trocar related complications. Further developments in robotic technology will help overcome the problem of robotic arm collision. Robotic hysterectomy via vaginal access is a novel approach that requires further validation. The extra cost and set up time of RTVNH and RVANH will also need to be assessed in comparison to the advantages they provide over a TVNH, VANH or total laparoscopic hysterectomy.

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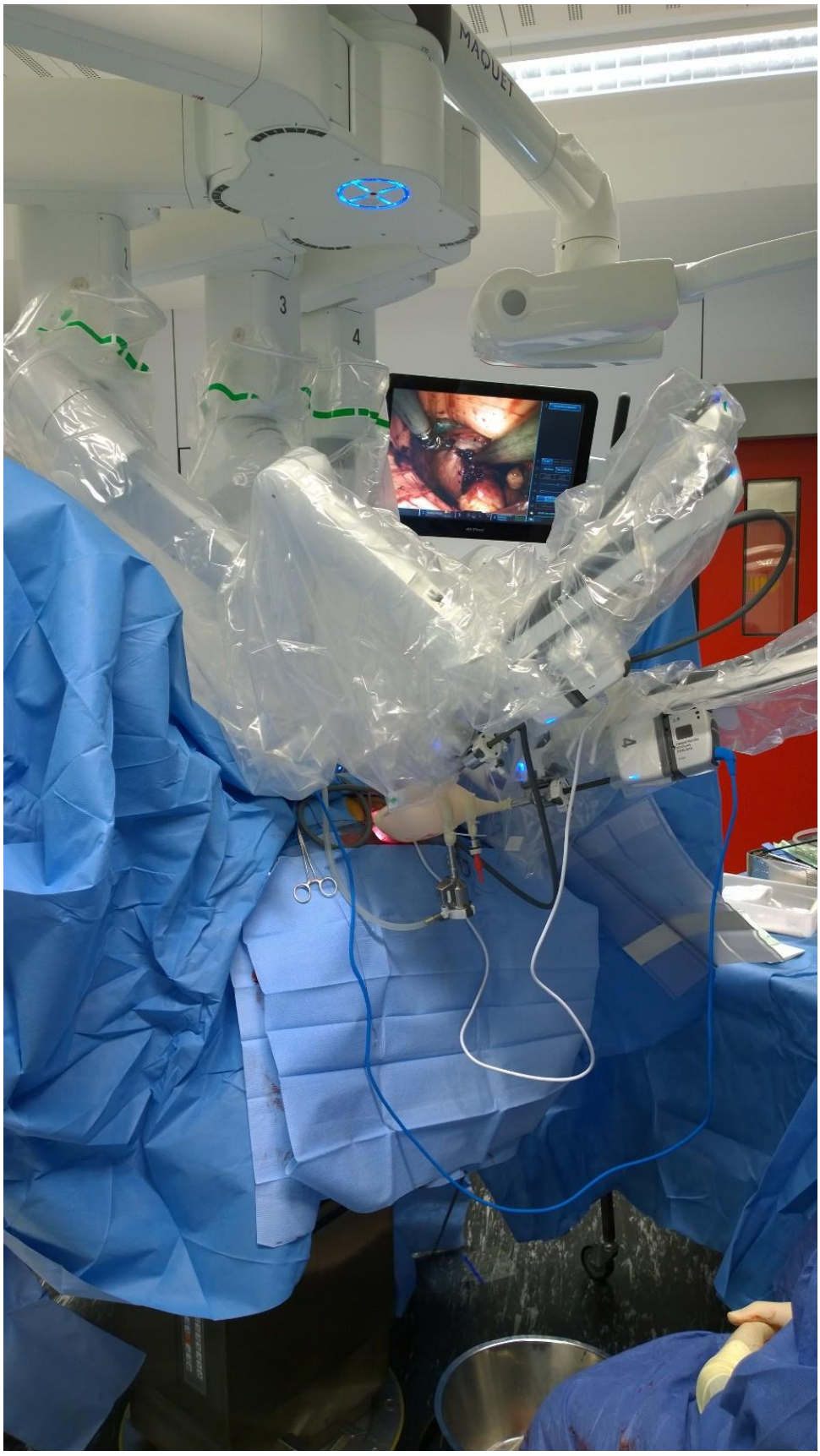
FIG. 1. Da Vinci Xi robot docked transvaginally for RTVNH



Abbreviation	Name	Description
TAH	Total Abdominal Hysterectomy	Total hysterectomy performed through a laparotomy under direct vision using conventional surgical instruments.
VH	Vaginal Hysterectomy	Total hysterectomy performed entirely through vaginal access under direct vision using conventional surgical instruments.
LASH	Laparoscopic Supracervical Hysterectomy	Subtotal Hysterectomy performed by transabdominal laparoscopy.
LAVH	Laparoscopically Assisted Vaginal Hysterectomy	Total hysterectomy where first the cranial part of the uterus is dissected via transabdominal laparoscopy and afterwards the caudal part of the uterus (including ligating the uterine vessels) is dissected under direct vision using conventional instruments.
LH	Laparoscopic Hysterectomy	Total hysterectomy where first the cranial part of the uterus is dissected via transabdominal laparoscopy (including ligating the uterine vessels) and afterwards part of the operation is performed vaginally under direct vision using conventional instruments.
TLH	Total Laparoscopic Hysterectomy	Total hysterectomy where the entire uterus is dissected via transabdominal laparoscopy.
VANH	Vaginally Assisted NOTES Hysterectomy	Total hysterectomy where first the caudal part of the uterus is dissected vaginally under direct vision and afterwards the rest of the hysterectomy

		is performed via transvaginal NOTES using an endoscopic camera and endoscopic instruments.
RVANH	Robotic Vaginally Assisted NOTES Hysterectomy	Total hysterectomy where first the caudal part of the uterus is dissected vaginally under direct vision and afterwards the rest of the hysterectomy is performed via transvaginal NOTES using a surgical robot.
TVNH	Total Vaginal NOTES Hysterectomy	Total hysterectomy where the entire uterus is dissected via transvaginal NOTES using an endoscopic camera and endoscopic instruments.
RTVNH	Robotic Total Vaginal NOTES Hysterectomy	Total hysterectomy where the entire uterus is dissected via transvaginal NOTES using a surgical robot.

Table 1. Types of hysterectomy

	RTVNH Mean	**RTVNH Range**	**RVANH Mean**	**RVANH Range**
Age (years)	49	40 – 73	63	46-84
BMI (kg/m^2)	26.4	20.5 – 40.2	27.8	21.2-37.9
Total operating time (min)	118	75 - 165	90	56-120
Serum haemoglobin drop (g/dl)	1.2	0.7– 2.5	1.3	0.5-2.6
Uterus weight (grams)	149	21-518	213	70-575
Postoperative pain score Day 1 Day 2	 2 2	 1 – 3 1 – 2	 2 2	 2 – 3 1 – 2

Table 2 Overview of patient and perioperative characteristics

Patient no.	Age (years)	BMI (kg/m^2)	Parity	History of vaginal delivery	Previous surgery	Indication	Type of surgery	Total operating time (min)	hemo-globine drop (g/dl)	(Peri-) operative complications	Specimen Weight (grams)	Postoperative pain score	
												D1	D2
1	45	20.5	P0G0	no	LLETZ	Cervical Dysplasia	RTVNH	85	2.5	-	21	2	1
2	54	26.4	P0G0	no	AE	Myomatous Uterus	RTVNH+USO	120	0.9	-	87	2	2
3	44	40.2	P0G0	no	-	Myomatous Uterus	RTVNH	75	1.1	-	174	2	2
4	49	21.5	P0G0	no	LLETZ, Bowel Resection	Myomatous Uterus	RTVNH	165	0.7	-	180	2	2
5	54	25	P2G2	no	CS x2	Myomatous Uterus	RTVNH	120	1.9	-	518	3	2
6	40	24.8	P0G0	no	-	Myomatous Uterus	RTVNH	115	1.6	-	163	2	1
7	46	23.7	P0G0	no	-	Myomatous Uterus	RTVNH	135	0.8	-	115	1	1
8	42	23.4	P0G0	no	LLETZ	Cervical Dysplasia	RTVNH	125	1.2	-	50	2	2
9	48	30.4	P0G0	no	-	Myomatous Uterus	RTVNH	120	1.0	-	114	2	1
10	73	28.4	P0G0	no	LS	ECa IA Grade 1	RTVNH+BSO	120	0.9	-	65	2	1
11	54	30.5	P2G2	yes	-	Myomatous Uterus	RVANH+BSO	105	0.8	Superficial Thrombophlebitis	575	3	2
12	60	22.7	P2G2	yes	AE laparotomy	Myomatous Uterus	RVANH	111	2.6	-	70	2	2
13	54	23.4	P3G3	yes	-	Myomatous Uterus	RVANH	56	0.5	-	506	2	2
14	46	21.2	P4G4	yes	CS x1, LLETZ	Myomatous Uterus	RVANH	61	1.6	-	132	2	2
15	48	28	P1G1	yes	AE, USO	Myomatous Uterus	RVANH	62	0.7	-	263	2	2
16	84	27.9	P1G1	yes	CABG	ECa IA Grade 1	RVANH+BSO	120	1.8	-	199	2	2
17	58	37.9	P2G2	yes	Gastric Bypass	ECa IA Grade 1	RVANH+BSO	100	1.2	-	101	2	2
18	78	31.6	P3G3	yes	-	ECa IA Grade 1	RVANH+BSO	120	1.1	-	84	3	2
19	68	31.2	P2G2	yes	Prolift	ECa IA Grade 1	RVANH+BSO	70	0.7	-	67	2	1
20	81	23.9	P2G2	yes		ECa IA Grade 1	RVANH+BSO	90	1.8	-	136	3	1

Table 3 Patient and perioperative data LLETZ = large loop excision of transformation zone; AE = appendectomy; CS = caesarean section; USO = unilateral salpingo-oophorectomy; RTVNH= robotic total vaginal NOTES hysterectomy; BSO= bilateral salpingo-oophorectomy; CABG = Coronary Artery Bypass Graft; LS = Laparoscopic Sterilisation; ECa Endometrial Cancer Stage IA Grade 1

Chapter 4

New hysterectomy techniques via NOTES

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Book Chapter: www.avidscience.com (first published April 2016)

New Hysterectomy Techniques via NOTES

This book chapter discusses four new hysterectomy techniques by pure transvaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES).

1. Introduction

Hysterectomy is the surgical removal of the uterus. Is it the most commonly performed major gynaecologic surgical procedure in the United States of America, where more than 400,000 hysterectomies are performed annually (1). The most common benign indications for a hysterectomy are: fibroids (30%), dysfunctional uterine bleeding (20%), endometriosis and/or adenomyosis (20%), genital prolapse (15%), chronic pelvic pain (10%) and endometrial hyperplasia (6%) (2).

Conrad Langenbeck performed the first reported elective hysterectomy in 1813 (Table 1) using a vaginal approach (3) and in 1863 the first elective abdominal (subtotal) hysterectomy was performed by Charles Clay (3). Harry Reich performed the first laparoscopic-assisted vaginal hysterectomy in 1989 and the first total laparoscopic hysterectomy in 1993 (3).

Traditionally a hysterectomy could be performed via these 3 approaches: abdominal hysterectomy (AH), vaginal hysterectomy (VH) and laparoscopic hysterectomy. The laparoscopic hysterectomy can be divided into 3 categories: Laparoscopic Assisted Vaginal Hysterectomy (LAVH), Laparoscopic Hysterectomy (LH) and Total Laparoscopic Hysterectomy (TLH). With the introduction of surgical robots, hysterectomies can now also be performed robotically (RH). The technique of a RH is similar to that of a TLH, but robotic arms hold the surgical instruments and the surgeon manipulates them remotely from behind a console. Laparoscopic and robotic hysterectomies can both be performed through multiple small abdominal incisions or through one larger umbilical incision. More recently a new approach to hysterectomy via Natural Orifice Transluminal Endoscopic Surgery (NOTES) has been introduced.

This book chapter will focus on the different hysterectomy techniques by NOTES, where the uterus is removed endoscopically leaving no visible scars.

2. Natural Orifice Transluminal Endoscopic Surgery

The advantages of laparoscopy over traditional laparotomy have been accepted worldwide for many years (4). To further reduce surgical morbidity, the evolutionary trend has been towards even less invasive techniques, such as single-incision laparoscopic surgery (SILS) and natural orifice transluminal endoscopic surgery (NOTES). Minimally invasive surgery improves cosmetic outcome, and also reduces surgical injury, which in turn decreases the inflammatory and neuroendocrine responses, and leads to less postoperative pain and quicker recovery (5).

NOTES reaches the abdominal cavity by scar-free means. To this end, numerous surgical procedures are performed via a natural body orifice. In recent years this technique has gained popularity among general surgeons, gynaecologists, urologists and gastroenterologists, and its feasibility and safety have been approved (6).

NOTES can be performed via a variety of approaches, including the stomach, oesophagus, bladder and rectum, but the majority of NOTES procedures have been performed transvaginally, as the vagina provides direct access to the peritoneal cavity (7). Culdotomy has been widely used for several surgical procedures, not only by gynaecologists but also by general surgeons for extraction of large specimens, and has been approved as safe and easy to close (8).

In hybrid NOTES the surgical procedure is performed through a natural body orifice with transabdominal assistance. The term pure NOTES refers to procedures that involve only transluminal access.

Four new hysterectomy techniques by pure transvaginal NOTES (vNOTES) will now be discussed:

VANH: Vaginally Assisted NOTES Hysterectomy

TVNH: Total Vaginal NOTES Hysterectomy

RVANH: Robotic Vaginally Assisted NOTES Hysterectomy

RTVNH: Robotic Total Vaginal NOTES Hysterectomy

3. Hysterectomy techniques via vNOTES

3.1 VANH

3.1.1 Technique:

A circular incision is made around the cervix using a cold knife. The Pouch of Douglas and then the vesico-uterine peritoneum, are opened using cold scissors. Both uterosacral ligaments are transected using cold scissors and tied off using a Vicryl-1 suture. A NOTES port is inserted into the peritoneal cavity, and CO^2 used to inflate it. An optic is inserted and the peritoneal cavity is inspected. The patient is now placed in the Trendelenburg position and the small intestine lifted out of the pelvis.

The ureter is identified, but not routinely dissected. The uterine artery is coagulated using a bipolar grasper and is transected. The ovarian artery and the meso of the Fallopian tube are coagulated using a bipolar grasper and transected. In patients requiring an adnexectomy, the infundibulopelvic ligament is coagulated using a bipolar grasper and is transected. Haemostasis is checked and the peritoneal cavity is rinsed. The NOTES port and the uterus are removed transvaginally and the pneumoperitoneum is deflated.

The colpotomy is closed using a resorbable suture.

3.1.2 Evidence:

Seven studies, including 731 study participants, have been published on VANH (Table 2.). These studies use different names to describe a similar procedure. None of the studies was a randomised controlled trial. One study was a preclinical study describing the technical feasibility of transvaginal NOTES hysterectomy on a female cadaver (9). One study was a case series (10), and two studies were retrospective comparative studies (11,12). Three studies were case series (13-15).

The authors concluded that hysterectomy for the treatment of benign diseases can be feasibly carried out via transvaginal NOTES but prospective studies are needed to determine its full clinical application.

3.1.3 Conclusion:

These preliminary studies demonstrate that VANH is feasible and that it can be used as an alternative for a total laparoscopic hysterectomy. There are no prospective randomised studies to further support the value of a VANH.

3.2 TVNH

3.2.1 Technique

A vNOTES port is inserted into the vagina, and CO_2 is insufflated to create a pneumovagina. An optic is inserted into the pneumovagina. A circular incision is made around the cervix using a monopolar laparoscopic hook, and the Pouch of Douglas is opened using laparoscopic scissors. The vesico-uterine peritoneum is opened using laparoscopic scissors. Both uterosacral ligaments are coagulated using a laparoscopic bipolar grasper and transected. The patient is now placed in the Trendelenburg position and the small intestine is lifted out of the pelvis.

The ureter is identified, but not routinely dissected. It is only dissected if it cannot be identified transperitoneally. The uterine artery and the ovarian artery are coagulated using a bipolar grasper and transected. The meso of the Fallopian tube is coagulated using a bipolar grasper and is transected. In patients requiring an adnexectomy, the infundibulopelvic ligament is coagulated using a bipolar grasper and is transected. Haemostasis is checked and the peritoneal cavity is rinsed. The NOTES port and the uterus are removed trans-vaginally and the pneumoperitoneum is deflated.

The colpotomy is closed using a resorbable suture.

The major difference between TVNH and a VANH lies in the opening of the anterior and posterior peritoneum and the transection of the uterosacral ligaments. This is performed entirely endoscopically in the TVNH, whereas it is performed by classical vaginal surgery in a VANH (Table 2). The TVNH technique can therefore also be used in nulliparous patients, patients without uterine prolapse, and patients with a narrow vagina where classical vaginal surgery can be more challenging (10,16).

3.2.2 Evidence

One case series has been published describing that TVNH for benign uteri being successfully performed in ten patients, using only conventional, reusable laparoscopic instruments and a self-constructed NOTES port (17). The procedures were completed within a reasonable operation time and without major complications, no conversion to laparotomy or standard laparoscopy was necessary. The study demonstrated that this technique can be used in parous and nulliparous women, provided that a different port is constructed to maintain a pneumovagina.

3.2.3 Conclusion:

This case series demonstrates that TVNH is feasible and that it can be used as an alternative for a total laparoscopic hysterectomy, both in parous and nulliparous patients. There are currently no prospective randomised studies to further support the value of a TVNH.

3.3 RVANH

The first case report on transvaginal robotic surgery was presented by Dr Jan Baekelandt at the 7th Annual SERGS Meeting on Robotic Gynaecological Surgery in June 2015 (18). From the first case series of 5 patients, a new technique of Robotic Vaginally Assisted NOTES hysterectomy (RVANH) was published (19).

3.3.1 Technique:

A robotic VANH was performed. The patient was placed in the lithotomy position as for a classical vaginal hysterectomy. The circumcision of the cervix, the opening of the anterior and posterior peritoneum, and the transection of both sacro-uterine ligaments was performed by classical vaginal surgery. A NOTES port was constructed by assembling a surgical glove, a wound protector, 4 Da Vinci 8mm trocars and 1 reusable 5mm trocar. The ring of the wound protector was then inserted transvaginally into the peritoneal cavity to create a pneumoperitoneum. A Da Vinci Xi surgical robot was side docked between the legs of the patient and three arms connected to the trocars in the glove port. The fourth arm was not used. Using a 30° optic, a fenestrated bipolar grasper, and a vessel sealer, the hysterectomy was performed via transvaginal NOTES using the surgical robot. Subsequently a bilateral adnexectomy was performed using the same method. Once the hysterectomy and bilateral adnexectomy were completed, the robot and glove port were removed. When the uterus was too large to extract in toto, it was manually morcellated so that it could be removed vaginally. The colpotomy was closed as in classical vaginal surgery. No abdominal incisions were made.

3.3.2 Evidence:

One case series has been published (19). It describes five case reports demonstrating that vaginal robotic surgery is possible and that it can be used to perform a hysterectomy. RVANH makes use of the advantages of robotic surgery to broaden the indications for vaginal hysterectomy and can help overcome its limitations, while the NOTES approach avoids abdominal wall wounds and trocar related complications. Further developments in robotic

technology will help overcome the problem of robotic arm collision. Robotic hysterectomy via vaginal access is a novel approach that requires further validation. The extra cost and set up time of RVANH will also need to be assessed in comparison to the advantages it provides over a VANH or total laparoscopic hysterectomy.

3.3.3 Conclusion:

This first case series demonstrates that RVANH is feasible and that it can be used as an alternative for a total laparoscopic hysterectomy (19). There are currently no prospective randomised studies to further support the value of a RVANH.

3.4 RTVNH

The first cases of Robotic Total Vaginal NOTES Hysterectomy were performed by Dr Jan Baekelandt in 2015.

3.4.1 Technique:

A NOTES port was constructed by assembling a surgical glove, a wound protector, 3 Da Vinci 8mm trocars and 1 reusable 5mm trocar. The ring of the wound protector was then inserted into the vagina to create a pneumovagina. A Da Vinci Xi surgical robot was side docked between the legs of the patient and three arms were connected to the trocars in the glove port. The fourth arm was not used. Using a 30° optic, a fenestrated bipolar grasper, and monopolar scissors, the hysterectomy was performed via transvaginal NOTES using the surgical robot. The Fallopian tubes were removed with the uterus. When indicated, the ovaries were removed as well. Once the hysterectomy was completed, the robot and glove port were removed. When the uterus was too large to extract in toto, it was manually morcellated so that it could be removed vaginally. The colpotomy was closed as in classical vaginal surgery. No abdominal incisions were made.

3.4.2 Evidence

The first case series comparing 10 RTVNH with 10 RVANH was published in Journal of Gynecologic Surgery(20).

3.4.3 Conclusion:

This first case series demonstrates that Robotic vNOTES Hysterectomy is feasible and that it can be used as an alternative for a total laparoscopic hysterectomy, both in parous and nulliparous patients (20). There are no prospective randomised studies to further support the value of a RVANH or RTVNH.

4. DISCUSSION:

4.1 Current Evidence

According to the Cochrane Database the preferred technique to perform a hysterectomy is via conventional vaginal surgery. When a vaginal hysterectomy is not possible, a laparoscopic hysterectomy may avoid the need for an abdominal hysterectomy (3). Vaginal hysterectomy can be safely performed for large uteri (21) and in nulliparous women (22). The risk of complications however is higher in nulliparous women (22). The accessibility of the vaginal passage, disease confined to the uterus, and the surgeon's experience are the major determining factors for the choice of route for hysterectomies (23). In recent years, the incidence of robotic hysterectomy and laparoscopic hysterectomy has increased, whilst the incidence of vaginal and abdominal hysterectomy has decreased (24). Conventional vaginal hysterectomy can be challenging in cases of enlarged uterus, undescensus, or because of restricted vaginal space in women who have never delivered (10). Making use of the advantages of endoscopic surgery vNOTES hysterectomy broadens the indications for vaginal hysterectomy and helps overcome its limitations, while the NOTES approach avoids abdominal wall wounds and trocar related complications.

When compared to classical vaginal hysterectomy, vNOTES hysterectomy offers good endoscopic visibility to operate, and perform haemostasis. Using the enlarged endoscopic view, the surgeon can operate accurately using endoscopic instruments, whereas in some conditions in conventional vaginal hysterectomy, certain steps can only be achieved by palpation (10). In addition, adnexal procedures in conventional vaginal surgery can be difficult due to limited accessibility in the restricted space (10). Salpingectomy, oophorectomy, ovarian cystectomy, or adhaesiolysis can be performed via the same NOTES approach during a vNOTES Hysterectomy (25,26). Due to the pneumovagina, TVNH and RTVNH can be performed in nulliparous women, whereas a narrow vaginal access can make a classical vaginal hysterectomy more challenging (10,22,23)

It has been demonstrated that very large uteri can be removed via VANH, and that ligating the uterine vessels transvaginally before dissecting the rest of the uterus, results in less blood loss compared to a transabdominal laparoscopic approach, where there is more manipulation before occlusion of the feeding vessels (10,15).

When compared to laparoscopic hysterectomy, vNOTES hysterectomies offer the advantage of no visible scarring. In addition, in patients with previous abdominal surgery, there is no need to perform adhaesiolysis to gain access to the pelvis in order to perform the hysterectomy via vNOTES approach, contrary to a laparoscopic approach.

vNOTES hysterectomy (TVNH and VANH) can provide surgeons with the comfort of operating under good endoscopic vision but via vaginal access without increasing the invasiveness of the procedure by making abdominal incisions. In addition, RTVNH and RVANH offer the extra advantages of robotic surgery including better ergonomics, better camera control and articulated wrist motion. However, these advantages need to be weighed against the longer operating time and higher cost. Further technical innovations in surgical robots will help overcome the problem of robotic arm collision and will therefore reduce the time of surgery.

Failure of VANH is almost always due to impedance of the transvaginal colpotomy (10). When compared to VANH, TVNH enables the surgeon to perform the colpotomy endoscopically instead of via classical vaginal surgery. This provides better visualization and, as in laparoscopic surgery, the CO_2 pressure helps identify and dissect the surgical planes. This enables easy performance of the anterior and posterior colpotomy in patients who had not delivered vaginally and in patients with previous caesarean sections.

Less post-operative pain and a quicker recovery are also potential advantages of vNOTES. The inability, during vNOTES, to overview the pelvic area, in particular the vesico-uterine pouch, is a major limitation that could lead to lesions, such as bladder endometriosis, being missed. Innovation of endoscopes is desirable to overcome this limitation and to have the ability with NOTES to explore the entire abdominal cavity (26).

One could argue the possibility of pelvic infection after vaginal surgery, however none of the patients presented with this complication after TVNH, RVANH or RTVNH procedure. Previous studies have also shown that post-operative pelvic infection is unlikely to happen particularly when prophylactic antibiotics are administered (10, 27). As the vaginal vault is closed in the same way as in a classical vaginal hysterectomy, no differences in incidence of dyspareunia are to be expected. As was the case for our study protocol, sexual abstinence should be

recommended for six to eight weeks, as is the recommendation for conventional transvaginal surgery (10).

A surgeon who wants to perform vNOTES hysterectomy should be confident in both classical vaginal hysterectomy and total laparoscopic hysterectomy (TLH). Being experienced in single incision laparoscopic surgery TLH and vNOTES for adnexal surgery certainly helps to keep the learning curve short. In addition, to perform RVANH and RTVNH, the surgeon also needs to be experienced in robotic surgery as the robotic setup for RVANH and RTVNH is complex. In our experience introduction of NOTES into the hysterectomy armamentarium did not influence the percentage of hysterectomies performed by classical vaginal hysterectomy, but reduced the percentage of TLH in favour of the less invasive NOTES approach.

VANH, TVNH, RVANH and RTVNH are novel approaches that require further validation. Their safety and complication risk have not been compared with laparoscopic hysterectomies in randomised controlled trials. The small case series that have been published indicate that the techniques are feasible in the hands of the few experts that perform these procedures and that they may have the abovementioned advantages over laparoscopic hysterectomies.

4.2 Future evidence:

HALON trial:

The HALON (Hysterectomy by transabdominal Laparoscopy Or NOTES) is the first prospective randomised controlled trial to compare vNOTES hysterectomy with Total Laparoscopic Hysterectomy. The trial is currently underway and the results are expected to be published in 2017.

The study protocol has been registered with the National Institutes of Health and can be found at ClinicalTrials.gov ID:NCT02631837

Brief Summary of the study protocol:

Objective: To compare vNOTES (vaginal Natural Orifice Transluminal Endoscopic Surgery) and established total laparoscopic hysterectomy for successful removal of the uterus for benign gynaecological pathology.
Study design: Randomised controlled/single centre/single-blinded/parallel-group/noninferiority/efficacy trial.

Study population: All women aged 18 to 70 years regardless of parity with a benign indication for hysterectomy.

Randomization: Women will be randomly allocated, immediately before surgery, to undergo one of two techniques for removal of the uterus by using a computer generated randomization list. Stratified randomization will be used according to the estimated uterine size on clinical examination.

Intervention: Women will be treated by a surgeon who is not blinded to the treatment allocation and who is equally skilled in performing both techniques. In the intervention group a vNOTES technique will be used.

Control: In the control group surgery will be done by a classical laparoscopic technique.

Main study parameters/endpoints:

Primary study outcome parameters: successful removal of the womb with the intended approach without conversion to an alternative approach.

Secondary outcomes: the proportion of women discharged the same day, based on their own preference; postoperative pain scores using a VAS (Visual Analogue Scale) measured between days 1 - 7 by the participating women following surgery and the total amount of analgesics used as described in the standardized pain treatment protocol from days 1 - 7; postoperative infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings; per- or postoperative complications according to the Clavien-Dindo classification detected during the first six weeks of surgery; hospital readmission within 6 weeks following surgery; duration of the surgical procedure; incidence and intensity of dyspareunia recorded by the participants at 3 and 6 months by self-reporting using a simple questionnaire and VAS (Visual Analogue Scale); sexual wellbeing recorded by the participants at 3 and 6 months by SSFS (Short Sexual Functioning Scale); direct costs up to 6 weeks after the hysterectomy associated with both procedures.

5. Conclusion

Hysterectomy has traditionally been performed by laparotomy or by conventional vaginal surgery. At the end of the 1980's and during the 1990's the first major paradigm shift occurred with the introduction of the laparoscopic hysterectomy. Hysterectomies could be performed through several small incisions, instead of through one large incision, using a camera that offered superior visualization, and long fine instruments. This less invasive approach allowed

quicker recovery and a cosmetically more appealing result. After a period of scepticism, it has now become commonplace in most gynaecology departments.

According to the pioneers and early adopters, vNOTES hysterectomy is now the next paradigm shift. After a period of research, it has become a realistic alternative for an abdominal and laparoscopic hysterectomy. Besides the obvious aesthetic advantage of not creating any visible scars while maintaining superior endoscopic visualization, other potential advantages include less surgical wound infection, fewer abdominal wall hernias and less abdominal wall pain, all leading to a quicker recovery and shorter hospitalization.

At the moment only observational studies have been published on vNOTES hysterectomy, demonstrating its feasibility and safety in the hands of expert surgeons. There are no results of randomised controlled trials to support the advantages of vNOTES hysterectomy. The results of the HALON trial and other randomised controlled trials need to be awaited to validate the value of vNOTES hysterectomy compared to laparoscopic hysterectomy.

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Table 1. History of Hysterectomy Techniques

Technique	Abbreviation	Year	Surgeon
Vaginal Hysterectomy	VH	1813	Conrad Langenbeck
Abdominal Hysterectomy (Subtotal)	AH	1963	Charles Clay
Laparoscopically Assisted Vaginal Hysterectomy	LAVH	1989	Harry Reich
Total Laparoscopic Hysterectomy	TLH	1993	Harry Reich
Robotic Hysterectomy	RH	2002	Concepcion Diaz-Arrastia
Vaginally Assisted NOTES Hysterectomy	VANH	2012	Chyi-Long Lee
Total Vaginal NOTES Hysterectomy	TVNH	2014	Jan Baekelandt
Robotic Vaginally Assisted NOTES Hysterectomy	RVANH	2015	Jan Baekelandt
Robotic Total Vaginal NOTES Hysterectomy	RTVNH	2015	Jan Baekelandt

Table 2. Overview of vNOTES Hysterectomy Studies

Procedure	Study	N	Population	Comparison
VANH	Chen 2012	8	female to male transsexuals	none
	Lee 2012	10	women with benign uterine disease	none
	Su 2012	16	women with benign uterine disease	none
	Lee 2014	137	women scheduled for laparoscopic hysterectomy	none
	Yang 2014	16	women with benign uterine disease	32 LAVH
	Wang 2015	147	women with benign uterine disease and no genital prolapse	365 LAVH
TVNH	Baekelandt 2015	10	5 nulliparous and 5 parous women	none
	Atallah 2015	1	Female cadaver	none
RVANH	Baekelandt 2015	5	women with myomatous uterus	none
RTVNH	Baekelandt 2016	8	women with myomatous uterus or cervical dysplasia	8 RVANH

Chapter 5

Postoperative outcomes and quality of life following hysterectomy by natural orifice transluminal endoscopic surgery (NOTES) compared to laparoscopy in women with a non-prolapsed uterus and benign gynaecological disease: a systematic review and meta-analysis.

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ABSTRACT

Natural orifice transluminal endoscopic surgery (NOTES) uses the natural orifices of the human body as an access route for performing endoscopic surgery. Since its introduction in 2004 several observational studies have suggested potential benefits including less postoperative pain, a shorter length of hospital stay and less complications.

This systematic review aims to critically appraise comparative studies that have evaluated the effectiveness and harms of NOTES for hysterectomy in women with a non-prolapsed uterus and benign gynaecological disease compared to classical laparoscopy.

Two authors searched independently in MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) for randomised controlled trials (RCTs), controlled (non-randomised) clinical trials (CCTs) and prospective/ retrospective cohort studies comparing NOTES with laparoscopy assisted vaginal hysterectomy (LAVH) or total laparoscopic hysterectomy (TLH) in the adult female population bound to undergo hysterectomy of a non-prolapsed uterus for benign gynaecological disease. Two authors selected studies, extracted data and assessed the risk of bias of the included studies independently. Any disagreement was resolved by discussion or arbitration.

We did not find RCTs but retrieved two retrospective cohort studies comparing NOTES with LAVH. The overall study quality assessed by the Newcastle-Ottawa scale was acceptable. Both studies reported no conversions to conventional laparoscopy or laparotomy. The operative time in women treated by NOTES was significantly shorter compared to LAVH: the mean difference was -22.04 minutes (95% CI -28.00 minutes to -16.08 minutes; participants = 342; studies = 2). There were no statistically significant differences for the intra- or postoperative complications in women treated by NOTES compared to LAVH: the RR was 0.57 (95% CI 0.17 to 1.91; participants = 342; studies = 2). The length of hospital stay was significantly shorter in women treated by NOTES compared to LAVH: the mean difference (MD) was -0.42 days (95% CI -0.59 days to -0.25 days; participants = 342; studies = 2). There were no statistically significant differences for the median VAS scores (ranges) at 12 hours between the women treated by NOTES (median 2, range 0 to 6) and the women treated by LAVH (median 2, range 0 to 6) (1 study, 48 participants). There were no statistically significant differences in the median additional analgesic dose request (range) in the women treated by NOTES (median 0, range 0 to 6) and women treated by LAVH (median 1, range 0 to 5) (1 study, 48 participants). According to one study the hospital charges in women treated by NOTES were significantly higher compared to LAVH: the mean difference was 137.00 € (95% CI 88.95 € to 185.05 €; participants = 294; studies = 1). Neither of the studies reported data on postoperative infection, dyspareunia, sexual wellbeing or quality of life. In conclusion, the body of evidence on the effectiveness of NOTES compared to conventional

laparoscopic hysterectomy is very limited. At the present NOTES should be considered as a new technique under evaluation for use in gynaecological surgery. Randomised controlled trials are needed to demonstrate its effectiveness.

INTRODUCTION

Rationale

Natural orifice transluminal endoscopic surgery (NOTES) uses the natural orifices of the human body as an access route to the abdominal cavity for performing surgery. Its first application was described in 2004 in the porcine model by researchers at the Johns Hopkins University (3). The feasibility of NOTES by gastroscopy has been demonstrated for performing appendectomy (4) or cholecystectomy (5). Several observational studies have reported less postoperative pain, a shorter length of hospital stay, less complications and improved cosmetic results (6). The majority of NOTES procedures in women have used the vagina as the access route (7). Colpotomy has been used widely for surgical procedures involving extraction of large specimens: it has been reported as a safe access (8, 9). Hysterectomy using a transvaginal NOTES approach was first described in the human by Su et al. in 2012 (10). Our group published on our own experience with transvaginal NOTES for doing hysterectomy in 2015 (11).

Objectives

To assess the efficacy/effectiveness and safety of NOTES for hysterectomy in women with a non-prolapsed uterus and benign gynaecological disease compared to the conventional laparoscopic technique.

We aim to answer the following questions:

1. Is NOTES equally effective compared to the laparoscopic approach for successfully removing the uterus without the need for conversion?

2. Is the removal of the uterus by NOTES faster compared to laparoscopy?

3. Does NOTES cause more complications, e. g. infection or other surgical adverse events compared to conventional laparoscopy?

4. What is the length of hospital stay in women treated by NOTES compared to laparoscopy?

5. What is the rate of hospital readmission after discharge in women treated by NOTES versus laparoscopy?

6. Do women treated by NOTES suffer less pain compared to women treated by laparoscopy in the postoperative period?

7. How is women's health after NOTES compared to laparoscopy concerning dyspareunia, sexual wellbeing or health-related quality of life?

8. What are the comparative economic costs of both techniques?

METHODS

Eligibility criteria

We selected studies according to the following criteria.

Study design, setting and language

We aimed to retrieve randomised controlled trials (RCTs), controlled (non-randomised) clinical trials (CCTs) and prospective/ retrospective cohort studies in human subjects. We excluded all other types of study designs that did not allow a direct comparison of NOTES to laparoscopy, e.g. case series, case reports and letters to the editor. We used no restrictions by type of setting. Our search was limited to the English/French/German/Dutch language but we aimed to include publications in any other language that could easily be translated using Google translate.

Participants

We included studies examining the target adult female population (aged 18 to 70 years) bound to undergo surgical removal of a non-prolapsed uterus for benign gynaecological disease. We excluded genital prolapse or gynaecological malignancy.

Interventions

Hysterectomy using the NOTES technique was the intervention of interest. We excluded abdominal or vaginal hysterectomy as the experimental intervention. Studies on single incision laparoscopic surgery (SILS) by the umbilicus were excluded as the experimental (but not control) intervention.

Comparators

Laparoscopy assisted vaginal hysterectomy (LAVH) or total laparoscopic hysterectomy (TLH) using the umbilicus as the primary entry site using single (SILS) or multiple ports (MP) was the comparator of interest. We excluded abdominal hysterectomy or vaginal hysterectomy as comparators. We used the definitions for the different types of hysterectomy as outlined in a recent Cochrane review (12).

Outcomes

Primary outcome

The proportion of women successfully treated by removing the uterus by the intended approach without conversion to any other technique of hysterectomy.

Secondary outcomes

Secondary outcomes were as follows: 1. The duration of surgery in minutes; 2. Intra- or postoperative complications using the Clavien-Dindo classification (13) and postoperative infection, defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings; 3. The proportion of women hospitalized after surgery; 4. Readmission to hospital after discharge; 5. Postoperative pain scores measured using a visual analogue scale (VAS) and by the total consumption of analgesics; 6. Incidence and magnitude of dyspareunia measured by a short questionnaire and VAS scale, sexual wellbeing measured using a disease specific validated tool (e.g. SSFS or Short Sexual Functioning Scale) and quality of life, measured using a generic validated tool (e.g. EQ-5D-3L); 7. Comparative economic costs.

Search strategy

We developed a literature search strategy by combining medical subject headings (MeSH, Emtree) and/or free text words, supported by a Health Sciences librarian at the 2 Bergen Biomedical Library of the KU Leuven. The MEDLINE search strategy is presented in Appendix 1.

Two reviewers (JJAB and JB) independently searched MEDLINE (PubMed interface from 1950 until 3 April 2016), EMBASE (Embase.com interface from 1974 until 3 April 2016) and the Cochrane Central Register of Controlled Trials (Wiley interface, Issue 4 of 12, April 2016).

We also searched the following additional sources of information: trial protocols in ClinicalTrials.gov (https://clinicaltrials.gov/) and the WHO ICTRP search portal (http://apps.who.int/trialsearch/), Web of Science (interface Thomson Reuters), the Centre for Reviews and Dissemination (http://www.crd.york.ac.uk/CRDWeb/), LILACS (http://lilacs.bvsalud.org/en/) and Open Grey (http://www.opengrey.eu/). To ensure literature saturation we hand-searched the journal

Gynaecological Surgery via Science Direct and the Journal of Minimally Invasive Gynaecology via ProQuest Central. We cross-checked the reference lists of the included studies.

Study records

Data management

We uploaded the search results to EndNote Web (https://www.myendnoteweb.com/) to remove duplicates.

Selection process

Two reviewers (JJAB and JB) independently screened the titles and abstracts yielded by the search against the inclusion criteria. We aimed to obtain full text reports for all those titles that appeared to meet the inclusion criteria or in case of uncertainty. The two reviewers then screened the full text reports and decided if these met the inclusion criteria. We asked additional information from study authors whenever necessary. We resolved any disagreement through discussion and sought arbitration by a third reviewer (SW) if needed. Neither of the review authors was blinded to the journal titles or to the study authors or institutions, following the guidance by the Cochrane Handbook (14).

Data collection process

Two reviewers (JJAB and JB) extracted data from each eligible study independently using standardized data extraction forms. Data extracted included demographic information, study design, characteristics and data of patients, interventions, comparators, length of follow-up and outcomes. Reviewers aimed to resolve disagreement by discussion and by seeking arbitration by a third reviewer (SW) when needed to adjudicate unresolved disagreements. We contacted study authors to resolve any uncertainties.

Risk of bias in individual studies

To assess the risk of bias for each included RCT, we aimed to collect information using the Cochrane Collaboration tool (15). We used the Newcastle-Ottawa scale (NOS) for assessing the risk of bias in observational studies. The risk of bias assessment was done by two authors independently (JJAB and JB). We resolved any disagreement by discussion and when needed by consulting a third review author (SW) for arbitration.

Data synthesis

Measures of treatment effect

We reported dichotomous data by using risk ratio (RR) with 95% confidence interval (CI): the RR is more intuitive than the more mathematically stable odds ratio (OR). We analysed ordinal outcomes as continuous outcomes. Continuous outcomes were analysed using mean differences (MD) with 95% CI or weighted standardised mean differences (SMD) with 95% CI if different measurement scales were used.

Unit of analysis issues

The primary unit of analysis was per individual woman randomised/treated.

Dealing with missing data

We aimed to use data analysed on an intention-to-treat basis (ITT) when reported by the authors of the primary studies. When data on the summary statistics were missing, we attempted to contact the original authors of the study to obtain the relevant missing data. When data on the outcomes of individual patients were missing, we reported the available data analyses rather than doing an ITT analysis or do imputation of missing outcome data tested by sensitivity analyses.

Assessment of heterogeneity

We tested the clinical diversity across all included studies by considering the variability in participant factors (for example age or BMI) and study factors (allocation concealment, blinding of outcome assessment, loss to follow-up, treatment type, co-interventions, etc.). We aimed to test for statistical heterogeneity using the Chi^2 test when enough studies could be included.

Data synthesis

We performed meta-analysis if the included studies were sufficiently homogenous in terms of design, setting, population, intervention and comparator. We combined each outcome and calculated a summary effect size using the statistical software Review Manager 5 according to guidance from the Cochrane Handbook (16). The Mantel-Haenszel method (M-H) for the fixed-effect model for dichotomous outcomes and the Inverse Variance method (IV) for the fixed-effect model for continuous outcomes were used. Due to the limited number of studies included no subgroup analyses or sensitivity analyses were done.

Meta-biases

Publication bias, reporting bias and within-study reporting bias are difficult to detect and correct for. We aimed to search for eligible studies as comprehensively as possible and by being alert in identifying duplicated reports of trials.

Confidence in cumulative evidence

We aimed to grade the quality of the evidence using GRADEPRO GDT software (version 3.2.2.20090501) (http://ims.cochrane.org/gradepro) for the primary outcome only if enough studies were retrieved.

RESULTS

Results of the search

We retrieved 302 records through searching in MEDLINE, EMBASE, and CENTRAL. We found 924 additional records by the supplementary search described above. After removing duplicates we screened 414 records for titles and abstracts. After excluding 292 records that were clearly not relevant, we assessed 122 full-text articles for possible eligibility. We excluded 120 records. Finally two studies were included for the present systematic review and meta-analysis (17, 18). We refer to Figure 1 for the PRISMA flow diagram.

Description of studies

We refer to Table 1 for the characteristics of the included studies (Table 1).

We retrieved no RCTs.

The study by Wang et al (17) is a retrospective cohort study conducted in 2015 in Chang Gung Memorial Hospital at Linkou, Taiwan. The study group consisted of 147 women aged 38 to 69 years with different indications scheduled to undergo transvaginal NOTES hysterectomy between April 2011 and October 2013. The comparison group consisted of 365 women receiving LAVH. All surgical procedures were done by the same surgeon. The authors used a propensity score matched analysis: the sample of 147 NOTES cases was compared with a similar number of LAVH treated women group using a ‘‘nearest neighbour’’ approach. The following outcomes were studied: the operative time, the estimated blood loss, complications, the length of postoperative hospital stay and the hospital charges.

The study by Yang et al (18) is a retrospective cohort study conducted in 2014 in Eulji University Hospital at Doonsandong Daejeon, South Korea. The study group consisted of 16 women undergoing hysterectomy by transvaginal NOTES between July 2012 and June 2013. The comparison group consisted of 32 women undergoing hysterectomy by single port LAVH during the same study period and who were matched by age, body mass index (BMI), parity, number of previous abdominal surgeries, and weight of uterus. All procedures were done by the same surgeon. The following outcomes were measured: the operative time, the estimated blood loss, complications, the length of postoperative hospital stay, the decrease in haemoglobin on postoperative day 1 and the total amount of analgesic drugs used.

Risk of bias in included studies

We used the Newcastle-Ottawa Scale for assessing the risk of bias of the two included observational (17, 18). We refer to Table 2.

Effects of interventions

1. Is the NOTES technique equally effective compared to the laparoscopic approach for successfully removing a uterus without the need for conversion to any alternative approach?

A pooled analysis of the two (17, 18) demonstrated no conversions to conventional laparoscopy or laparotomy neither in the NOTES group (N = 163) nor the LAVH group (N = 179). A summary effect size is not estimable.

2. Is the removal of a uterus by NOTES faster compared to laparoscopy?

According to a pooled analysis of the two included studies (17, 18) NOTES is significantly faster compared to LAVH: the mean difference was -22.04 minutes (95% CI -28.00 to -16.08; participants = 342; studies = 2). We refer to Figure 2.

3. Does NOTES cause more pelvic infection or other surgical complications compared to the use of the laparoscopic approach?

None of the included studies reported postoperative infection. One study (18) reported no cases of febrile complication in both comparison groups. The second study (17) demonstrated no statistically significant differences in postoperative fever in the women treated by NOTES (2/147) compared to women treated by LAVH (10/365): the risk ratio was 0.50 (95% CI 0.11 to 2.24, 1 study, P = 0.36). There were no statistically significant differences for intra- or postoperative complications in women treated

by NOTES compared to women treated by LAVH according to a pooled analysis of the two studies (17, 18): the RR was 0.57 (95% CI 0.17 to 1.91; participants = 342; studies = 2). We refer to Figure 3.

4. Are women treated by NOTES less frequently hospitalized when admitted to the day care unit compared to treatment by laparoscopy?

All women were hospitalized. Women treated by NOTES had a significantly shorter length of hospital stay compared to LAVH according to the statistical pooling of two studies (17, 18): the mean difference (MD) was -0.42 days (95% CI -0.59 days to -0.25 days; participants = 342; studies = 2). We refer to Figure 4. We have used the instructions of the Cochrane handbook (13) to convert data reported by median and ranges for the length of hospital stay from one study (18) to mean and standard deviations. The median can be used as the best estimation for the mean for an unknown distribution with a sample size n where $25<n\leq70$ (19). The best estimate of the standard deviation under these conditions is one quarter of the typical range of data values (19). The Cochrane Handbook points out that this method of converting ranges is not robust and therefore recommends that it should not be used (13). The data from this pooled analysis should therefore be interpreted with great caution.

5. Does the use of NOTES result in more hospital readmissions compared to laparoscopy?

One study (18) reported no readmissions to hospital for major complications in either of the two comparison groups.

6. Do women treated by NOTES suffer less pain compared to women treated by laparoscopy in the postoperative period?

One study reported on postoperative pain scores measured by a VAS at 12 and 24 hours after surgery (18). There were no statistically significant differences for the median VAS scores (ranges) at 12 hours between the women treated by NOTES (median 2, range 0 to 6) and the women treated by LAVH (median 2, range 0 to 6). For the VAS scores measured at 24 hours the differences between the women treated by NOTES (median 0, range 0 to 4) and the women treated by LAVH (median 0.5, range 0 to 8) were not statistically significant. The same study (18) also measured the total requests for other parenteral analgesics than those administered according to the standardized pain protocol of the study during the postoperative hospitalization period. There were no statistically significant differences in the median additional analgesic dose request (range) in the women treated by NOTES (median 0, range 0 to 6) and women treated by LAVH (median 1, range 0 to 5).

7. Does the use of NOTES cause more women to report dyspareunia, less sexual wellbeing or any decrease in quality of life in the longer term when compared to women treated by laparoscopy?

None of the included studies have reported data on these outcomes.

8. What are the comparative economic costs of both techniques?

One study (17) reports significantly higher costs for hospital charges in women treated by NOTES compared to LAVH: the mean difference was 137.00 € (95% CI 88.95 € to 185.05 €; participants = 294; studies = 1). We converted the costs for the hospital charges from New Taiwanese Dollar (NTD) to Euro (€) based on the current exchange rate (1 NTD = 0.0283 €). We refer to Figure 5.

DISCUSSION

Summary of main results

Our search for intervention studies on the effectiveness of NOTES compared to the conventional laparoscopic approach for hysterectomy in women with benign gynaecological disease and absent prolapse did not retrieve randomised controlled trials. We retrieved two retrospective cohort studies of acceptable quality. There was no substantial clinical diversity in study design, setting, population, intervention, comparison and outcomes. We judged that statistical pooling of the two included studies was appropriate.

There were no conversions to conventional laparoscopy or laparotomy in either of the two studies. NOTES is significantly shorter in duration compared to LAVH. There were no statistically significant differences for intra- or postoperative complications in women treated by NOTES compared to LAVH. One study (18) reported no readmissions to hospital for major complications after discharge. There were no data on the incidence of postoperative infection. NOTES has a shorter length of hospital stay compared to LAVH but this conclusion should be interpreted with caution. There were no statistically significant differences neither for the median VAS scores measured at 12 or 24 hours in women treated by NOTES compared to women treated by LAVH nor in the median analgesic dose request. We found no data on the incidence or intensity of dyspareunia, sexual wellbeing or quality of life following surgery. One study reported significantly higher costs for hospital charges in women treated by NOTES compared to LAVH associated with the use of more costly disposable devices in the NOTES group.

Overall completeness and applicability of evidence

The available evidence is not sufficient to answer all 8 research questions posed in the objectives section. Important outcomes highly relevant for women e.g. quality of life, sexual wellbeing and incidence or intensity of dyspareunia after surgery were not reported.

We agree with Yang et al (18) that NOTES has not become a standard surgical technique in gynaecological surgery. Our search retrieved only two comparative studies performed in tertiary centres with a high proficiency for doing this advanced surgery.

Quality of the evidence

The quality of the available evidence assessed by the Newcastle Ottawa Scale is acceptable.

Potential biases in the review process

Despite doing a comprehensive search for all possible eligible studies we cannot exclude publication or reporting bias.

Agreements and disagreements with other studies or reviews

The conclusion of this SR that more research is needed to determine the full clinical application of the new technique is in agreement with a small non-comparative study including 16 women treated by transvaginal NOTES at a tertiary referral medical centre in Taiwan (10).

The shorter operative time and the shorter length of hospital stay in favour of the NOTES technique are in disagreement with the findings of a systematic review (20) comparing single incision laparoscopic hysterectomy with conventional laparoscopic hysterectomy: a pooled analysis of the data of five RCTs demonstrated no statistically significant differences neither for the mean operative time nor for the length of hospital stay (20). For the outcome postoperative pain, the findings of the systematic review (20) are in agreement with our findings.

AUTHORS' CONCLUSIONS

Implications for practice

Transvaginal NOTES should at the present be considered as a new technique under evaluation. More research is needed: we refer to the guidance of the IDEAL Collaboration on the implementation of innovative surgical techniques (21, 22, 23).

Implications for research

More research is needed: our group presently conducts a non-inferiority pilot RCT comparing hysterectomy by transvaginal NOTES with total laparoscopic hysterectomy in women with a non-

prolapsed uterus and benign gynaecological disease. The protocol of the HALON trial has been registered as NCT02631837 and is available as an open access paper for comments and criticisms (24).

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Appendix 1: MEDLINE strategy

* MEDLINE (PubMed interface)

(((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh]) ())) AND ((((("Hysterectomy"[Mesh]) OR hysterectomy)) AND ((((((((((VANH) OR VAMIS) OR TVNH) OR glove port) OR single port) OR single-port laparoscopy) OR single incision laparoscopic surgery) OR SILS) OR Natural orifice transluminal endoscopic surgery) OR "Natural Orifice Endoscopic Surgery"[Majr]) OR NOTES OR laparo-endoscopic single site))

Figure 1: PRISMA 2009 Flow Diagram NOTES versus laparoscopy for hysterectomy

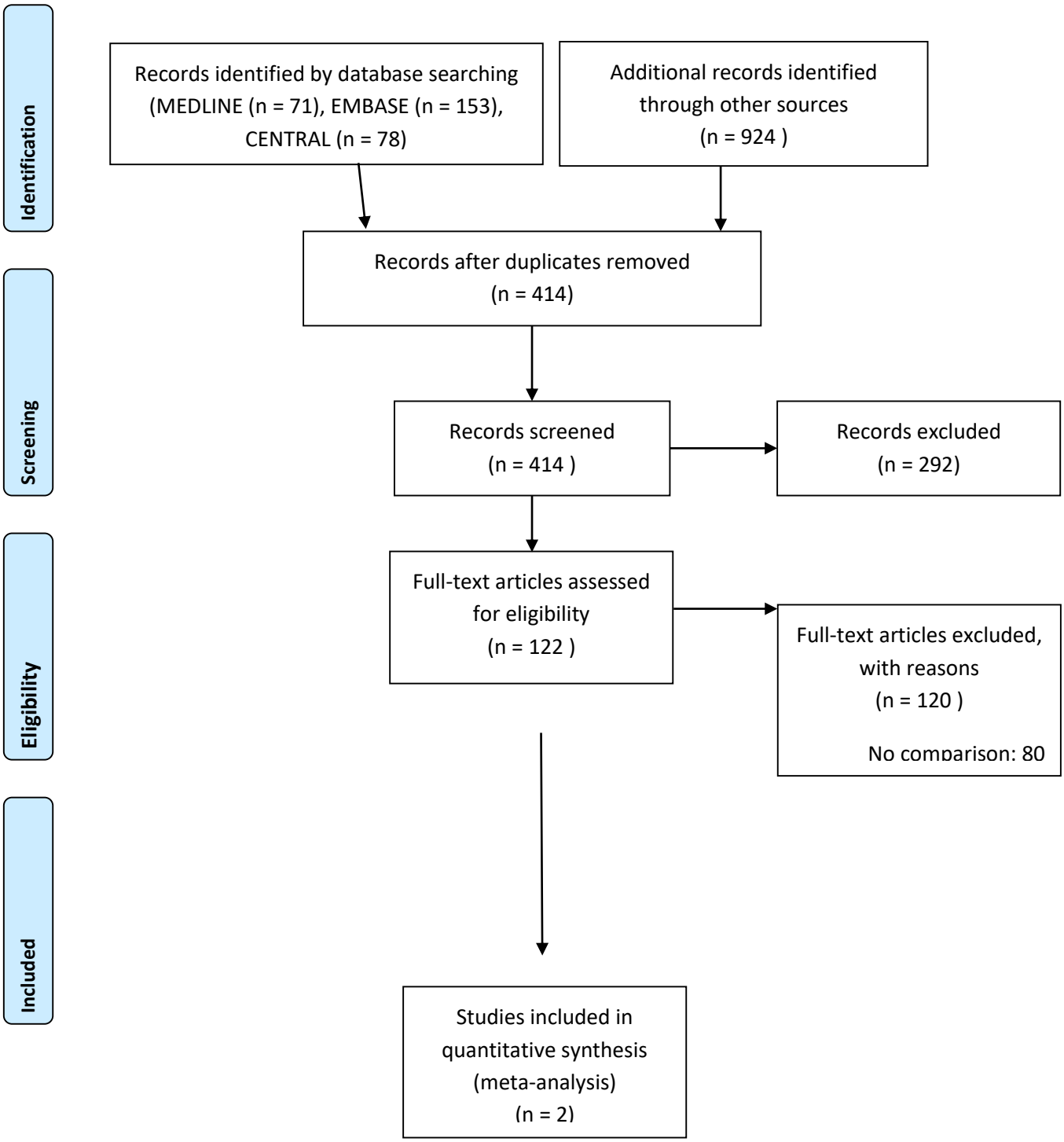


Table 1: Characteristics of the included studies

Item	Yang 2014	Wang 2015
Study design	Retrospective chart analysis (Canadian Task Force Classification II-1)	Retrospective chart analysis (Canadian Task Force Classification II-1)
Study setting	Single centre university affiliated hospital, South Korea	Single centre tertiary referral hospital, Taiwan
Population	**Source population**: Women undergoing hysterectomy for benign uterine diseases	**Source population**: Women undergoing hysterectomy for benign uterine diseases in a non-prolapsed uterus
	Inclusion criteria: Women with benign uterine disease documented by results from ultrasound examinations and who fulfilled the inclusion criteria, which included no history of pelvic inflammatory disease or medical illness.	**Inclusion criteria:** The indications for surgery in these women included uterine myomas, adenomyosis, severe cervical dysplasia, and menometrorrhagia.
	Exclusion criteria: Women who had a history of severe adhesions, suspected severe endometriosis, suspicion of gynaecologic malignancy, or a fixed uterus and strong pelvic adhesions noted at pelvic examination were excluded.	**Exclusion criteria:** Women with a history of abdominal–pelvic surgery with adhesion formation suspected, uterine prolapsed (international continence society classification Stage III or IV), suspected severe endometriosis, and complete obliteration of the posterior Douglas pouch noted at pelvic examination. A history of caesarean section and nulliparity were not considered as contraindications for tVNOTEH.
	Intervention group: n = 16 Mean age (SD): 47.3 ± 4.6 years Mean BMI (SD): 23.8 ± 2.3 Uterine weight (SD): 299 ±186 g Median parity (range): 2 (0-3) N prior surgery (%): 7 (43.8%) PID: exclusion criterion.	**Intervention group**: n = 147 Mean age (SD): 46.1 ± 4.7 years Mean BMI (SD): 24.5 ± 3.8 Uterine weight (SD): 397 ± 182 g Median parity (range): no data Prior abdominal surgery: no data PID: no data available
	Control group: n = 32 Mean age (SD): 45.8 ± 5.4 years Mean BMI (SD): 23.9 6 3.7 Uterine weight (SD): 293 ± 136 g Median parity (range): 2 (0-4) N prior surgery (%): 11 (34.4%) PID: exclusion criterion.	**Control group**: n = 365 Mean age (SD): 45.9 ± 4.7 years Mean BM (SD): 24.7 ± 3.9 Uterine weight: 480 ± 306 g Median parity (range):no data Prior abdominal surgery: no data PID: no data available

Intervention	**NAVH: NOTES- assisted vaginal hysterectomy** **Technique**: All procedures of this study in both comparison groups were performed by the same surgeon. The vaginal approach was performed up to the disconnection of the uterine artery and trachelectomy as a transvaginal volume reduction technique. Anterior and posterior colpotomies were completed. After clearing all of the pedicles, the detached uterus was removed vaginally. A combined bisection, morcellation, coring, and/or myomectomy was required transvaginally in all uteruses ≥ 500 g and in some instances in uteruses < 500 g to facilitate delivery of the uterus through the vagina. **Instrumentation**: NAVH using a novel homemade NOTES system comprised a glove-wound retractor NOTES port. The remaining lateral connections of the uterus containing the upper branches of the uterine vessels, the broad ligaments, and the round ligaments were secured and divided step by step using the LigaSure or monopolar electrode. **Mean duration of surgery (SD)**: 70.6 ± 12.8 minutes. **Type and dosage of antibiotics**: not reported. **Type and dosage of analgesics**: IV patient-controlled analgesia with fentanyl (total dose of 20 mg/kg).	**t-VNOTEH: Transvaginal natural orifice transluminal endoscopic hysterectomy** **Technique**: All procedures of this study in both comparison groups were performed by the same surgeon. Anterior and posterior colpotomies were created by using traditional vaginal surgical techniques. The colpotomy incisions were extended laterally by digital pressure. Two long Heaney retractors were placed into the anterior and posterior cul-de-sac to elevate urinary bladder and depress the rectum, respectively. The cardino-uterosacral ligament complexes were well exposed and then cut and sutured with 1–0 polyglycolic acid suture. The parametrium was then dissected along the uterus to the level of the uterine artery with the same manner. A wound retractor (Alexis, Small; Applied Medical Resources Corp., Rancho Santa Margarita, CA) was then inserted transvaginally. A surgical glove was attached to the outer ring of the wound retractor. Two 10-mm and one 5-mm sheaths were inserted through cut edges of the thumb, the middle and the little finger tips, respectively, and tied with elastic bandage to prevent desufflation of pneumoperitoneum. Once the single-port device placement was completed, a 0 degree 10-mm laparoscope attached with a video camera and conventional rigid straight laparoscopic instruments were inserted and the procedures began. **Instrumentation**: The energy source was a 5-mm LigaSure vessel sealer (Covidien, Mansfield, MA) designed for laparoscopy. Use of disposable Alexis wound retractor.

	Fentanyl infusion involved an automatic, continuous infusion of 0.1 mg/kg/h (total regimen of 100 mL) of fentanyl and a 0.1-mg/kg bolus with a lockout interval of 15 minutes when self-administered. After a soft diet loxoprofen 60 mg was administered 3 times daily as the primary analgesic medication if there was no demand for other analgesics from the patient. In addition, the postoperative use of other parenteral analgesics (Dicknol prescribed as 90-mg IM injection) was administered when the patients requested. **Follow up in hospital ward**: mean length of stay (range): 3.5 (3–5) days. **Nursing protocol**: not reported	**Mean duration of surgery (SD and range):** 76.7 ± 25.0 (35–180) minutes. **Type and dosage of antibiotics**: IV cephalothin 1 g as prophylaxis. **Type and dosage of analgesics**: not reported. **Follow up in hospital ward**: mean length of stay (SD and range): 2.1 ± 0.5 (1–4) days. **Nursing protocol**: not reported.
Comparison	**SP-LAVH: Single port laparoscopy-assisted vaginal hysterectomy** **Technique**: All procedures of this study in both comparison groups were performed by the same surgeon. All the surgical procedures were performed as a standard LAVH technique. A combined bisection, wedge resection, morcellation, coring, and/or myomectomy was required transvaginally in all uteruses ≥ 500 g and in some instances in uteruses < 500 g to facilitate delivery of the uterus through the vagina in SP-LAVH. **Instrumentation**: To prepare the umbilical glove port, the Alexis wound retractor was inserted trans-umbilically, and the outer rim was draped with a surgical glove. **Mean duration of surgery (SD):** 93.2 ± 21.4 minutes. **Type and dosage of antibiotics**: not reported.	**Laparoscopically assisted vaginal hysterectomy (LAVH)** **Technique:** All procedures of this study in both comparison groups were performed by the same surgeon. The patient was placed in the lithotomy Trendelenburg position with both legs protected by elastic bandages, and a Foley catheter was inserted for constant urinary drainage. Laparoscopic examination of the pelvis and lower abdomen was performed first to determine accessibility of the surgical field, and spaces between the rectum and cervix, and parametrium and ureter. Three or four trocars were used according to complexity of surgery. A disposable laparoscopic grasper, scissors, and suction-irrigator were used to perform various procedures such as holding, cutting, exploring, and dissecting. **Instrumentation:** A bipolar forceps with an electrosurgical bipolar unit (Elmed, Addison, IL) or a 5-mm LigaSure vessel sealer (Covidien, Mansfield, MA) was applied to complete haemostasis and desiccation.

	Type and dosage of analgesics: IV patient-controlled analgesia with fentanyl (total dose of 20 mg/kg). Fentanyl infusion involved an automatic, continuous infusion of 0.1 mg/kg/h (total regimen of 100 mL) of fentanyl and a 0.1-mg/kg bolus with a lockout interval of 15 minutes when self-administered. After a soft diet loxoprofen 60 mg was administered 3 times daily as the primary analgesic medication if there was no demand for other analgesics from the patient. In addition, the postoperative use of other parenteral analgesics (Dicknol prescribed as 90-mg IM injection) was administered when the patients requested. **Follow up in hospital ward**: mean length of stay (range): 4 (3–6) days. **Nursing protocol**: not reported.	**Mean duration of surgery (SD and range):** 98.4 ± 39.5 (35–260) minutes. **Type and dosage of antibiotics:** IV cephalothin 1 g as prophylaxis. **Type and dosage of analgesics:** not reported. **Follow up in hospital ward**: mean length of stay (SD and range): 2.1 ± 0.5 (1–4) days. **Nursing protocol:** not reported.
Outcomes	1. Operative time measured in minutes-no definition of beginning and end of procedure. 2. Estimated blood loss measured in mL-no clarification on the method of estimation or time point measured. 3. Intra- and postoperative complications-classification system not reported and time point of measurement not reported. 4. Length of postoperative hospital stay measured in days. 5. Conversion to conventional laparoscopy, measured at the time of the intervention. 6. Blood transfusion-time point of measurement no reported. * Decrease in haemoglobin measured on postoperative day 1	1. Operative time measured in minutes-no definition of beginning and end of procedure. 2. Estimated blood loss measured in mL-no clarification on the method of estimation or time point measured. 3. Intra- and postoperative complications-classification system not reported and time point of measurement not reported. 4. Length of postoperative hospital stay measured in days. 5. Conversion to conventional laparotomy, measured at the time of the intervention. 6. Blood transfusion-time point of measurement no reported.

	* Amount of analgesic drugs used- time point of measurement not reported. * Febrile complication- time point of measurement no reported. * Analgesic dose request- time point of measurement no reported. * Postoperative pain score measured by VAS scale at 12 and 24 hours. The study does not report who assessed the outcomes and if blinding was used.	* Hospital charges measured in New Taiwan Dollars- time point of measurement not reported. The study does not report who assessed the outcomes and if blinding was used.
Statistical power analysis	Done.	Not done.
Completeness of data	Yes: 100% complete.	Yes: 100% complete.
Adjustment for confounding	Yes	Yes

Table 2: Overall study quality using the Newcastle-Ottawa Scale

Study ID	Selection	Comparability	Outcome
Yang 2014	★★★★	★★	★★
Wang 2015	★★★★	★★	★★

Figure 2: Forest plot of comparison: NOTES versus LAVH, outcome: Operative time.

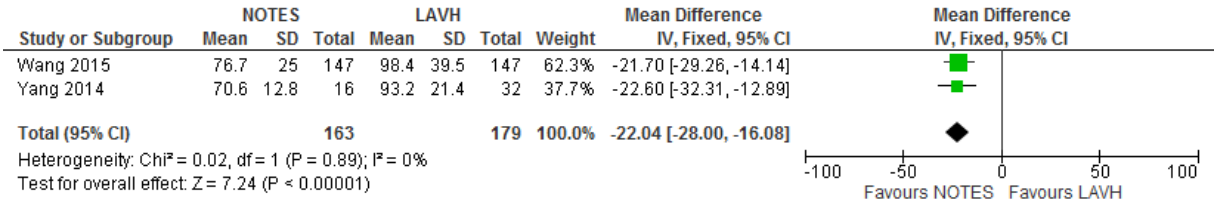


Figure 3: Forest plot of comparison: NOTES versus LAVH, outcome: Intra- or postoperative complications.

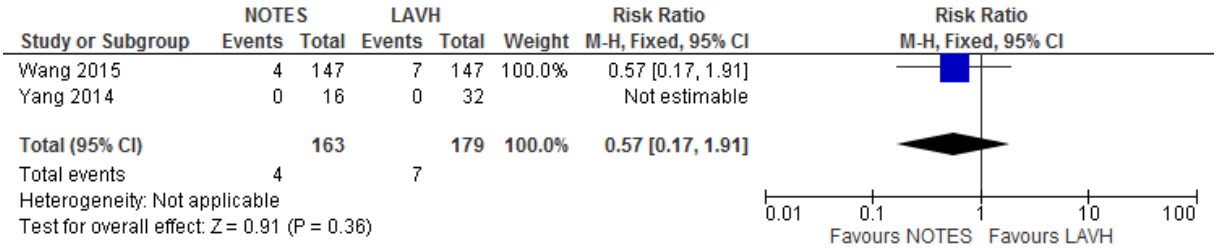


Figure 4: Forest plot of comparison: NOTES versus LAVH, outcome: Length of postoperative hospital stay.

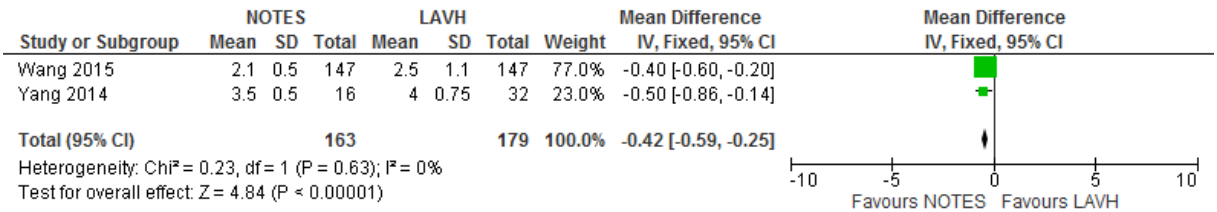
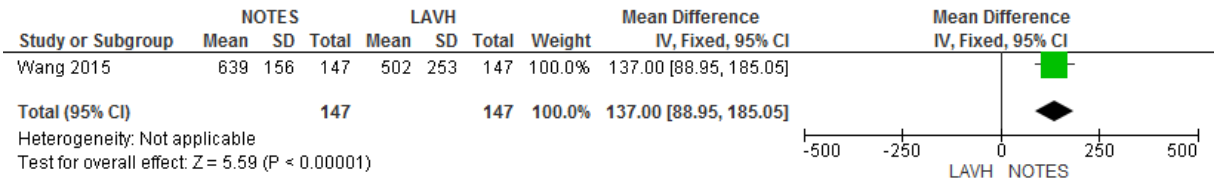


Figure 5: Forest plot of comparison: NOTES versus LAVH, outcome: Comparative hospital costs in Euro.



Chapter 6

6.1 HALON – hysterectomy by transabdominal laparoscopy or natural orifice transluminal endoscopic surgery: a randomised controlled trial (study protocol)

Jan Baekelandt, Peter De Mulder, Ilse Le Roy, Chantal Mathieu, Annouschka Laenen, Paul Enzlin, Steven Weyers, Ben WJ Mol, Jan Bosteels

BMJ Open 2016;6(8):e011546. DOI: 10.1136/bmjopen-2016-011546.

6.2 Hysterectomy by Transvaginal Natural Orifice Transluminal Endoscopic Surgery versus laparoscopy as a day-care procedure; a randomised controlled trial

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6.1 HALON – Hysterectomy by transabdominal laparoscopy or natural orifice transluminal endoscopic surgery: a randomised controlled trial (study protocol)

ABSTRACT

Introduction: Natural Orifice Transluminal Endoscopic Surgery (NOTES) uses natural body orifices to access the cavities of the human body to perform surgery. NOTES limits the magnitude of surgical trauma and has the potential to reduce postoperative pain. This is the first randomised study in women with a non-prolapsed uterus bound to undergo hysterectomy for benign gynaecological disease comparing NOTES with classical laparoscopy.

Methods and analysis: All women aged 18- 70 years, regardless of parity, consulting at our practice with a non-prolapsed uterus and an indication for hysterectomy due to benign gynaecological disease will be eligible. After stratification according to uterine size on clinical examination, participants will be randomised to be treated by laparoscopy or by transvaginal NOTES. Participants will be evaluated on day 0, days 1 to 7, and at 3 and 6 months. The following data will be collected: the proportion of women successfully treated by removing the uterus by the intended approach as randomised; the proportion of women admitted to the in- patient hospital for at least one night observation; postoperative pain scores measured twice daily by the women from day 1-7; the total amount of analgesics used from day 1-7; readmission during the first six weeks; presence and intensity of dyspareunia and sexual wellbeing at baseline, 3 and 6 months (SSFS scale); duration of surgery; postoperative infection or other surgical complications; direct and indirect costs incurred up to 6 weeks following surgery. The primary outcome will be the proportion of women successfully treated by the intended technique; all other outcomes are secondary.

Ethics and dissemination: The study was approved on December, 1st 2015 by the Ethics Committee of the Imelda Hospital, Bonheiden, Belgium. The first patient was randomised on 17 December 2015. The last participant randomised should be included and treated before 30 November 2017. The results will be presented in peer- reviewed journals and at scientific meetings within 4 years after starting recruitment.

Trial registration number: NCT02631837

Chapter 6

INTRODUCTION

Background

The evolution from traditional open surgery to laparoscopic surgery has led to a reduction in surgical morbidity and mortality. Minimally invasive surgical techniques have progressed since the introduction of single incision laparoscopic surgery (SILS) and natural orifice transluminal endoscopic surgery (NOTES), and are often facilitated by robot assistance.

NOTES is a technique using the natural orifices (mouth, vagina, urethra and rectum) as an access route to the peritoneal cavity for endoscopic surgery. It was described for the first time in 2004 in a porcine model by researchers at Johns Hopkins University (1). The clinical application of NOTES has been reported in general surgical procedures, such as trans gastric appendectomy (2) and cholecystectomy (3), and demonstrated reduced pain, a shorter length of hospital stay and less complications. Improved cosmetic results due to scar-free surgery in combination with reduced wound (trocar) complications, supports the increasing use of this new surgical technique.

NOTES has gained popularity amongst general surgeons, urologists and gastroenterologists over the past few years and its feasibility and safety have been reported (4,5). It can be performed via various entry approaches including the stomach, oesophagus, bladder and rectum. The vast majority of NOTES procedures in women have been performed through the vagina as this allows direct access to the peritoneal cavity (6). Culdotomy has been used widely for several surgical procedures involving extraction of large specimens: it has been reported as a safe access that is easy to close afterwards (7,8). In hybrid NOTES the surgical procedure is performed through a natural body orifice with transabdominal assistance, whereas the term pure NOTES refers to procedures that involve only transluminal access.

Hysterectomy using a transvaginal NOTES (vNOTES) approach was described for the first time in a human patient by Su et al. in 2012 (9).

Objectives and hypotheses

We conducted a systematic review of the literature by searching MEDLINE, EMBASE and The Cochrane Library from inception to 25 August 2015 using '*Natural Orifice Endoscopic Surgery*' and '*hysterectomy*' as MeSH terms or key words. The results of this systematic review (SR) will be published in 2016; we will adhere to the PRISMA-P guidelines (10) for writing the protocol of this SR. The protocol has been registered in PROSPERO, the international prospective register of systematic reviews, at the Centre for Reviews and Dissemination (CRD), University of York, United Kingdom (11), with the protocol number CRD42016033023. To the best of our knowledge no randomised controlled studies comparing NOTES with the classical laparoscopic approach for hysterectomy have been reported in the literature: this is the main objective of the HALON study. A randomised controlled trial (RCT) is a study design that has the advantage to control for all possible known and unknown confounding variables due to the random sequence generation as opposed to observational studies where confounding and bias may be more problematic. High-quality RCTs are generally considered as being the gold standard design for the study of the effectiveness of interventions. The rationale and the objectives of this trial are in accordance with the guidelines of the IDEAL collaboration (12-14).

The study hypothesis states that hysterectomy by transvaginal NOTES may be at least as effective for removing a non-prolapsed uterus without the need for conversion to an alternative technique compared to the classical laparoscopic approach. A conversion means the use of any other technique than the one allocated by the random sequence generation. The following example illustrates a conversion: a study entrant may be allocated to the NOTES group but due to technical problems or a complication the surgeon decides to switch to laparoscopic, abdominal or vaginal hysterectomy in the interest of the patient. Transvaginal NOTES may offer several advantages compared to laparoscopy: the avoidance of abdominal scars, more women leaving the day care unit on the day of the intervention and less postoperative pain in the first seven days following surgery.

METHODS

Trial design and study analysis

This is a single-centre parallel-group randomised controlled trial conducted at the Department of Gynaecology of the Imelda Hospital in Bonheiden, a general hospital in Belgium serving an estimated population of 150,000 people. A cohort of women aged 18-70 years with a non-prolapsed uterus bound to undergo hysterectomy for benign gynaecological disease will be invited to participate in the study, if eligible. Prior to randomisation, all eligible women will be stratified based on the uterine size on clinical examination: category A= uterine size smaller than 10 weeks of pregnancy, category B= uterine size between 10 to 16 weeks of pregnancy, category C= uterine size larger than 16 weeks of pregnancy. We considered the size of the uterus to be the most important determinant to affect the primary outcome (successful removal of the uterus). The surgery will be done by one surgeon (JBae) who is equally skilled in operating with both techniques: he has introduced and refined the NOTES approach since November 2013. Our group published three small case series on adnexal removal (N=20) (15), salpingectomy (N=5) (16) and hysterectomy (N=10) (17) performed between November 2013 and February 2015. A non-inferiority study design will be used. The protocol adheres to the SPIRIT standards (http://www.spirit-statement.org/) as documented by the SPIRIT check-list that was sent to BMJ Open Editorial Office.

Participants

The HALON trial will recruit eligible women aged 18-70 years, regardless of parity, with a non-prolapsed uterus in need of a hysterectomy for benign indication and who provide informed consent prior to surgery. There is no cut-off for the uterine size to exclude women from participating in the HALON study. Concomitant uni- or bilateral salpingo-oophorectomy when needed, is not an exclusion criterion per se: in our observational personal experience, adnexal masses up to 20 cm diameter can be removed successfully without spilling. Women will be excluded from participation if they present any of the following conditions: history of rectal surgery, suspected rectovaginal endometriosis or malignancy, history of pelvic inflammatory disease (PID), active lower genital tract infection, virginity, pregnancy or failure to provide written informed consent.

Intervention, procedures and standard care

Women in both groups will be admitted to the day care unit on the day of hysterectomy. Clindamycin vaginal cream will be administered on admission.

In the operating theatre, the patient will be placed in the lithotomy position in a vacuum mattress. The abdomen, vulva and vagina will be disinfected with an alcoholic betadine solution and draped. A Foley catheter will be inserted into the bladder. Cefazolin 2g and metronidazole 1.5g will be administered IV during the procedure in both groups.

Control group: laparoscopic approach

When randomised to the laparoscopic approach a reusable Hohl uterus manipulator will be inserted through the vagina. A small vertical intra-umbilical skin incision will be made. A Verress needle will be inserted into the peritoneal cavity; the correct position of the needle tip will be checked with the Semm test. CO_2 will be insufflated until a maximal intraperitoneal pressure of 15mm Hg. The Verress needle will then be removed and replaced by a 10mm reusable trocar. An optic will be inserted through the 10 mm trocar and the peritoneal cavity will be inspected. The woman will be placed in the Trendelenburg position. Three reusable 5mm trocars will be inserted under direct vision in the left and right iliac fossa lateral of the epigastric vessels, and in the suprapubic region. The small intestine will be gently lifted out of the pelvis using atraumatic forceps. The ureter will be identified, but not routinely dissected unless indicated. The mesosalpinx will be coagulated from lateral to medial using a reusable bipolar grasping forceps and cut using cold scissors. The ovaries will be left untouched or removed based on the absence or presence of pathology as counselled to the patient. The round ligament will be coagulated using a bipolar grasper and cut using cold scissors. The parametria will be opened and the bladder will be dissected from the cervix and cranial part of the vagina. The uterine artery will be coagulated using a bipolar grasper and cut using cold scissors. The same procedure will be repeated on the contralateral side. The vagina will be opened over the cup of the Hohl manipulator using a reusable monopolar hook. The cervix will be excised in a circular fashion using the vaginal cup of the retractor as a backstop. The uterus will be extracted through the vagina. Haemostasis will be done using a bipolar grasper. The vaginal vault will be closed laparoscopically using three figure of eight vicryl-1 sutures. The peritoneal cavity will be rinsed and haemostasis checked. No drains will be left in the peritoneal cavity unless indicated (difficult haemostasis). The 5 mm trocars will be removed under direct vision. The 10 mm trocar will be removed. The fascial layer will not be sutured. The umbilicus and other incisions will be disinfected with a betadine solution. The skin incisions will be closed using a Monocryl 3/0 intradermal suture and steristrips. The wound sites will be covered with a standard bandage. A vaginal plug (betadine gauze 10cm x 5m) will be placed to be removed three hours later together with the Foley catheter.

Intervention group: vNOTES

When randomised to the vNOTES approach, three non-therapeutic superficial skin incisions will be made on the same location as in the classical laparoscopic approach. The surgeon will assess whether the anterior and posterior colpotomy and the transection of both sacro-uterine ligaments are best performed with either laparoscopic instruments (TVNH), or with classical instruments for vaginal surgery (VANH).

For VANH:

A circular incision will be made around the cervix using a cold knife. The Pouch of Douglas will be opened using cold scissors. The vesico-uterine peritoneum will be opened using cold scissors. Both sacro-uterine ligaments will be cut using cold scissors and tied off using a vicryl-1 suture. A GelPOINT advanced access platform (Applied Medical) will be used as vNOTES port and inserted into peritoneal cavity. CO_2 will be insufflated until a maximal intraperitoneal pressure of 15 mmHg. An optic will be inserted and the peritoneal cavity inspected. The patient will be placed in the Trendelenburg position. The small intestine will be lifted out of the pelvis.

For TVNH:

GelPOINT mini advanced access platform (Applied Medical) will be used as vNOTES port and inserted into the vagina. CO_2 will be insufflated until a maximal pressure of 15 mmHg. An optic will be introduced into the pneumovagina. A circular incision will be made around the cervix using a monopolar laparoscopic hook. The Pouch of Douglas will be opened using cold laparoscopic scissors. The vesico-uterine peritoneum will be opened using cold laparoscopic scissors. Both sacro-uterine ligaments will be cut using a laparoscopic bipolar grasping forceps. An optic will be inserted and the peritoneal cavity inspected. The patient will be placed in the Trendelenburg position. The small intestine will be lifted out of the pelvis.

The following steps of the procedure are identical for both VANH and TVNH:

The ureter will be identified, but not routinely dissected unless indicated. The uterine and ovarian arteries will be coagulated using a bipolar grasper and cut. The mesosalpinx will be coagulated and cut using a bipolar grasping forceps and scissors. In women requiring adnexectomy, the infundibulopelvic ligament will be coagulated using a bipolar grasping forceps and cut. Haemostasis will be checked and the peritoneal cavity will be rinsed. The NOTES port and the uterus will be removed through the vagina and the pneumoperitoneum will be deflated. The colpotomy will be closed using a running vicryl-1

suture. A vaginal plug (betadine gauze 10 cm x 5m) will be placed and removed after 3 hours together with the Foley catheter.

The pain management for both groups will be identical using a standardised protocol developed by the anaesthesiologists involved in the clinical trial.

The decision to discharge the study participant from the day care unit or alternatively to admit her to the in-hospital ward will be primarily decided by the patient based on how she feels following surgery. Both the patient and the outcome assessor (JBo), who will supervise the discharge, will be blinded to the approach used for the hysterectomy. The outcome assessor will overrule the participant's decision only in her health's interest e.g. when vital parameters indicate a life-threatening condition or based on the presence of complications during the surgical intervention as indicated in the patient record. All study participants will receive a standard list including instructions to avoid sexual intercourse and physical exercise/work for a period of six weeks after hysterectomy.

All women will be asked to measure postoperative pain using a VAS scale twice daily from day 1 until day 7 following surgery, regardless of being at home or in hospital. A dedicated nurse of the day care unit will give detailed instructions to all participants on how to measure the VAS scores. One measurement will be done in the morning after bed rest at night (rest) and the other will be done in the evening before going to bed after physical activity (active). All study participants will note in a pain log book the name, dosage, and route of administration of any analgesic drug taken from day 1-7.

Outcome measure

We searched the COMET (18) database for a core outcome set for surgery (intervention) in gynaecology (health area) in women aged 18 to 70 years (target population): we did not retrieve a standardised set of outcomes relevant to laparoscopic hysterectomy (19).

Primary outcome measure

The proportion of women successfully treated by removing the uterus by the intended approach without conversion to another approach will be used as a measure of efficacy.

Secondary outcome measures

The secondary outcomes are as follows: 1.The proportion of women admitted to the in-patient hospital for at least one night observation. Women can decide for themselves to leave the day care unit or stay overnight based on how they feel after the surgical procedure. The goal is to recover at home with their family for a fixed period of 6 weeks. The aim of this study was not to examine if

participants were able to reengage in their professional activities sooner with NOTES compared to laparoscopy; 2. Postoperative pain scores measured using a VAS scale (20) twice daily from day 1-7; 3. The use of analgesics taken during the first week following surgery; 4. Postoperative infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings detected during the first six weeks of surgery; 5. Intra- or postoperative complications according to the Clavien- Dindo classification (21) detected during the first six weeks of surgery; 6. Readmission during the first six weeks of surgery; 7. Frequency and intensity of dyspareunia recorded by the participants at baseline, 3 and 6 months by self-reporting using a simple questionnaire and VAS scale; 8. Sexual wellbeing at baseline, at 3 and 6 months by self-reporting the Short Sexual Functioning Scale-SSFS. The "Short Sexual Functioning Scale" is a self-developed questionnaire consisting of four items that address sexual dysfunctions: decreased sexual desire, dry vagina, arousal, and orgasmic dysfunction. Each of these items are scored on a four-point scale ranging from 0 (not or doubtfully present) to 3 (extremely present). Reliability analysis of the SSFS revealed an excellent internal consistency (Cronbach's α 0.92) in two prospective controlled studies on sexual functioning after mastectomy compared to breast conserving therapy for early-stage breast cancer (22) and after surgical treatment of vulvar malignancy (23). The SSFS has been used as a research tool in several other publications (24, 25, 26); 9. The duration of surgery measured in minutes from the insertion of the bladder catheter to the end of vaginal/abdominal wound closure; 10. Direct and indirect costs for both techniques incurred up to 6 weeks following surgery.

Randomisation and blinding

After stratification according to the uterine size on clinical examination, all participants will be randomly assigned to either the intervention (vNOTES) or the control group (laparoscopic technique) using a computer-generated randomisation schedule after stratifying for the size of the uterus. Sequentially numbered, opaque, sealed envelopes will be used to ensure allocation concealment.

Trial participants and the outcome assessor will be blinded to group allocation.

The use of the NOTES technique avoids the use of abdominal incisions. Participants randomised to the intervention group will have three superficial non-therapeutic skin incisions similar to those routinely done with the laparoscopic technique to blind all study participants, personnel and the outcome assessor. Wound dressings of all the study participants will be left untouched until the postoperative visit on day 7. The practice of performing non-therapeutic skin incisions has been reported in some surgical trials to minimise performance and detection bias when measuring subjective outcomes (e.g.

pain) (27). The decision to use non-therapeutic skin incisions is justified by the risk/benefit ratio of the two interventions under comparison (28).

Statistical methods

Sample size calculation

A sample size calculation was performed for the primary outcome: an appropriate level of statistical power was applied to preclude any clinically important inferiority of NOTES compared to laparoscopy. The assumptions for the conversion rates are based on evidence retrieved from a Dutch prospective cohort study in 42 hospitals including 1534 laparoscopic hysterectomies between 2008 and 2010 (29): this study reports a 4.6% conversion rate. We assume that vNOTES would be the treatment of choice for the majority of women primarily related to the cosmetic results (no abdominal scars) even if 15 % less women had successful removal of their uterus with the NOTES compared to the laparoscopic approach. Non inferiority will be concluded when 15% lies above the upper limit of the 95% confidence interval calculated for the difference in the proportion of women successfully treated with either of both techniques. To achieve 80% power to demonstrate non-inferiority under the assumption of similar success rates of 95% in both groups a sample size of 54 participants (27 women per group) will be required. The target sample size was increased to 64 participants (32 women per group) to account for a drop-out rate of 15%.

We aim to report the actual conversion rates at the end of the study. We predefine that the trial validity is not compromised if the conversion rates are below 10% and similar in both comparison groups. The study design (non-inferiority) is based on the assumption that the conversion rates are similar in both comparison groups, which will be cross-checked at the end of the study.

Statistical analyses

A 95% confidence interval of the difference in the proportions of women with a successful removal of the uterus by the intended technique as randomised will be calculated. Non inferiority will be concluded when 15% lies above the upper limit of this 95% confidence interval. For this primary analysis, adjustments for prognostic factors will not be made in the first instance. Body Mass Index (BMI) > 35, age > 65 years, uterine weight 200-500g or uterine weight > 500 g have been identified as prognostic factors for the risk of conversion based on the findings of the earlier cited Dutch prospective cohort study (25) : the risk of conversion was increased at BMI >35 (OR, 6.53; $p < 0.001$), age >65 years (OR, 6.97; $p = 0.007$), uterine weight 200 to 500 g (OR, 4.05; $p < 0.001$) and uterine weight >500 g (OR, 30.90; $p < 0.001$). The effect of BMI and age will be explored as a secondary analysis. We aimed to include women without genital prolapse in the HALON trial because we do not

consider the NOTES technique to be an alternative for vaginal hysterectomy in women with genital prolapse. Nulliparous women with a narrow vagina could certainly represent an impediment when performing the NOTES technique. In practice NOTES can be done using a VANH or a TVNH approach. The VANH approach is used when the vaginal vault can be reached to open the Pouch of Douglas in a comfortable way. In nulliparous women with a narrow vagina we will use another approach: with the TVNH approach the cervix is circumcised using a monopolar hook and the pouch is opened using laparoscopic scissors. The presence or absence of enough prolapse of the vaginal vault could affect the conversion rates: we will explore this effect in a secondary analysis but we will be very cautious in presenting definitive conclusions for this predefined subgroup analysis: given the limited number of included participants, it is likely that differences even when really present, will fail to reach statistical significance.

Ordinal measures (VAS scores) will be analysed using analysis of covariance (adjusting for baseline value). Multilevel modelling for repeated measurements will be used to compare the mean differences in VAS pain scores between both comparison groups over all time points, thereby maximizing the power of the data available.

Analysis will be performed on an 'intention to treat' basis in the first instance, as recommended in the Consolidated Standards of Reporting Trials -CONSORT- statement (30). A sensitivity analysis will be performed using 'per protocol' data to test the robustness of findings. As a conservative measure, estimates of effect sizes between the two arms will be presented as point estimates with two tailed 95% confidence intervals.

Descriptive statistics will be used to summarise patients' characteristics and baseline outcome data in the two treatment groups. Baseline characteristics of the women enrolled in the two groups will be compared to ensure that the randomisation has produced comparable groups of participants, and will be covariates in the modelling procedure.

The statistical significance test for the primary analysis will be one-tailed, and $p<0.05$ will be considered as significant. All tests of the secondary analyses will be two tailed, and $p<0.05$ will be considered as significant. All statistical analyses will be done by an experienced biostatistician (AL) who is a co-investigator in the present research.

RESULTS

Participant flow diagram

Figure 1 shows the study flow reported according to the CONSORT statement and checklist (30).

Recruitment time frame

All women with a non-prolapsed uterus, aged 18 to 70 years, regardless of parity, in need of a hysterectomy for benign indication and meeting the inclusion criteria will be invited to participate in the trial. Only eligible women with written informed consent obtained before randomisation will be included in the trial.

Based upon the mean number of hysterectomies performed for benign gynaecological disease in women without genital prolapse at the Department of Gynaecology annually (N=168) we estimate that 40 % of the eligible women should be willing to participate to recruit sample size needed (N=64) within one year. Based upon the follow up (6 months) and the period of analysis/reporting (6 months) the total study period is estimated to be 2 years.

Data collection

The following patient characteristics will be recorded at baseline: age, BMI, volume of the uterus in weeks, concomitant medication, dyspareunia questionnaire and the Short Sexual Functioning Scale (SSFS).

On the day of surgical intervention (day 0) the following data will be collected: duration of the intervention, successful removal of the uterus by the technique as randomised without conversion to another technique with or without cleaving the womb, admission of the participant to the in-hospital ward for at least one night observation based on her own preference, the total amount of analgesics used at the recovery and day care unit and the maximum VAS pain score on the day 0.

On days 1 to 7 the pain scores will be collected as reported by the study participant twice daily (one in the morning and one in the evening). The total amount of analgesics used during the first postoperative week will be recorded by the participants and collected by the outcome assessor.

On day 7 and day 42 pelvic infection defined by lower abdominal pain with fever > 38°C and positive clinical signs or laboratory findings, readmission and postoperative complications according to the Clavien- Dindo classification detected during the first six weeks after the intervention will be assessed and recorded by the outcome assessor.

On month 3 and 6 following surgery the dyspareunia questionnaires and the SSFS questionnaires will be filled in by the study participants and collected. See Table 1

DISCUSSION

Strengths and weaknesses

The main strength of the HALON study is its design as a randomised controlled trial rather than an observational comparative study. A RCT has the advantage to control for all possible known and unknown confounding variables due to the random sequence generation as opposed to observational studies where confounding and bias may be more problematic. High-quality RCTs are generally considered to be the gold standard for studying the effectiveness of an intervention.

Restricting this single-centre RCT to one surgeon's practice may be considered a major limitation. We nevertheless have carefully balanced the pros and cons of this decision. There can be no discussion on to the learning curves or differences in surgical skills among the participating surgeons if all study participants are treated by one surgeon equally skilled at doing both techniques. A multicentre prospective cohort study could add credibility to the generalizability of the findings, but may pose problems with respect to the learning curves and the differences in surgical skills of the surgeons involved. The aim of the present pilot study is to study the efficacy (can NOTES work under ideal experimental conditions?). The HALON trial does not address the effectiveness of the new intervention (does NOTES work in a real life setting when performed by several surgeons?). Multicentre trials on the effectiveness of NOTES should be done when there is evidence of efficacy and after proper training of a larger group of dedicated surgeons as suggested by the IDEAL recommendations.

The conditions in this small efficacy study are experimental and in many instances opposed to 'real life' conditions: all women are treated by one surgeon equally skilled in using both techniques, women are given better care in this study when compared with standard clinical practice, the dosage of anaesthetic drugs is calculated to limit the possible side effects such as nausea and vomiting that may prevent women leaving the hospital the same day, all outcomes measured are very relevant for women in general, women with adverse outcomes (e.g. dyspareunia and sexual dysfunction) will be recalled after the end of the study for counselling and therapy, etc…The results of the HALON trial will therefore have a limited generalizability and their interpretation will be done cautiously.

By making three ‘non therapeutic incisions ‘on the abdomen in the NOTES group it could be argued that this intervention may confound the assessment of the pain outcome. We judged it necessary to blind participants, personnel and the outcome assessor by using these ‘non therapeutic incisions’ similar to the ones used in the laparoscopic technique. If we would stuck to the pure NOTES technique without scars on the abdominal wall, participants in the intervention arm (NOTES) would have known with certainty that they had undergone the ‘new promising technique’ : this could have introduced substantial bias and would have compromised the internal validity of the HALON trial. After carefully balancing the pros and cons, all the investigators agreed to sacrifice a potential benefit of the NOTES technique (less pain and better cosmetic results by not using abdominal incisions) rather than compromising the study validity by introducing information bias. We accept a possible decrease in the magnitude of a potential benefit and we will report this balanced judgement in the final review.

We considered stratifying for other determinants than the uterine size (BMI and parity) but given the scope and the limitations of this small pilot RCT study we decided to stratify only for the uterine size on clinical examination.

Many outcomes of the present study are patient-reported and patient-centred. The secondary

outcome ‘ the proportion of women admitted to the in-patient hospital for at least one night observation could equally confound the study results if there would be a different and substantial proportion of women wishing to stay for reasons not related to the surgery itself (e.g. social reasons) across both comparison groups. Women in the HALON trial can decide for themselves to leave the day care unit or stay overnight based on how they feel after the surgical procedure. The goal is to recover at home with their family for a fixed period of 6 weeks. The aim of this study was not to examine if participants were able to reengage in their professional activities sooner with NOTES compared to laparoscopy. We admit that the reasons to stay overnight are not necessarily medical. In cases where the reason to stay overnight was not purely medical and as such reported by the participant, we noted this as an additional remark in the clinical research file. The primary analysis will be done based on the fact of staying overnight or leaving the day care unit without taking into account the nature of the reasons for staying. We assume that by using the random sequence generation women wishing to stay overnight for social reasons should be equally distributed among both comparison groups. This will be cross-checked if all study data are available. We will do sensitivity analyses if differences are found across the comparison groups for the reasons reported by participants for staying overnight to test the robustness of the data.

Implications for clinical practice

We stress that the HALON trial is a pilot study on the efficacy of the NOTES technique. The two techniques under comparison are done by one single surgeon (JBae) who is equally skilled in using both. The surgeon has been using the new approach since November 2013. During this two-year period the new technique and suitable instruments used were pilot-tested by the usual "trial and error" method used for centuries in surgical practice (14) and adapted into its present form. The feasibility and preliminary safety of the new technique was reported in three observational studies performed in our department (15-17) in accordance with the principles outlined in the three article series on the IDEAL statement (12-14). According to the terminology used by the IDEAL collaboration (14) this study should be classified as an IDEAL stage 2b trial. The full PICO research question is as follows: will a surgeon who is equally skilled at performing both techniques, and beyond his learning curve for the new technique (NOTES), succeed in removing a non-prolapsed uterus in women with benign gynaecological disease at least as often with the new pilot-tested transvaginal NOTES approach compared to the standard transabdominal laparoscopic approach without having to convert to an alternative approach? The findings of the HALON study have limited generalizability. Adequate training of other surgeons and more research e.g. prospective multicentre prospective cohort studies or large electronic registries will be needed to monitor the long term outcomes (e.g. surgical complications). The reader should be aware that a proof of efficacy by a single-centre pilot study is by itself not sufficient to implement the technique into clinical practice.

We do not consider the NOTES approach as being a more suitable alternative for the vaginal hysterectomy in cases of genital prolapse. The aim of the HALON study is to compare NOTES with laparoscopic hysterectomy in women with non-prolapsed uterus for benign gynaecological pathology. Although NOTES could have been compared with classical vaginal hysterectomy and one might be tempted to consider vaginal hysterectomy as a NOTES technique, our goal was to remove uteri that in a setting outside of the trial would have been removed by a total laparoscopic approach or open abdominal approach, i.e. without sufficient prolapse to do a classical vaginal hysterectomy. The NOTES technique moreover uses a device to create and maintain a pneumoperitoneum in contrast to a vaginal hysterectomy. We hypothesise that gynaecologists will feel more familiar with using NOTES for removing a non-prolapsed uterus compared to doing a total laparoscopic approach: NOTES avoids suturing laparoscopically which requires considerable skill. If the uterus is bulky, the NOTES approach will enable the surgeon more direct access to the uterine blood supply as opposed to the laparoscopic approach. Trying to coagulate the uterine vessels in a bulky uterus filling the pelvic cavity can be quite

challenging.

Implications for further research

As suggested by the IDEAL collaboration more research (large multicentre trials performed by adequately trained surgeons in centres of clinical excellence and large prospective registries cumulating data on the safety of the new technique over many years) and adequate surgical training will be needed before NOTES can be offered as a standard daily care surgical practice by a majority of gynaecological surgeons for all women bound to undergo hysterectomy for benign gynaecological disease. HALON should therefore be considered as a necessary kick-off' in a long and scientifically rigorous evaluation of a complex surgical intervention. A randomised pilot study on the efficacy of NOTES is needed at this moment in its evolution before this technique becomes too widely implemented into daily clinical practice without properly evaluating its potential benefits and harms: the latter scenario is not in accordance with good clinical practice and may harm women in the longer term.

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Table 1

Table 1 Patient's characteristics and data collection														
Data collection	**Days**													
	BL*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**42**		**3 m**	**6m**	
Age	X													
BMI**	X													
Uterine volume	X													
Concomitant medication	X	X	X	X	X	X	X	X	X					
Dyspareunia: frequency and intensity	X											X	X	
SSFS***	X											X	X	
Duration of surgery		X												
Successful removal		X												
Dismissal day 0		X												
Total amount of analgesics used		X	X	X	X	X	X	X	X					
VAS score****		X	X	X	X	X	X	X	X					
Readmission within six weeks										X				
Pelvic infection									X	X				
Other postoperative complications		X							X	X				
Direct costs up to 6 weeks after surgery										X				

* BL: baseline

** BMI: Body Mass Index

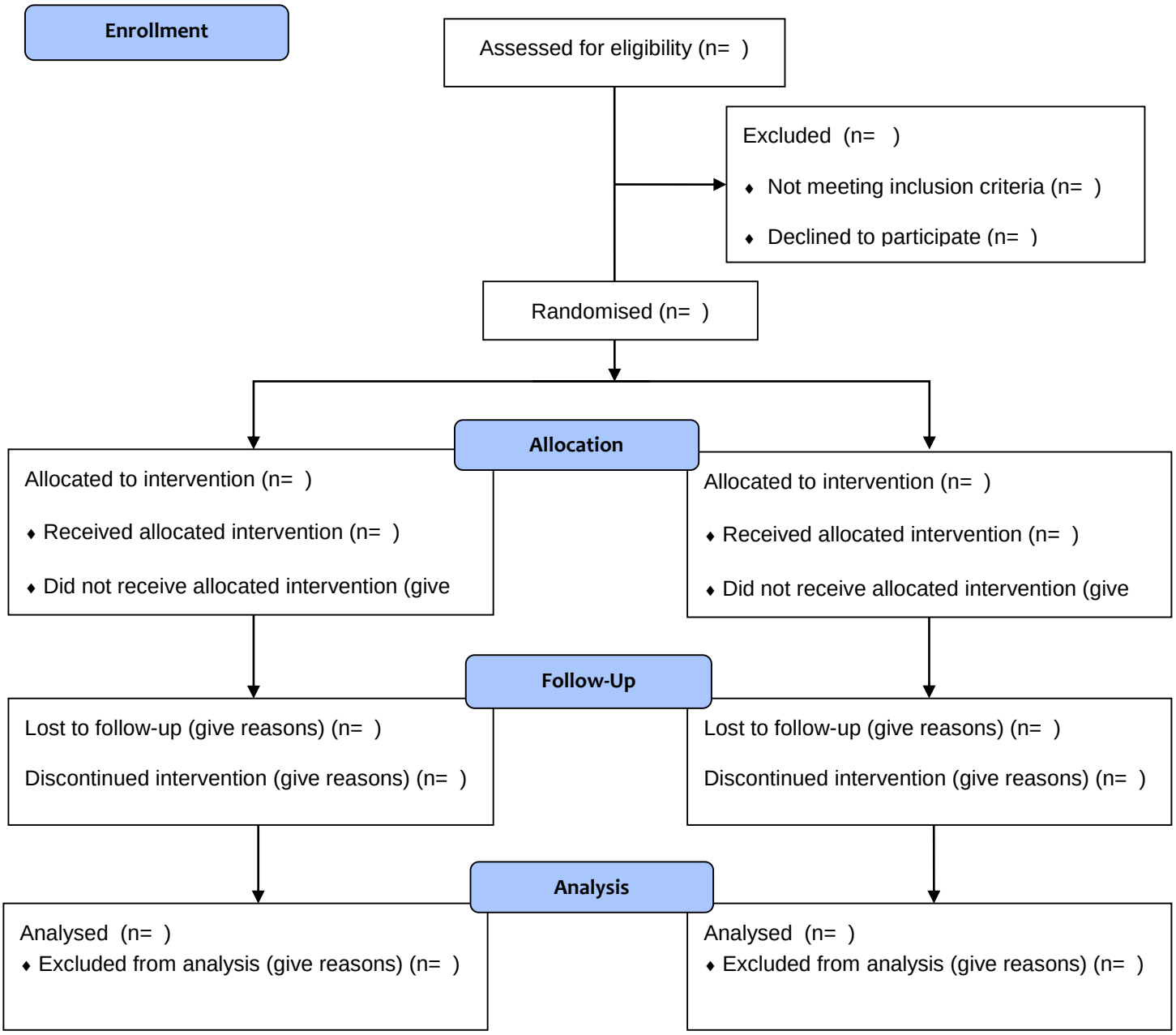
*** SSFS: Short Sexual Functioning Scale

**** VAS: Visual Analogue Scale

FIGURE 1

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



6.2 Hysterectomy by Transvaginal Natural Orifice Transluminal Endoscopic Surgery versus laparoscopy as a day-care procedure; a randomised controlled trial

ABSTRACT

OBJECTIVE

To compare hysterectomy by Transvaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES) versus total laparoscopic hysterectomy (TLH) as a day-care procedure.

DESIGN

Parallel group, 1:1 randomised, single-centre, single-blinded trial, designed as a non- inferiority study with a margin of 15%.

SETTING

Belgian teaching hospital.

POPULATION

Women aged 18-70 years bound to undergo hysterectomy for benign indication.

METHODS

Randomisation to TLH (control group) or vNOTES (experimental group). Stratification according to uterine volume. Blinding of participants and outcome assessor.

MAIN OUTCOME MEASURES

The primary outcome was hysterectomy by the allocated technique. We measured the proportion of women leaving within 12 hours after hysterectomy and the length of hospital stay as secondary outcomes.

RESULTS

We randomly assigned 70 women to vNOTES (n=35) or TLH (n=35). The primary endpoint was always reached in both groups: there were no conversions. We performed a sensitivity analysis for the primary outcome, assuming one conversion in the vNOTES group and no conversions in the TLH group: the one-sided 95% upper limit for the differences in proportions of conversion was estimated as 7.5%, which is below the predefined non-inferiority margin. More women left the hospital within 12 hours after surgery after vNOTES: 77 versus 43%, difference 34% (95%CI, 13 to 56%), P=0.007. The hospital stay was shorter after vNOTES: 0.8 versus 1.3 days, MD, -0.5 days, (95%CI, -0.98 to -0.02), P=0.004.

CONCLUSIONS

vNOTES is non-inferior to TLH for successfully performing hysterectomy without conversion. Compared to TLH, vNOTES may allow more women to be treated in a day-care setting.

TRIAL REGISTRATION

Trial registration: ClinicalTrials.gov NCT02631837; www.clinicaltrials.gov

—HALON study.

INTRODUCTION

Hysterectomy is worldwide the most frequently performed major surgical procedure in gynaecology. There are currently four approaches to hysterectomy: abdominal hysterectomy (AH), vaginal hysterectomy (VH), laparoscopic hysterectomy (LH) - either totally laparoscopic (TLH) or laparoscopy-assisted (LAVH) - and robotically-assisted hysterectomy (RH). A Cochrane review including 47 randomised trials (RCTs) in 5102 women advises VH to be the preferred technique in women in whom this is feasible. When VH is not applicable, LH may be used as an alternative approach, but at the cost of an increased risk of urinary tract injury.[1] Overall hysterectomy rates and the proportions of the different types vary markedly across countries. Based on data of the National Institute for Health and Disability Insurance in Belgium in 2016 the relative contribution of the different techniques was as follows: AH 18%, VH 28%, LAVH 17% and TLH 31%. Out of 11364 hysterectomies only 86 procedures (0.7%) were done as a day-care surgical procedure.

Natural Orifice Transluminal Endoscopic Surgery (NOTES) uses the natural orifices of the human body as a surgical access route. Its first use in an animal model was reported in 2004.[2] Su et al. published the first series of 16 women undergoing transvaginal NOTES (vNOTES) hysterectomy in humans in 2012.[3]

We report on the first randomised controlled trial of Transvaginal Natural Orifice Transluminal Endoscopic Surgery hysterectomy for benign disease. The study objective was to compare vNOTES hysterectomy with total laparoscopic hysterectomy (TLH) as a day-care procedure. Our study hypothesis was that the new experimental technique (vNOTES) was non-inferior to the established effective technique (TLH) for successfully removing the uterus while being superior for one or several secondary outcomes predefined in the study protocol (Appendix S1).

The non-inferiority design was based on the superiority of TLH to avoid open surgery when vaginal hysterectomy is not feasible. [1]

METHODS

Study design and participants

Our study, the Hysterectomy by trans-Abdominal Laparoscopy Or NOTES (HALON) – a parallel group 1:1 randomised controlled non-inferiority trial- was conducted from December 2015 to June 2017 at the department of Obstetrics and Gynaecology of the Imelda hospital, a teaching hospital in Belgium. The study was approved by the ethics board of the Imelda hospital (B689201526261**)** and was conducted in compliance with the ICH Good Clinical Practice guideline and the Belgian Law of May 7,

2004 related to experiments on humans. The trial was registered as NCT 02631837. We published the study protocol as an open access paper.[4]

Women between 18 and 70 years were eligible for the study if they were scheduled to undergo hysterectomy for benign disease. Common surgical indications for hysterectomy were: symptomatic uterine fibroids, adenomyosis, high grade cervical dysplasia, treatment refractory dysfunctional uterine bleeding, atypical endometrial hyperplasia and BRCA positive women 45 years of age or older. Women with a history of rectal surgery, suspected rectovaginal endometriosis, suspected malignancy, pelvic inflammatory disease (PID), active lower genital tract infection, virginity or pregnancy were not eligible. There were no limitations with respect to the Body Mass Index (BMI) or uterine volume. All participants needed to provide written informed consent before surgery.

Procedures

On the day of the planned hysterectomy (Thursday or Friday) all participating women were admitted to the surgical day-care unit from 07:30 am. The nursing staff administered clindamycin cream on admission. All surgeries were scheduled as a first or second case from 08:00 am. All hysterectomies were done by one surgeon (JFB); he had introduced NOTES in our department since November 2013 and had performed at least 200 vNOTES procedures before the beginning of the trial. In women allocated to the experimental arm the surgeon (JFB) performed a vNOTES hysterectomy (VNH) . First, four superficial non therapeutic skin incisions were made in all women of the vNOTES group, identical to those in the control group to blind participants, personnel of the day-care unit and the outcome assessor. The surgeon (JFB) created access to the peritoneal cavity by circumcising the cervix, performing an anterior and posterior colpotomy, and cutting the uterosacral ligaments as done in conventional vaginal surgery when possible (VANH technique: Vaginally Assisted NOTES Hysterectomy). In some cases classical colpotomy was not possible: the surgeon (JFB) used the vNOTES port (GelPOINT® Advanced Access Platform, Applied Medical, Rancho Santa Margarita, California, US) and the endoscopic instruments to make an anterior or posterior incision in the vaginal vault (TVNH technique: Total Vaginal NOTES Hysterectomy). After obtaining access to the peritoneal cavity a vNOTES port was inserted through the vagina into the peritoneal cavity to establish a pneumoperitoneum. This device enables inserting several trocars through a single port. A standard 10 mm rigid 0° laparoscope (Olympus Corporation, Tokyo, Japan) was used through one trocar and two endoscopic instruments (Olympus Corporation, Tokyo, Japan) through the other two trocars. The ureters were identified but not routinely dissected. The surgeon performed the hysterectomy by dissecting from caudally to cranially using endoscopic instruments with bipolar coagulation (HiQ+ Bipolar, Olympus Corporation, Tokyo, Japan; Voyant, Applied Medical, Rancho Santa Margarita, California, US). The Fallopian tubes were removed in all women after counselling, the ovaries were

removed when indicated. At the end of the hysterectomy, the surgeon removed the vNOTES port and the uterus through the vagina. The vaginal cuff was closed similar to conventional vaginal surgery.

In women allocated to the control arm, the surgeon performed a TLH using the laparoscopic closed entry technique with the insertion of a Veress needle (Karl Storz, Tuttlingen, Germany), one 10 mm intra-umbilical primary trocar and three 5 mm accessory trocars. A standard 10 mm rigid mm 30° laparoscope (Olympus Corporation, Tokyo, Japan) was used. The ureters were identified but not routinely dissected. A Hohl uterine manipulator (Karl Storz, Tuttlingen, Germany) was used. The hysterectomy was performed by dissecting from cranially to caudally using bipolar coagulation. The vaginal cuff was sutured laparoscopically using intracorporeal knot tying for 3 separate figure 8 sutures.

At the end of all hysterectomies a vaginal plug (betadine gauze 10cmx5m) was left in place to be removed after 3 hours together with the Foley catheter. Cefazolin 2g and metronidazole 1.5g were administered intravenously at the beginning of each procedure. The care given by the anaesthesiologists and the nursing staff was standardised and similar in both groups. A study specific pain protocol was developed by the anaesthesiologists involved in the trial (PADM and ILR). A nursing protocol was written by a senior nurse of the surgical day-care (IV) unit for the purpose of standardising nursing care. (Appendix I and II) At 6:00 pm the outcome assessor (JJAB) evaluated the condition of all participants. He checked the vital parameters and enquired if women preferred to leave the day-care unit or not. In accordance with the day-care unit discharge policy participants were discharged when assessed as well enough and able to cope independently or with assistance from a partner or relative who stayed with them at home. The outcome assessor ensured that clinical notes were completed and filed correctly in the electronic patient file. A discharge letter was handed for the family physician as well as telephone numbers for contact in case of adverse events. Follow-up visits by the outcome assessor were done at days 7 and 42. Questionnaires were sent at three and six months following hysterectomy. For a detailed description of the trial interventions and the follow-up visits we refer to the published study protocol.[4] The HALON trial was registered as NCT 02631837 in ClinicalTrials.gov.

Outcome measurements

The primary outcome was removal of the uterus according to the allocated technique. Secondary outcomes were duration of the surgical procedure, the proportion of women leaving the hospital within 12 hours after surgery, length of hospital stay, total amount of analgesics used and the VAS pain scores measured twice daily during the first week following surgery. We searched the CROWN database (http://www.crown-initiative.org) for a core outcome set on hysterectomy for benign disease and found no match. We contacted ten women treated by total vaginal NOTES hysterectomy in an observational study published by our group for a short interview by telephone[5]. We asked women

if they would have preferred leaving the hospital on the day of the hysterectomy and the risk of conversion of a new surgical technique they would accept if this new technique could avoid visible surgical scars. We used these patient reported outcomes as a basis for the sample size calculation.

Direct health-related costs were measured using the total hospital bill for all costs incurred up to six weeks as a parameter. Occurrence and severity of dyspareunia before surgery and at three and six months after hysterectomy were assessed using a simple questionnaire and VAS score. Quality of life was measured at baseline and at three and six months after hysterectomy using the two part EQ-5D-3L questionnaire (VAS and descriptive system) with permission of the EuroQol Research Foundation.

We measured the following adverse events: postoperative infection, complications during surgery and in the first six weeks after hysterectomy and hospital readmission within six weeks after surgery. We used the 2004 modified Clavien-Dindo classification of surgical complications for postoperative complications[6]. Any deviation -even asymptomatic- from the normal postoperative course constitutes a surgical complication.

Sample size calculation

The study was designed as a non-inferiority study. Our hypothesis was that women would accept a higher conversion rate of 15% for vNOTES driven by their preference to avoid visible scars. We refer to the telephone interview of ten women treated by total vaginal NOTES hysterectomy[5]. Women were asked to choose among five cut-off rates (5%, 10%, 15%, 20% or 25%). Most women indicated 15%. We had informed women that the mean conversion rate from LH to AH was 5% (range 0% to 19%), reported in the literature [7]. We would conclude non-inferiority when the upper limit of the one-sided 95% confidence interval for the difference in the proportions of women who had the uterus removed by the allocated technique would be below 15%. Before starting the trial, we calculated that we needed to include 54 women to demonstrate non-inferiority of vNOTES compared to TLH for the primary outcome (power 80%, alpha error of 5%). To account for a potential drop-out of 15%, the final sample size was set at 64 participants (32 women per group).

Randomisation, blinding and treatment allocation

Eligible women were informed about the trial by a gynaecologist working at the department. After written informed consent, all women were randomised for vNOTES or TLH using computer generated random number lists. Randomisation was stratified for the clinically estimated uterine volume into category A (uterine size < 10 weeks), category B (uterine weight 10 to 16 weeks) or category C (uterine size > 16 weeks), and performed by an officer, who was otherwise not involved in the trial, using a list of random numbers (0 or 1) generated using free online software (https://www.randomizer.org).

Allocation was concealed by sequentially numbered, opaque sealed envelopes. The day before surgery, participants were randomly allocated to the intervention (vNOTES) or control (TLH) group.

All procedures in the study (vNOTES and TLH group) were performed by one surgeon (JFB). To assure blinding of participants, personnel of the day- care unit and the outcome assessor, four superficial non therapeutic skin incisions were made in all women of the vNOTES group, identical to those in the TLH group. Intra- and postoperative care was standardised to minimise the risk of performance bias. Post-operative assessment of all participants and data collection were done by a second surgeon (JJAB) who was blinded for the type of procedure performed. When writing the study protocol we decided not to do a formal evaluation of the success of blinding in the HALON trial: at the present, none of the methods of formal assessment of blinding in clinical trials are commonly used or regarded as standard.[8]

Statistical analysis

We refer to the statistical analysis plan (Appendix S2). All analyses were performed by the intention-to-treat principle. Data analysis was done by a biostatistician who was otherwise not involved in the daily conduct of the trial or data collection. A non-inferiority analysis was performed for the primary endpoint by estimating the one-sided 95% upper confidence limit for the difference in conversion rate between vNOTES and TLH. Superiority analysis and two-sided tests were applied for all secondary endpoints. For dichotomous secondary outcome measures, comparisons between the two arms were performed by applying Fisher exact test or Chi-square test, as appropriate. Cross-sectionally measured continuous secondary outcomes were analysed using an independent T-test or Mann–Whitney U- Test, as appropriate. Longitudinally measured continuous secondary outcomes were analysed using multilevel modelling. A sensitivity analysis was performed using multiple imputation for missing values. P-values of less than 0.05 were considered to indicate statistical significance. Data analysis was performed by A.L. using SAS software (version 9.4 SAS® System for Windows, SAS Belgium, Tervuren, Belgium).

RESULTS

Figure 1 shows the CONSORT flow chart of the trial. Between December 9, 2015, and February 23, 2017, 194 women were screened for eligibility: 108 preferred hysterectomy by vNOTES outside the trial to avoid visible scars, nine had a strong preference for a specific technique and seven declined to

participate in a clinical trial. The 70 women who provided written informed consent were randomly allocated to vNOTES (n=35) or TLH (n=35). Data on the primary outcome were available for all women.

Baseline characteristics were comparable between the two groups except for a lower proportion of dyspareunia at baseline in the TLH group (OR 0.29, 95% CI 0.09 to 0.86, P = 0.03). The baseline characteristics of women in the HALON trial were comparable with those of 124 women who were eligible for inclusion but declined to provide written informed consent (Table 1).

Primary outcome

In both groups, the uterus was removed by the allocated technique in all women (Table 2). There were no conversions, hence the confidence interval for the difference between both comparison groups cannot be determined. We performed a sensitivity analysis for the primary outcome while assuming one case of conversion in the vNOTES group and no conversions in the control group: the one-sided 95% upper confidence limit for the differences in proportions was estimated as 7.5%. This upper limit is below the predefined 15% non-inferiority margin.

Secondary outcomes

We refer to Table 2 for the findings of the main secondary outcomes of the HALON trial. The duration of a vNOTES hysterectomy was shorter compared to TLH (41 versus 75 minutes; MD, -34 minutes; 95% CI, -46 to -22 minutes; P<0.001). More women left the hospital within 12 hours of hysterectomy after a vNOTES procedure versus TLH (77% versus 43%; difference, 34%; 95% CI, 13% to 56%; P=0.007). Hysterectomy by vNOTES was associated with a shorter length of hospital stay compared to TLH (0.8 versus 1.3 days; MD, -0.50; 95% CI, -0.98 to -0.02 days; P=0.004). The total amount of analgesics used during the first seven days following surgical treatment was less in the vNOTES group (8 versus 14 units; MD, - 6 units; 95% CI, -10 to -2 units; P=0.006), where women also self-reported lower VAS pain scores (P=0.003) (Fig. 2).

There were less postoperative complications in women treated by vNOTES (9.0 % versus 37 %; RD, -28 %; 95% CI, -47 to -10%; P = 0.009). There were no differences between vNOTES hysterectomy and TLH for the occurrence of postoperative infection, intra-operative complications or hospital readmission within six weeks.

There were no differences between both comparison arms for the other predefined secondary outcomes (direct health-related costs incurred up to six weeks after hysterectomy based on the hospital bill, occurrence and severity of pain on sexual intercourse at three and six months and health-related quality of life at three and six months). These findings are presented online as Table S1. Finally

table S2 presents an overview of the types of surgical complications and the reasons for hospital readmission in both treatment arms. The majority of all surgical complications (14/16 or 87.5%) were grade I-II according to the Clavien-Dindo classification: these are minor events. There were three grade III-IV complications (2/16 or 12.5%): these are major events. There was one intraoperative complication. There were no deaths or lasting disabilities caused by surgery in the trial.

DISCUSSION

Main findings

In this first ever-reported randomised trial comparing vNOTES and TLH we found that vNOTES was non-inferior to TLH for doing hysterectomy by the allocated technique without conversion: based on the findings of a sensitivity analysis we can state with confidence that non-inferiority of vNOTES has been demonstrated in the more disadvantageous situation of one conversion for the experimental treatment (vNOTES) compared to no conversions in the control group (TLH). vNOTES was associated with a shorter length of hospital stay and more women leaving the day-care unit within 12 hours after the intervention. There was no evidence of differences between both techniques for postoperative infection or hospital readmission rates at six weeks after surgery.

Strengths and limitations

This is the first ever randomised controlled trial studying the efficacy and short term safety of vNOTES. We assessed several patient-reported outcomes. Recordings of patient-reported outcome measures (PROMs), such as pain and quality of life reflect, even in this small study, the benefits of vNOTES. PROMs are important to measure the impact of surgery on the daily life of women; in our opinion these should be included in all trials evaluating novel surgical techniques.[9] The secondary outcomes measured in the HALON study can be used to develop a core outcome set (COS) for hysterectomy in women with benign disease.

Besides these strengths our pilot study has several limitations. HALON is a single-centre trial and all procedures were done by one expert surgeon (no conversions in both groups), which limits the generalisability of the study findings. We intended to blind personnel, participants and the outcome assessor for not compromising the internal validity of the trial.[10] To this aim, we used similarly looking incisions in all participants: this “sham” surgery was approved by the ethics board.[11] To our judgement this seemed to us a more reliable method of blinding: “sham” abdominal dressings or identically sized plasters still leave room for bias.[12, 13] We cannot exclude that some women may have been able to

guess the allocated technique since the use of a transabdominal approach in the TLH group must inevitably cause more pain around the umbilicus as opposed to the vNOTES technique. Blinding in surgical trials remains very difficult, if not impossible.

Being a small single-centre study, HALON is but a first step in a long process of rigorous evaluation of the effectiveness and safety of vNOTES, as outlined by the IDEAL Collaborative Group, an international cooperation between biostatisticians, clinical trial specialists and surgeons.[14-16] We are fully aware that our study findings may raise some controversy due to the perception of a thin line between vaginal hysterectomy and vNOTES hysterectomy. The HALON trial's intention was to compare vNOTES versus laparoscopy for doing a hysterectomy when VH is not an option. This was based on clinical judgment rather than using the Pelvic Organ Prolapse Quantification system (POP–Q) system in the eligibility criteria. This methodological weakness adds further to the limitations on the generalisability.

Interpretation (in light of other evidence)

The findings of a shorter length of hospital stay with vNOTES are consistent with the findings of a systematic review and meta-analysis including two observational studies.[17, 18] Based on the findings of this systematic review length of hospital stay was shorter with vNOTES compared to LAVH. There were no data on quality of life, sexual wellbeing or dyspareunia in this systematic review.[19]

This systematic review demonstrated that vNOTES was less cost efficient. The results of the HALON trial however do not demonstrate any difference in total hospital bill between VNH and TLH. If one would take into account the shorter surgical time, shorter hospitalisation time, reduced use of analgesia and potential quicker return to normal activity, vNOTES may potentially reduce the total health care cost.

The lower postoperative complication rate for vNOTES when compared with TLH is remarkable and cannot be explained based on other papers. The very standardized VNH technique that was used and is technically less challenging than a TLH could be a contributing factor.

The findings of the HALON trial demonstrating less postoperative pain after vNOTES are consistent with the results of a recently reported systematic review including six RCTs and 21 non-randomised trials in 2186 patients undergoing abdominal surgery.[20]

Less postoperative pain, a criterion for discharge from the day-care unit, allowed more women to return home within 12 hours of surgery.

CONCLUSION

Besides avoiding visible scars and while being non-inferior to TLH, vNOTES allows more women to undergo hysterectomy as a day-care surgical procedure. The promising findings of our single-centre pilot RCT constitute a basis on which to design and conduct pragmatic multi-centre trials involving several surgeons beyond their surgical learning curve on the cost-effectiveness of vNOTES. A randomised comparison between vNOTES and VH is equally needed to assess the comparative cost-effectiveness of both techniques. Prospective complication registries should be used to monitor the long term safety of this new technique.

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CONSORT 2010 Flow Diagram

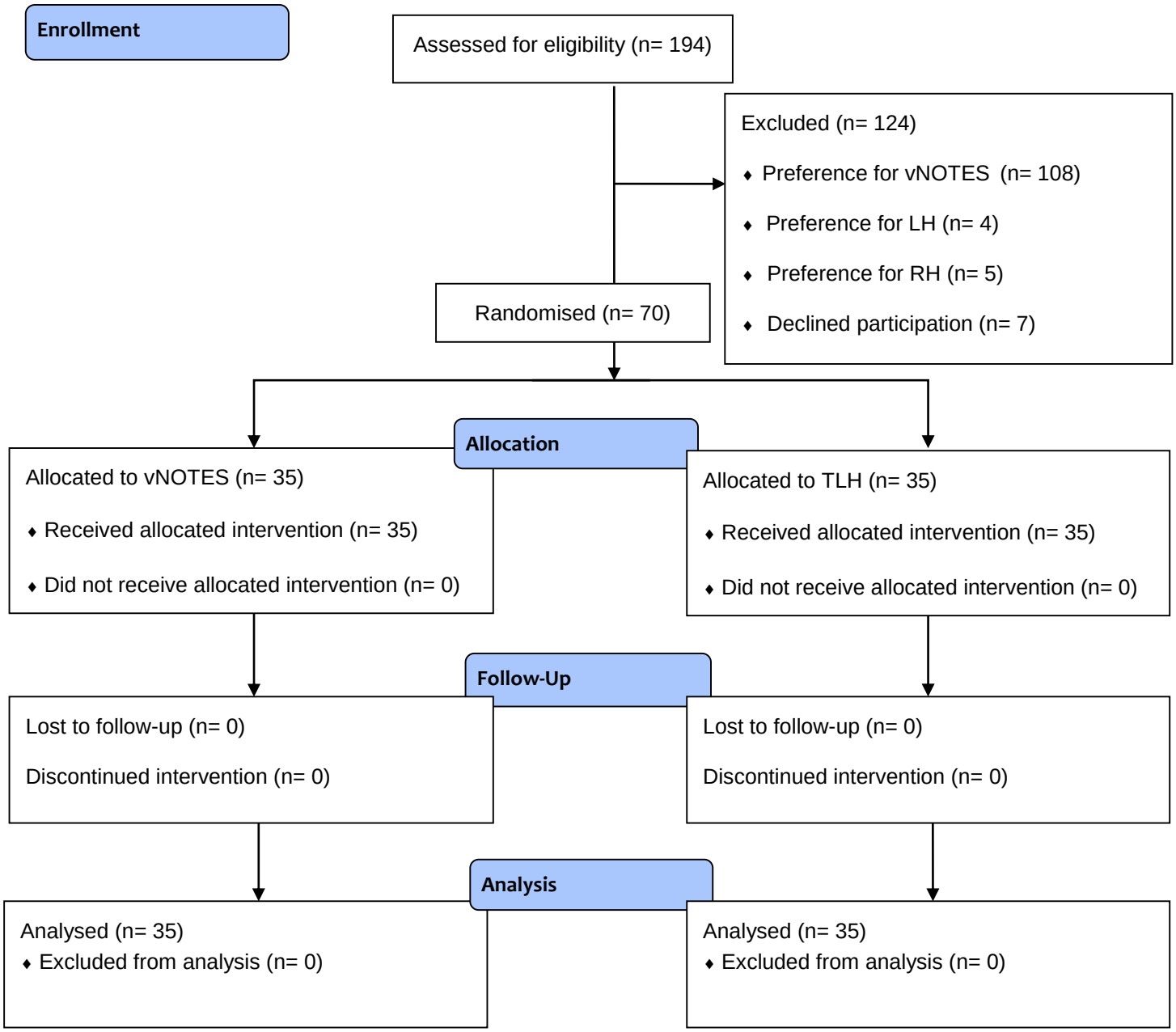

Figure 1. Trial profile

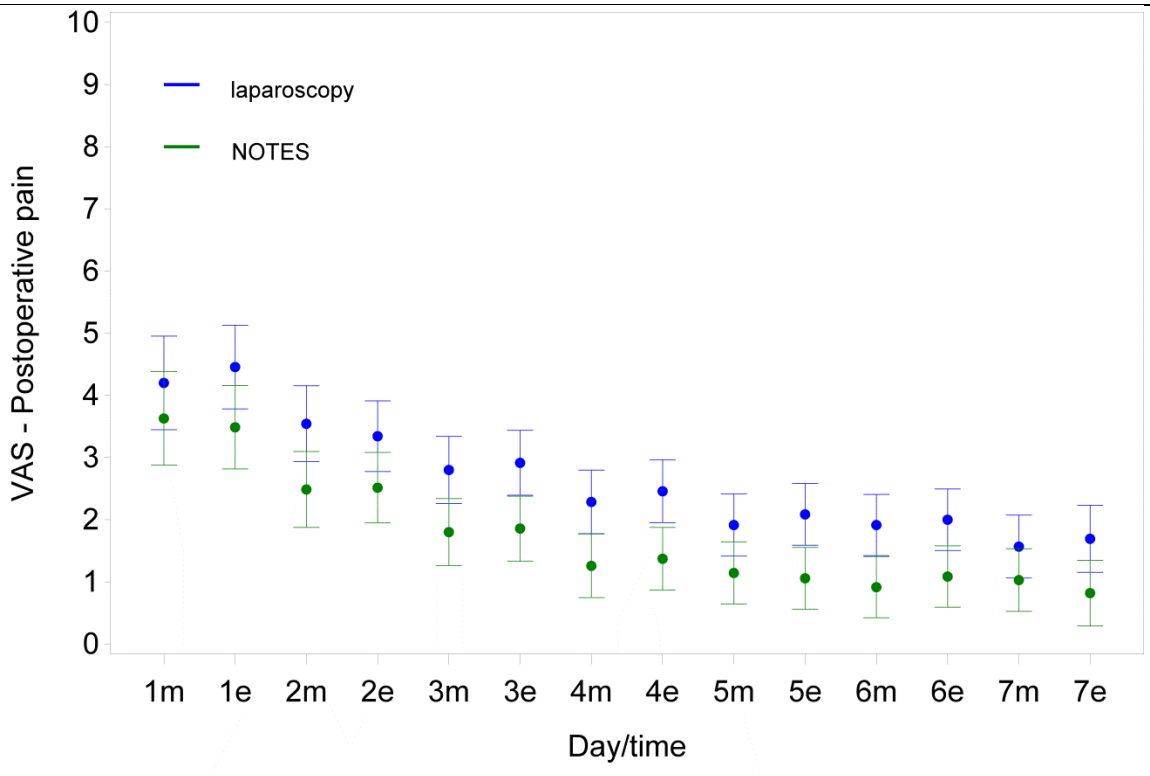

Figure 2. VAS Pain scores.

VAS scores during the first postoperative week by treatment arm and time (+95% CI). The blue dots/ whiskers represent TLH and the green represent vNOTES.

Mean difference, MD; - 0.89; 95% CI, - 0.31 to - 1.5; P = 0.003.

Number 1-7: postoperative day 1-7 m: morning e: evening

Table 1	TLH (N=35)	vNOTES (N=35)	Non-randomised (N=124)
Age (y) (mean,range)	49 (34 to 68)	46 (24 to 65)	49 (24 to 68)
BMI (kg/m²) (mean,range)	26 (19 to 43)	27 (18 to 44)	26 (18 to 44)
N vaginal births (mean,range)	1.3 (0 to 3)	1.4 (0 to 4)	1.5 (0 to 4)
Prior surgery (n, %)	16 (46 %)	20 (57 %)	50 (40 %)
Prior Caesarean section (n, %)	5 (14 %)	8 (23 %)	12 (10 %)
Uterine weight (g)† (mean,range)	177 (28 to 590)	206 (44 to 788)	206 (28 to 788)
Indication for surgery (n, %)			
myomatous uterus	16 (45%)	17 (49%)	51 (41%)
adenomyosis	6 (17%)	6 (17%)	16 (13%)
cervical dysplasia	7 (20%)	4 (11%)	24 (19%)
treatment resistant DUB	2 (6%)	5 (14%)	17 (14%)
atypical endometrial hyperplasia	2 (6%)	2 (6%)	10 (8%)
BRCA positive breast cancer	2 (6%)	1 (3%)	3 (2%)
Pain vagina (n, %) ∫	6 (17%)	15 (43%)	Not available
VAS pain vagina (median ±IQR)	0 (0 - 0)	0 (0 – 4))	Not available
Pain pelvis (n, %)	8 (23%)	12 (34%)	Not available
VAS pain pelvis (median ±IQR)	0 (0 -0)	0 (0 – 4)	Not available
Quality of life (mean ±SD)	77 (18)	75 (18)	Not available

Table 1. Baseline characteristics of the intention-to-treat population*

* There were no significant differences (P<0.05) between the two groups in the baseline characteristics except for pain in the vagina at baseline (∫ P = 0.03 - logistic regression analysis)

† Uterine weight was not measured in two women (one from each group).

DUB: dysfunctional uterine bleeding

IQR: interquartile range

SD: standard deviation

TLH: Total Laparoscopic Hysterectomy

VAS: Visual Analogue Scale

	TLH (N=35)	vNOTES (N=35)	Effect size (95%CI)
Conversions	0	0	Not estimable
Duration of surgery (minutes) (mean ±SD)	75 (27)	41 (22)	MD -34 (- 46 to - 22) ∫
Discharge day 0 (n, %)	15 (43%)	27 (77%)	RD + 0.34 (+ 0.13 to + 0.56) †
Length of hospital stay (days) (mean ±SD)	1.3 (1.2)	0.8 (0.77)	MD – 0.50 (- 0.98 to – 0.02)§
Total use analgesics (units) (mean ±SD)	14 (11)	8 (6.5)	MD -5.9 (- 10 to - 1.8) ‡
Complications:			
- Intra-operative (n, %)	0 (0 %)	1 (3 %) bladdertrauma:n=1	*
- Postoperative (n, %)	13 (37 %)	3 (9 %)	RD - 0.29 (- 0.47 to - 0.10) Δ
	Type I: 2	Type I: 1	
	Type II: 9	Type II: 2	
	Type III: 1	Type III: 0	
	Type IV: 1	Type IV: 0	
Postoperative infection (n, %)	2 (6 %)	1 (3 %)	*
Readmission < 6 weeks (n, %)	6 (17 %)	1 (3 %)	*

Table 2. HALON trial main outcomes

CI: confidence interval

MD: mean difference

RD: risk difference

SD: standard deviation

∫ P < 0.001 (Mann-Whitney U test)

† P = 0.007 (Fishers Exact test)

§ P = 0.004 (Mann-Whitney U test)

‡ P = 0.006 (Mann-Whitney U test)

Δ P = 0.009 (Fishers Exact test)

* There were no significant differences (P<0.05) between the two groups (Fishers Exact test)

Table S1. HALON trial secondary outcomes.

	TLH (N=35)	vNOTES (N=35)	Effect size (95%CI)
Total hospital bill (USD) (mean ±SD)	4,103 (1,348)	3,599 (914)	MD -504 (-1,044 to + 36)*
Pain vagina at 3 months (n, %)	9 (26 %)	8 (23%)	RD -0.03 (- 0.23 to + 0.17)**
VAS pain vagina at 3 months (median ±IQR)	0 (0-1)	0 (0-1)	MD + 0.30 (- 0.88 to + 1.5)*
Pain vagina at 6 months (n, %)	8 (23%)	5 (14%)	RD – 0.09 (- 0.27 to + 0.10)**
VAS pain vagina at 6 months (median ±IQR)	0 (0-1)	0 (0-0)	MD – 0.10 (- 0.97 to + 0.77)*
Pain pelvis at 3 months (n, %)	8 (23%)	6 (17%)	RD – 0.06 (- 0.24 to + 0.13)**
VAS pain pelvis at 3 months (median ±IQR)	0 (0-0)	0 (0-0)	MD 0.0 (- 0.94 to + 0.94)*
Pain pelvis at 6 months (n, %)	5 (14%)	4 (11%)	RD – 0.03 (- 0.19 to + 0.13)**
VAS pain pelvis at 6 months (median ±IQR)	0 (0-0)	0 (0-0)	MD – 0.10 (- 0.88 to + 0.68)*
Quality of life at 3 months (mean ±SD)	80 (18)	84 (14)	MD + 4.0 (- 3.5 to 12)*
Quality of life at 6 months (mean ±SD)	87 (9)	88 (11)	MD + 1.0 (- 3.7 to + 5.7)*

CI: confidence interval

IQR: interquartile range

MD: mean difference

RD: risk difference

SD: standard deviation

THB: total hospital bill

USD: US Dollar ($)

VAS: Visual Analogue Scale

* There were no significant differences (P<0.05) between the two groups (Mann- Whitney U test)

** There were no significant differences (P<0.05) between the two groups (Fishers Exact test)

Table S2. HALON trial types of complications and reasons for readmission.

TLH (N=35) (grade, n)	vNOTES (N=35) (grade, n)
Type of intra operative complications	
N=0	N=1 • bladder trauma:n=1(R/ intraoperative repair)
Type of postoperative complications	
N=13 • Pain (I): n=2 (R/ analgesia) • Vaginal cuff infection (II): n=2 (R/ AB) • Vaginal cuff hematoma (II): n=1 (No R/) • Cystitis (II): n=4 (R/ AB) • Transfusion (II): n=1 • Ileitis (II): n=1 (R/ supportive) • Repair vesicovaginal fistula (IIIb): n=1 (R/ surgical repair) • ICU admission pulmonary emboli (IVa): n=1 (R/ anticoagulants)	N=3 • Readmission to exclude DVT (I): n=1 (No R/) • Infected hematoma (II):n=1 (R/ AB) • Transfusion (II): n=1
Reasons for hospital readmission < 6 weeks	
N=6 • Pain: n=2 • Vaginal cuff infection: n=1 • Vaginal cuff hematoma: n=1 • Repair vesicovaginal fistula: n=1 • ICU admission pulmonary emboli: n=1	N=1 • CT angiography to exclude DVT: n=1

DVT: deep venous thrombosis

ICU: intensive care unit

APPENDIX I Pain protocol

PROTOCOL vNOTES – DR. BAEKELANDT

ASA I & ASA II PATIËNTEN

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1. INDUCTIE ANESTHESIE

- Propolipid 2,5mg/kg
- Sufentanil 0,15µg/kg
- Rocurorium 0,6mg/kg
- Dexamethasone 5mg
-

2. ONDERHOUD ANESTHESIE

- O_2/ lucht 50/50
  DES 1 MAC

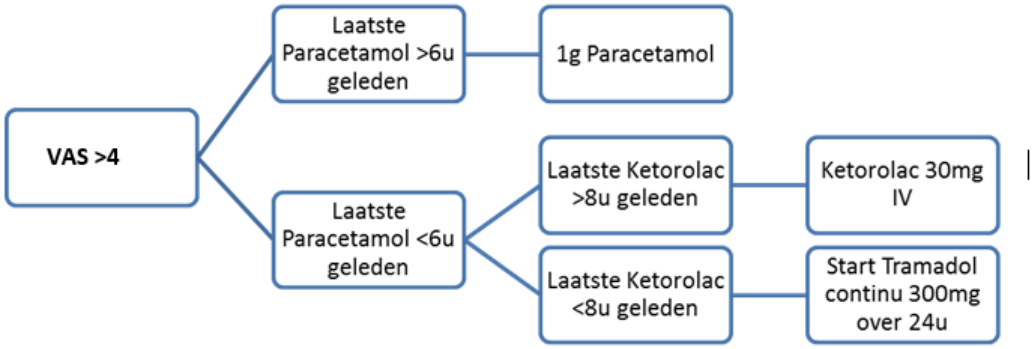
- Zo nodig bolus Alfentanil 5mg/kg
- 30min. voor einde IV toediening van
  - 1g Paracetamol
  - Ketorolac 0,5mg/kg met maximum van 30mg

3. POSTOPERATIEF

RECOVERY

- Bij VAS >4: 1g Paracetamol IV
- Herevaluatie na 30min.
  - Bij VAS >4: 2,5mg Piritramide IV

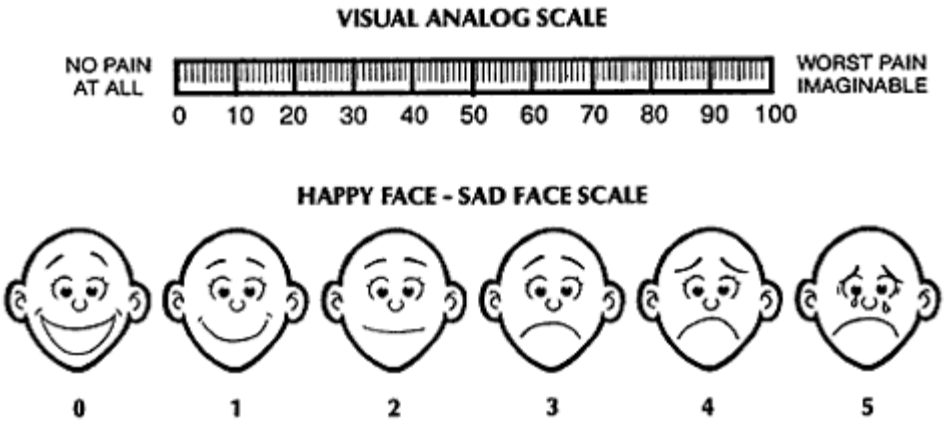
VERPLEEGAFDELING



Na 30min. herevaluatie + herstarten bovenstaand schema.

Indien VAS >4 blijft, ondanks starten van Tramadol continu: contacteer anesthesist

APPENDIX II VAS scale



Chapter 7

Discussion and Conclusion

Discussion and Conclusion

INTRODUCTION

Transvaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES) is a new surgical approach enabling surgeons to perform intraabdominal surgery without any abdominal incision using the vagina as the access route for the endoscopic instruments and the video camera.

My initial experience in the early stages of development and standardization of the vNOTES technique suggested that this new technique could offer numerous advantages for patients over conventional laparoscopic surgery[1],[2],[3]. Besides the obvious aesthetic advantages, less postoperative pain and quicker recovery was observed in women treated by vNOTES. After the learning curve a shorter duration of surgery when compared to laparoscopy was observed. Convinced that vNOTES had the potential to become the next paradigm shift towards a less invasive hysterectomy technique, my further practice and research into Single Incision Laparoscopic Surgery[4] was abandoned and focus was fully turned to developing vNOTES. In 2015 a new approach to hysterectomy was published: Total Vaginal NOTES Hysterectomy[5]. This thesis described research into the assessment of vNOTES for doing hysterectomy in women with benign gynaecological disease.

OUTLINE OF THESIS

Chapter 1 predefines the four major research questions of the present thesis:

1. To assess the use of an access port for vNOTES that had not yet been validated for this approach
2. To assess the feasibility of robotic NOTES hysterectomy
3. To summarize and critically appraise the current evidence for hysterectomy via vNOTES
4. To study the efficacy and short term safety of vNOTES hysterectomy compared to TLH for benign gynaecological disease in women with non-prolapsed uteri

As no access ports had been validated for vNOTES, exploration was first needed into different approaches to gain transvaginal access to the peritoneal cavity, while maintaining a good CO_2 seal. Initial research into vNOTES (2012 to 2015) used self-constructed glove ports: this low cost access port was constructed each time before the start of the procedure using a wound protector, a powder free surgical glove, reusable trocars and sterilized cable ties or Vicryl sutures. This DIY approach was not

user-friendly so commercially available ports were investigated as possible candidates for this new surgical approach. As vNOTES was still in its infancy, no port developed for transvaginal endoscopic access existed. Investigation was therefore started to determine whether any ports manufactured for trans-umbilical single incision surgery could be used for the new transvaginal endoscopic approach. These ports were tested in an off-label setting.

Chapter 2 demonstrates that the Gelpoint advanced access platform, a platform developed for trans-umbilical SILS, is suitable for vNOTES Hysterectomy[6]. The Gelpoint consists of two parts: a wound protector , as used in a glove port, sealed off by a cap that can be attached to the wound protector. The cap contains a gel cushion that can be perforated by several accessory trocars. It ensures a tightly sealed off CO_2 pneumoperitoneum and provides excellent access to the peritoneal cavity both in slim and obese patients. Between March and October 2015 110 vNOTES procedures including hysterectomy, salpingectomy, adnexectomy and cystectomy were performed by the doctorandus using the Gelpoint port off-label for transvaginal access. Two Gelpoint sizes were commercially available at the time of the study: Gelpoint and Gelpoint Mini. For all hysterectomies a VANH technique was performed using a Gelpoint. Using this large port maximized access and exposure. In all other procedures a Gelpoint Mini was used as they were performed through a small colpotomy in the Pouch of Douglas that does not allow placement of the larger Gelpoint. The procedures were all completed within reasonable operating time (the mean operating time for VANH was 56 minutes and 25.5 minutes for adnexal surgery). There were no per-operative complications. Postoperatively there were only minor complications: 7 patients were treated for a postoperative cystitis. The main advantages of the Gelpoint over a self-constructed glove port are shorter setup time, easier instrument transfer through the trocars, better ergonomics, and a less fragile port. The greatest disadvantage is the higher cost. There is also a limitation to 4 trocars compared to 5 when using the glove port. In this study, all procedures were performed without difficulty using only 3 trocars, as easier port transfer reduces the need for a larger number of ports. It was therefore concluded that Gelpoint advanced access platform is a suitable port for this new hysterectomy technique via vNOTES. It is more user friendly than the self-constructed glove ports used in initial research into the development of the vNOTES approach. It can therefore assist in making the vNOTES approach more reproducible by other surgeons.

Chapter 3 demonstrates that this new hysterectomy technique via vNOTES is also feasible via robotic surgery[7],[8]. These are the first reports worldwide of transvaginal robotic surgery. Initial research into vNOTES demonstrated that the technical drawbacks of transvaginal surgery, which include limited visualization to attempt good haemostasis and difficulty in performing adnexectomy in case of

adhesions between the adnexa and the uterus, can be overcome by performing transvaginal NOTES[5]. Robotic surgery offers advantages over conventional laparoscopic surgery: better ergonomics, better camera control, and articulated wrist motion. In this chapter the aim was to assess whether these advantages of robotic surgery could be combined with the advantages of a vNOTES approach. Initial assessment was to determine whether transvaginal robotic surgery was feasible, as this had never been reported. Two new techniques for robotic vNOTES hysterectomy were developed: Robotic Vaginally Assisted NOTES Hysterectomy (RVANH) and RTVNH (Robotic Total Vaginal NOTES Hysterectomy (RTVNH). In a small cohort of 20 patients it was demonstrated that transvaginal robotic surgery is feasible. The advantages of robotic surgery (improved ergonomics, better camera control and articulated wrist motion) were also confirmed in this new vNOTES approach. However, the currently available surgical robots are developed for transabdominal use and therefore frequent robotic arm collisions were encountered and the docking time was long, causing longer surgical times when compared to non-robotic vNOTES: the mean operating time for RTVNH was 118 minutes and 90 minutes for RVANH. With the current robotic technology it is therefore more efficient to perform vNOTES hysterectomy with conventional laparoscopic instruments than using robotic operated instruments; the main reason why this current research has focused on non-robotic vNOTES hysterectomy. It is foreseen that aided by future developments in robotic technology, this surgical field is very likely to develop further to offer patients the combination of the benefits of vNOTES plus those of robotic surgery. Especially in more challenging hysterectomies we foresee that the better camera angles and instrument dexterity of future vNOTES robots will offer benefits over conventional vNOTES.

Chapter 4 describes standardization of 4 different vaginal NOTES hysterectomy techniques[9]: Vaginally Assisted NOTES Hysterectomy (VANH), Total Vaginal NOTES Hysterectomy (TVNH), Robotic Vaginally Assisted NOTES Hysterectomy (RVANH) and, Robotic Total Vaginal NOTES Hysterectomy (RTVNH). In a Vaginally Assisted NOTES Hysterectomy (VANH) the initial part of the procedure is performed under direct vision using conventional surgical instruments. Circumcising the cervix, making the anterior and posterior colpotomy, and transecting the uterosacral ligaments is performed as in a conventional vaginal hysterectomy. Afterwards a vNOTES port is inserted via the vagina into the peritoneal cavity to create a pneumoperitoneum. The remainder of the procedure is performed via vNOTES using an endoscopic camera and endoscopic instruments.

In a Total Vaginal NOTES Hysterectomy (TVNH) the entire hysterectomy is performed via vNOTES. A vNOTES port is placed into the vagina and a pneumovagina is created. The entire hysterectomy (including circumcising the cervix, making the anterior and posterior colpotomy and transecting the

uterosacral ligaments) is performed via vNOTES using and endoscopic camera and endoscopic instruments.

In a Robotic Vaginally Assisted NOTES Hysterectomy (RVANH) the initial part of the procedure is performed under direct vision using conventional surgical instruments. Circumcising the cervix, making the anterior and posterior colpotomy, and transecting the uterosacral ligaments is performed as in a conventional vaginal hysterectomy. As a second step a vNOTES port is inserted via the vagina into the peritoneal cavity to create a pneumoperitoneum and a surgical robot is docked transvaginally; the next part of the surgical intervention is done via vNOTES using a robotically operated endoscopic camera and robotic instruments.

In a Robotic Totally Vaginal NOTES Hysterectomy (RTVNH) the entire hysterectomy is done via vNOTES. A vNOTES port is placed into the vagina and a pneumovagina is created. The entire hysterectomy (including circumcising the cervix, making the anterior and posterior colpotomy and transecting the uterosacral ligaments) is performed via vNOTES using a robotically operated endoscopic camera and robotic instruments.

After standardizing the new techniques we summarized and critically appraised the body of evidence on the benefits and harms of hysterectomy via vNOTES versus conventional laparoscopy in women with benign disease. The findings of a systematic review with meta-analysis are presented in **chapter 5**[10]. No randomised controlled trials were found. A comprehensive literature search retrieved only two retrospective cohort studies of sufficient methodological quality. The evidence demonstrates that hysterectomy by vNOTES is shorter compared to LAVH (MD -22 minutes, 95% CI -28 to -16; participants 342, studies=2). There is no evidence of statistically significant differences between vNOTES and LAVH for intra-or postoperative complications (RR 0.57, 95% CI 0.17 to 1.91; participants 342, studies=2). There were no data on the incidence of postoperative infection. There is evidence of statistically significant differences in favour of vNOTES for the length of hospital stay but the clinical relevance of this difference seems trivial (MD 0.42 days; 95% CI 0.59 to 0.25; participants 342, studies=2). There was no evidence of statistical differences between vNOTES and LAVH for the pain VAS scores or the mean analgesic use. There were no data on the incidence or severity of dyspareunia, sexual wellbeing or quality of life following surgery. One study reported higher costs for hospital charges in women treated by vNOTES (MD 168$; 95% CI 109 to 227$; participants 294, studies=1). In conclusion, the limited evidence is not sufficient to assess the effectiveness and safety of vNOTES hysterectomy. Therefore vNOTES hysterectomy should be considered as a technique under evaluation: there is a need for further research as outlined by the IDEAL collaboration guidelines on the implementation of innovative surgical techniques.

Based on the findings of the systematic review, preliminary observations with vNOTES and following the IDEAL guidelines[11] a -blinded randomised controlled trial was designed and conducted to compare vNOTES hysterectomy with the currently most used technique for doing hysterectomy in Belgium, total laparoscopic hysterectomy (Fig. 1). The protocol of the HALON (Hysterectomy by transabdominal Laparoscopy or NOTES) trial, as presented in **chapter 6**, was registered at the National Institutes of Health at ClinicalTrials.gov and was published in BMJ Open[12]. The objective of the study was to compare the efficacy of VNH with Total Laparoscopic Hysterectomy (TLH). The primary outcome measure of efficacy was the successful removal of the uterus without conversion in women bound to undergo hysterectomy for benign gynaecological disease, regardless of BMI, parity or uterine size. The study design was a randomised controlled, single centre, blinded, parallel group, non-inferiority efficacy study. The target population included women aged 18-70 bound to undergo hysterectomy for benign gynaecological disease. The intervention was a VNH. The comparator was a TLH. The primary outcome measure was the successful removal of the uterus with the intended approach without conversion. For multiple hypothesis testing the following secondary outcomes were studied; the proportion of women discharged on the same day, postoperative pain scores and analgesics used, incidence of postoperative infections, peri- and postoperative complications, hospital readmissions, duration of the procedure, incidence of dyspareunia, sexual wellbeing, and costs. Standardized pre-, peri-, and postoperative protocols were used and participants and outcome assessors were blinded by sham incisions in the intervention group.

One of the few blinded randomised controlled trials on hysterectomy techniques, and the first ever-reported blinded RCT comparing VNH and TLH, was conducted and successfully completed. The results of the HALON trial are presented in **Chapter 7**. 194 patients were assessed to be eligible for participation in the HALON trial. 124 patients declined participation, 70 patients were included and randomised into 35 VNH and 35 TLH. No patients were lost to follow up and 70 patients were included in the analysis. The baseline characteristics of the trial participants were similar in the intervention, control and non-randomised group. There were no conversions in either group, so for the primary outcome measure it can be concluded that VNH is equally efficacious to TLH. The mean duration of the surgery was significantly shorter in the vNOTES group (MD -34 minutes; 95% CI -46 to -22; p<0.001); the number of women discharged on the day of the surgery was significantly higher in the vNOTES group (RD +0.34; 95% CI +0.13 to +0.56; P=0.007); the length of hospital stay was significantly shorter in the vNOTES group (MD -0.50; 95% CI -0.98 to -0.02; P=0.004); the total use of analgesics was significantly lower in the vNOTES group (MD -5.9; 95% CI -10 to -1.8; P=0.006); the incidence of postoperative complications was significantly higher in the TLH group (RD +0.03; 95% CI -0.05 to +0.10; P=0.009). There was no evidence of statistically significant differences between VNH and TLH for the

outcomes of intra-operative complications, postoperative infections, hospital readmissions up to 6 weeks after the surgery, or total hospital bill. There was no evidence for statistically significant differences between the two comparison groups for the following patient reported outcomes: incidence and VAS score of pelvic pain at 3 and 6 months postoperatively, incidence and VAS score of vaginal pain at 3 and 6 months, quality of life at 3 and 6 months postoperatively. It can be concluded that vNOTES hysterectomy is equally efficacious to TLH for removal of the uterus, while it results in shorter duration of surgery, more women leaving the hospital within 12 hours after surgery, shorter length of hospital stay, less complications during the first six weeks of surgery, less use of analgesics and lower pain scores during the first seven days. There were no differences between the techniques in the prevalence or severity of pain during sexual intercourse at three or six months after hysterectomy.

SUMMARY

In summary the 4 research questions that were set out at the onset of this thesis were answered.

The first research question of this thesis was to assess the use of an access port for vNOTES that had not been validated for this approach and it was concluded that Gelpoint advanced access platform is a suitable port for VNH. The second research question was to assess the feasibility of robotic NOTES hysterectomy. The first transvaginal robotic surgery ever reported was performed and it was determined that robotic NOTES hysterectomy is feasible via two different new techniques: RVANH and RTVNH. The conclusion was that transvaginal robotic surgery is a surgical field that is very likely to develop further to offer patients the combination of the benefits of vNOTES and of robotic surgery, but that further technical innovations in robotic surgery are needed first. The remainder of the thesis therefore focused on non-robotic vNOTES hysterectomy. The third research question of this thesis was to assess the current evidence for hysterectomy via vNOTES. A systematic review and meta-analysis were performed and it was concluded that the limited evidence is far from sufficient and that further research into vNOTES was needed. Following the IDEAL guidelines to further research vNOTES hysterectomy, a blinded surgical RCT comparing VNH with TLH was designed. The fourth research question of this thesis was to compare the efficacy and short term safety of vNOTES hysterectomy with the currently most used hysterectomy technique in Belgium, the TLH. A blinded randomised controlled trial comparing vNOTES hysterectomy with TLH was conducted and completed. The results are summarized in the previous paragraph.

IMPLICATIONS

After reviewing the results of this thesis the future perspectives need to be critically addressed. First the implications of the findings for daily clinical practice will be discussed followed by the implications for research.

1. Implications for clinical practice

There can be no doubt that it is too early to implement vNOTES into routine clinical practice. This thesis demonstrates that vNOTES hysterectomy is a very promising technique (more patients leaving the hospital on the day of the surgery, shorter hospitalisation, lower pain scores, less analgesics used, less complications) but the current evidence is limited to the experience of a single experienced vNOTES surgeon beyond his surgical learning curve for vNOTES surgery. The "experimental" study design of the HALON trial cannot be generalized at this moment. Being a small single-centre study, the HALON trial is a first step in the process of scientific evaluation of the effectiveness and safety of a new surgical technique, as outlined by the IDEAL Collaborative Group, an international cooperation between biostatisticians, clinical trial specialists and surgeons[11]. The HALON study was not adequately powered to determine the long-term safety of vNOTES compared to TLH. Current findings justify the evaluation of vNOTES in large multicentre RCTs. If such studies confirm these findings, large prospective registries are needed to monitor the occurrence of adverse events caused by the new technique, both short and long term.

The learning curve of the surgeon was long, despite having had the advantage of being a gynaecologic oncologic surgeon experienced in transvaginal Schauta surgery as well as level 4 laparoscopic surgery. The results of the HALON trial demonstrate short operating times for VNH, but the surgeon was already experienced in vNOTES at the onset of the trial; it is important to stress that the initial cases took a very long operating time. Research into vNOTES was started by the doctorandus in 2012 and at that time there was no possibility to go and learn the technique from other surgeons. The doctorandus adapted the technique numerous times during his first 100 cases and constantly fine-tuned it until approximately 500 cases were completed. As the technique is now standardized, the learning curve of future vNOTES surgeons should be significantly shorter. Whilst the technique is still under evaluation, it is suggested that for now only experienced surgeons, skilled in both conventional vaginal surgery and laparoscopic surgery, start learning this technique. A rigorous teaching process in different stages should be adopted, for example: theoretical sessions, followed by dry lab sessions and finally live case observations, tutorials, and proctoring. These surgeons could be followed up and their data

prospectively registered in an international complication database. Based on this data , centres could be selected where the caseload is high enough and surgeons have performed sufficient cases to have passed their learning curve. Once there are enough centres with enough surgeons that have passed their learning curve, it will be possible to perform prospective large multicentre RCTs. Only once the results of these multicentre RCTs confirm the benefits of VNH demonstrated in the HALON trial, can VNH be included in the general training of OBGYNs.

2. Implications for research

HALON 2.0 and prospective complication database

Following the principles of the IDEAL collaboration adhered to for this research, the next step in the development of a new surgical technique could possibly be a multicentre RCT comparing VNH with TLH. Another option could be to compare VNH with VH which is the gold standard technique for performing hysterectomy in women with benign gynaecological disease when technically feasible, according to a Cochrane review of hysterectomy techniques[13] . To study the long-term safety of this new surgical technique it is necessary to collect data in large international prospective complication databases. The HALON trial was a single centre study, which had the advantage that all the procedures were performed by one surgeon and the efficacy of the techniques could be compared without being biased by measuring differences in skills between surgeons. The search for proof of efficacy by designing an "experimental" non-pragmatic single-centre single surgeon trial was however at the cost of uncertainty about the generalizability of the trial's findings. Currently more and more surgeons are taking their first steps in performing vNOTES surgery[14],[15],[16]. However, before a HALON 2.0 multicentre study can commence, all surgeons should first pass their learning curve for vNOTES surgery to ensure that their learning curve is not a bias for the results of the HALON 2.0 trial. At the same time it is important to collect a high volume of data in a large prospective complication database to further validate vNOTES.

Scarless surgery

The obvious aesthetic advantage of vNOTES over conventional laparoscopy was not specifically investigated in this thesis. The evidence for this speaks for itself. The importance of "scarless" surgery became apparent from the findings in women that declined participation in the HALON trial. In order to include 70 patients, we assessed 194 patients. Out of the 124 patients who declined participation in the HALON trial, 108 declined participations because they specifically requested a vNOTES procedure. Only 4 patients specifically requested a laparoscopic hysterectomy. The other 12 patients

who declined participation for other reasons also opted, after being given the choice laparoscopy of vNOTES, for transvaginal NOTES. Whereas aesthetics were not an important factor in our assessment of the benefits of vNOTES hysterectomy, our experience from counselling patients for HALON trial inclusion, taught us that abdominal scars are not such a trivial factor for patients. This is an interesting field for further research into patient's choices when different hysterectomy techniques are offered. It demonstrates the importance of including outcomes that are relevant to patients, and not only outcomes that reflect the surgeon's interest in surgical trials.

Cost of surgery

From a health care perspective the cost of surgery is a very important topic. The HALON trial did not demonstrate higher costs with vNOTES as reported by Wang and co-workers[17]. In our randomised controlled trial there was no evidence for statistically significant differences between VNH and TLH for the direct costs incurred up to 6 weeks after surgery as measured by the total hospital bill. By allowing a shorter length of hospital stay and the potential to do more hysterectomies as day care surgical procedures vNOTES may impact substantially on the health care budget. This is an important topic for further study. Similarly the potential quicker return to normal activity due to quicker recovery after vNOTES surgery should be investigated, further taking into account its impact on the total health care cost.

Outpatient surgery

A recently published systematic review concluded that outpatient hysterectomy (laparoscopic and conventional vaginal) is feasible in a well selected patient population with a low risk of complications and readmissions[18]. The vast majority of studies in this review were observational studies and there was no blinding. The authors therefore conclude that these data should be confirmed in RCT's. The HALON trial already partly answers their question. It demonstrates in a blinded RCT that outpatient hysterectomy is feasible with a low complication and a low readmission rate (even in a non-preselected population) and adds that the surgical technique has a significant influence on how many patients choose to go home on the same day of the operation. Significantly more patients choose to go home on the day of the surgery after a vNOTES hysterectomy than after a laparoscopic hysterectomy. As same day discharge is an increased trend in contemporary surgery and will most likely be implemented for more procedures, it is important to investigate this further for hysterectomy as well. The implementation of vNOTES may play an important role in successfully introducing outpatient hysterectomy. Based on the data of the National Institute for Health and Disability Insurance (RIZIV) outpatient hysterectomy in Belgium is almost non-existent as opposed to data from the US. In 2016 55 out of 12638 and in 2017 86 out of 11364 hysterectomies were done as day care surgical procedures

(Fig. 2). A superior surgical technique alone is not the only factor that predicts a successful outpatient procedure. It is important that this is set within a well-developed and structured framework. For outpatient hysterectomies in this research a standardized pre,-peri-, and postoperative protocol was used with meticulous attention to anaesthetic protocols and personalized nursing attention for the women. It would be interesting to implement these same protocols for conventional vaginal hysterectomy and prospectively compare vNOTES hysterectomy with conventional vaginal hysterectomy instead of with total laparoscopic hysterectomy, where one could predict a significantly higher conversion rate in the conventional vaginal hysterectomy group. A recent retrospective study comparing vNOTES with conventional vaginal hysterectomy in female-to-male transgender men demonstrated a significant decrease in post-operative pain and analgesics use in the vNOTES group with an equivalent safety.[19]

Robotic surgery

A recently published large retrospective cohort study of more than 500000 women who underwent a benign hysterectomy between 2008 and 2014 in the USA shows significantly higher rates of outpatient hysterectomy in the USA[20]. It is however important to stress that the definition of an outpatient hysterectomy in that study was discharge within 24 hours after the surgery, whereas in a European setting outpatient is considered to be on the same day of the surgery, i.e. within 12 hours. Nevertheless these data convincingly demonstrate an increasing trend in the USA towards shorter hospitalization for hysterectomy. The US data demonstrate a significant increase in laparoscopic and robotic transabdominal hysterectomy between 2008 and 2014, and a significant shift from inpatient to outpatient hysterectomy. The observational US data suggest that robotic transabdominal hysterectomy may facilitate the shift to outpatient hysterectomy more than laparoscopic hysterectomy. As the current data suggest that vNOTES hysterectomy may facilitate this shift in a 12 hour outpatient setting, and the US data that robotic transabdominal hysterectomy does the same in a 24 hour outpatient setting, it would be interesting to compare vNOTES hysterectomy with robotic hysterectomy. A priori it would be good to combine the best of both worlds and continue the research on the new technique of transvaginal robotic NOTES hysterectomy as described in chapter 3. This technique combines the benefits of vNOTES surgery with the benefits of robotic surgery. New less bulky robotic devices (e.g. Da Vinci SP, Memic Hominis, Versius – all currently not available in Europe yet) may facilitate the use of robotics via vNOTES.

Frugal innovations

On the other hand, robotic surgery at this moment still requires substantial investments and is therefore only accessible for a small percentage of the world's population. From a global and

humanitarian perspective, it is necessary to stimulate further research in frugal innovations in endoscopic surgery that may benefit women globally. Low cost innovations can facilitate the worldwide introduction and dissemination of minimally invasive surgery and vNOTES into low resource settings.

CONCLUSION

This thesis confirms our initial hypothesis that this new hysterectomy technique by vNOTES is feasible and very promising for doing hysterectomy as a day care procedure in women with benign gynaecological disease. When performed by an experienced vNOTES surgeon beyond his or her surgical learning curve aided by a competent team of care takers vNOTES enables more hysterectomies to be performed as a day care surgical case compared to TLH. The findings clearly need to be supported by more multicentre trials and large prospective complication registries before a change in treatment policy can be advocated, let alone implemented.

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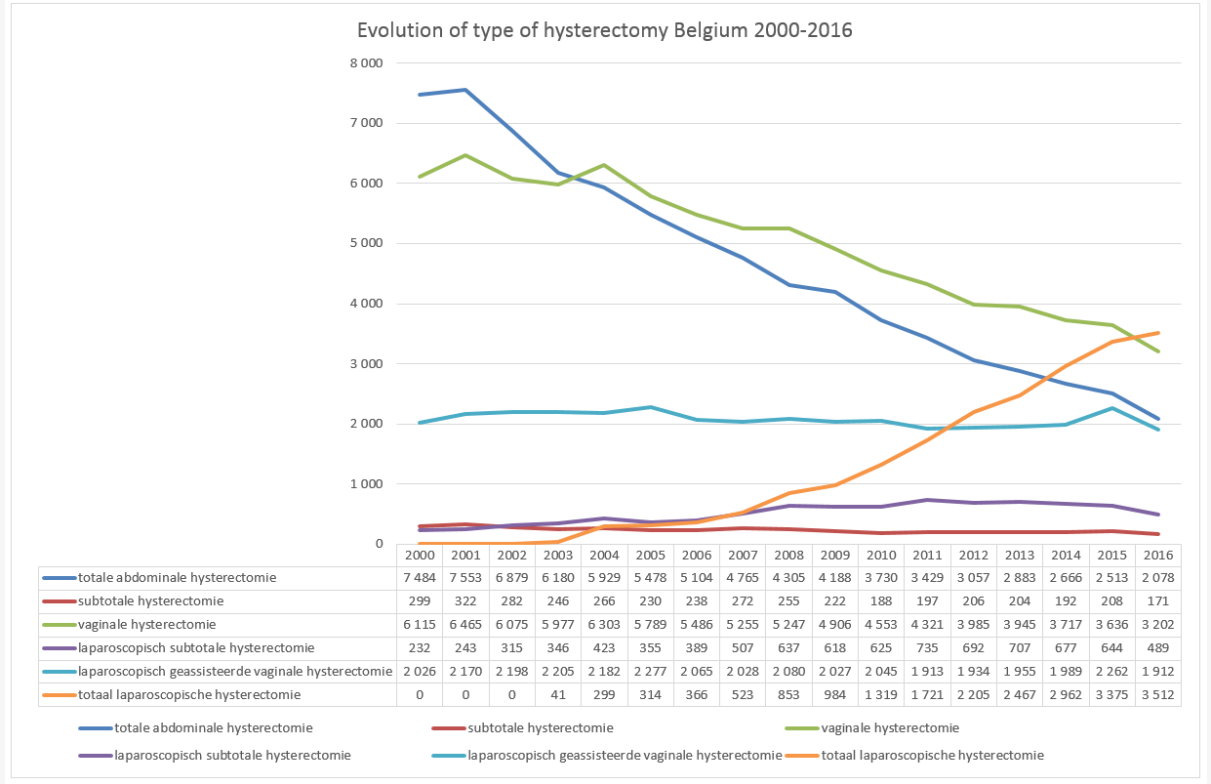

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
totale abdominale hysterectomie	7 484	7 553	6 879	6 180	5 929	5 478	5 104	4 765	4 305	4 188	3 730	3 429	3 057	2 883	2 666	2 513	2 078
subtotale hysterectomie	299	322	282	246	266	230	238	272	255	222	188	197	206	204	192	208	171
vaginale hysterectomie	6 115	6 465	6 075	5 977	6 303	5 789	5 486	5 255	5 247	4 906	4 553	4 321	3 985	3 945	3 717	3 636	3 202
laparoscopisch subtotale hysterectomie	232	243	315	346	423	355	389	507	637	618	625	735	692	707	677	644	489
laparoscopisch geassisteerde vaginale hysterectomie	2 026	2 170	2 198	2 205	2 182	2 277	2 065	2 028	2 080	2 027	2 045	1 913	1 934	1 955	1 989	2 262	1 912
totaal laparoscopische hysterectomie	0	0	0	41	299	314	366	523	853	984	1 319	1 721	2 205	2 467	2 962	3 375	3 512

Fig. 1 Evolution of type of hysterectomy in Belgium between 2000 and 2016 (Source: National Institute for Health and Disability Insurance.)

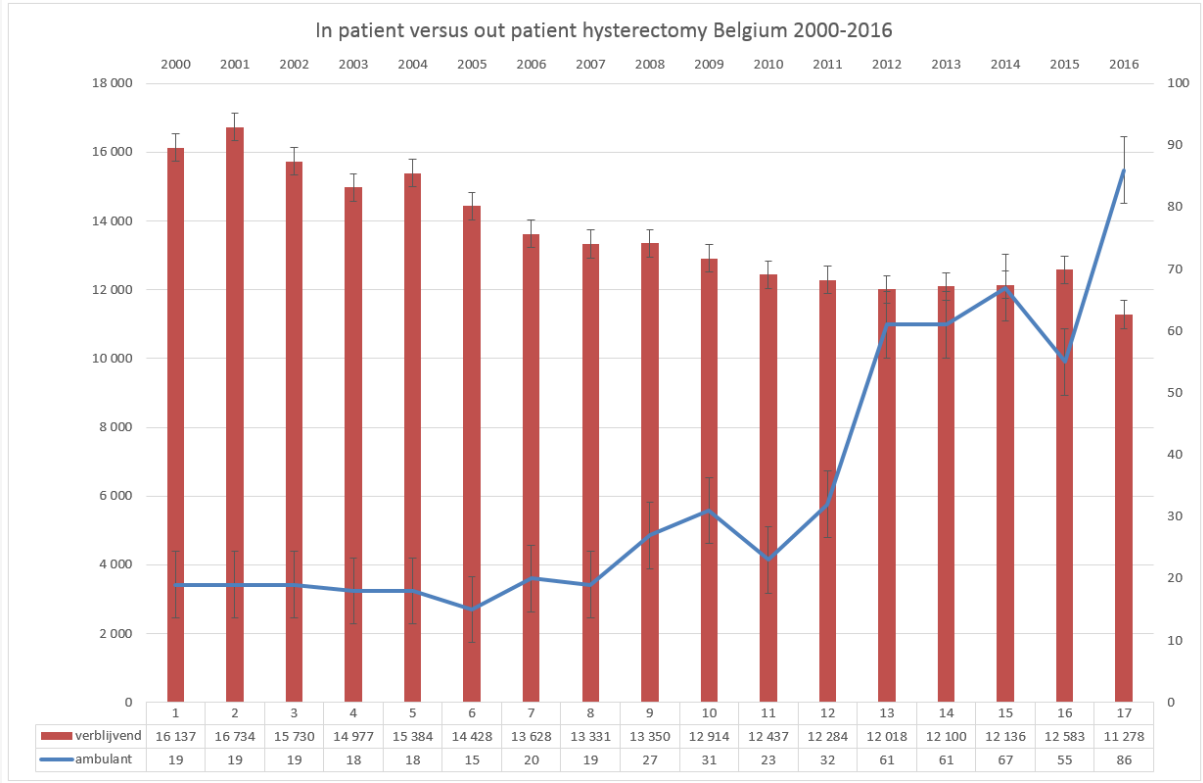

Fig.2. In-patient versus out-patient hysterectomy in Belgium between 2000 and 2016 (Source: National Institute for Health and Disability Insurance)

Chapter 8

8.1 THESIS SUMMARY

8.2 SAMENVATTING PROEFSCHRIFT

8.1 THESIS SUMMARY

My initial experience in the early stages of development and standardization of the vNOTES technique suggested that this new technique could offer numerous advantages for patients over conventional laparoscopic surgery. Besides the obvious aesthetic advantages, less postoperative pain and quicker recovery were observed in women treated by vNOTES. After the learning curve a shorter duration of surgery when compared to laparoscopy was observed. Convinced that vNOTES had the potential to become the next paradigm shift towards a less invasive hysterectomy technique, my further practice and research into Single Incision Laparoscopic Surgery was abandoned and focus was fully turned to developing vNOTES. In 2015 a new approach to hysterectomy was published: Total Vaginal NOTES Hysterectomy. This thesis described research into the assessment of vNOTES for performing hysterectomy in women with benign gynaecological disease.

As no access ports had been validated for vNOTES, we first needed to explore different approaches to gain transvaginal access to the peritoneal cavity while maintaining a good CO_2 seal. In chapter 2 we demonstrated that Gelpoint advanced access platform, a platform developed for transumbilical SILS, is suitable for vNOTES Hysterectomy. It provides a good CO_2 seal and good access to the peritoneal cavity in slim and in obese patients. The main advantages over a self-constructed gloveport are shorter setup time, easier instrument transfer through the trocars, better ergonomics and a less fragile port.

In chapter 3 we demonstrated that this new hysterectomy technique via vNOTES is also feasible via robotic surgery. These are the first reports worldwide of transvaginal robotic surgery. We demonstrated that transvaginal robotic surgery is feasible and that with the help of future developments in robotic technology, this is a surgical field that is likely to develop further to offer patients the combination of the benefits of vNOTES and of robotic surgery.

We then proceeded to standardize the 4 different hysterectomy techniques via vNOTES and described them in detail in chapter 4: Vaginally Assisted NOTES Hysterectomy (VANH), Total Vaginal NOTES Hysterectomy (TVNH), Robotic Vaginally Assisted NOTES Hysterectomy (RVANH) and, Robotic Total Vaginal NOTES Hysterectomy (RTVNH).

After standardizing the new techniques we critically appraised the existing studies on the benefits and harms of hysterectomy via vNOTES versus conventional laparoscopy in women with benign disease. The results of this systematic review and meta-analysis are presented in chapter 5. Our literature search did not retrieve any randomized controlled trials. There are only two retrospective cohort studies of acceptable quality. The data suggest that vNOTES hysterectomy is faster than LAVH

with no statistically significant differences for intra-or postoperative complications. There were no data on the incidence of postoperative infection. The length of hospital stay seems shorter for vNOTES but this result should be interpreted with caution. There was no statistical difference in VAS scores or mean analgesic use. We found no data on the incidence or severity of dyspareunia, sexual wellbeing or quality of life following surgery. One study reported higher costs for hospital charges in women treated by vNOTES. We conclude that the scant evidence is not sufficient and that vNOTES should be considered to be a technique under evaluation and need of further research in accordance with the IDEAL collaboration guidelines on the implementation of innovative surgical techniques.

Following the IDEAL guidelines we decided to perform a prospective randomised controlled trial comparing vNOTES hysterectomy with the current gold standard technique for hysterectomy: total laparoscopic hysterectomy. The protocol of the HALON (Hysterectomy by transAbdominal Laparoscopy or NOTES) trial, as presented in chapter 6, was registered at the National Institutes of Health at ClinicalTrials.gov and was published in BMJ Open.

We proceeded to perform this prospective blinded randomised controlled trial comparing vNOTES and TLH. The results of the HALON trial are presented in Chapter 6 and are published in BJOG. We conclude that vNOTES hysterectomy is equally efficacious to TLH for removal of the uterus, while the secondary outcome measures demonstrate a shorter duration of surgery, more women leaving the hospital within 12 hours after surgery, shorter length of hospital stay, less complications during the first six weeks of surgery, less use of analgesics and lower pain scores during the first seven days. There were no differences between both techniques in the prevalence or severity of pain during sexual intercourse at three or six months after hysterectomy.

In summary we answer the four research questions that were set out at the onset of this thesis.

1. *To assess the use of an access port for vNOTES that had not been validated for this approach.*
   We assessed that Gelpoint advanced access platform is a suitable port for vNOTES hysterectomy.
2. *To assess the feasibility of robotic NOTES hysterectomy.*
   We performed the first transvaginal robotic surgery ever reported and assessed that robotic NOTES hysterectomy is feasible via two different techniques: RVANH and RTVNH
3. *To assess the current evidence for hysterectomy via vNOTES.*
   We performed a systematic review and meta-analysis and concluded that the scant evidence is not sufficient and that vNOTES further research is necessary. We then followed the IDEAL guidelines to further research vNOTES hysterectomy.
4. *To prospectively compare vNOTES hysterectomy to the gold standard TLH.*

We performed a prospective blinded randomised controlled trial comparing vNOTES hysterectomy with TLH. The results are summarized in the previous paragraph.

We conclude that we have successfully answered the four research questions of this thesis and that vNOTES hysterectomy is indeed a very promising new technique. In the hands of an experienced vNOTES surgeon it can offer significant advantages over other hysterectomy techniques: surgery without visible scars, shorter operating times, more patients leaving the hospital on the day of the surgery, shorter length of hospital stay, lower pain scores and less complications. These data will need to be confirmed in the hands of other surgeons in multicentre randomised controlled trials.

8.2 SAMENVATTING PROEFSCHRIFT

Mijn eerste ervaringen in de vroege ontwikkelings- en standaardisatiestadia van vNOTES toonden dat deze nieuwe techniek verschillende voordelen voor de patiënten kon bieden ten opzichte van conventionele laparoscopische heelkunde. Naast de voor de hand liggende esthetische voordelen, werd vastgesteld dat vrouwen die geopereerd waren via vNOTES sneller leken te herstellen en minder pijn hadden. Eens de chirurg zijn leercurve doorlopen had, werd ook een kortere operatietijd dan bij laparoscopie vastgesteld. In mijn overtuiging dat vNOTES het potentieel had om een nieuw paradigma van een minder invasieve hysterectomietechniek in te leiden, werd beslist om verder onderzoek en implementatie van Single Incision Laparoscopic Surgery (SILS) te staken en mijn focus volledig te leggen op de ontwikkeling van vNOTES. In 2015 werd een nieuwe hysterectomietechniek gepubliceerd: Total Vaginal NOTES Hysterectomy. Dit proefschrift beschrijft het verder onderzoek naar de evaluatie van het uitvoeren van hysterectomies via vNOTES bij vrouwen met goedaardige gynaecologische pathologie.

Gezien er nog geen toegangspoorten voor vNOTES gevalideerd waren, moesten eerst verschillende manieren geëxploreerd worden om transvaginaal toegang te bekomen tot de peritoneale caviteit met behoud van een goed CO_2 pneumoperitoneum. In hoofdstuk 2 wordt aangetoond dat het Gelpoint advanced access platform, een platform ontwikkeld voor transumbilicale SILS, geschikt is voor gebruik in een vNOTES hysterectomie. Het zorgt voor een goed afgesloten CO_2 pneumoperitoneum en verzekert goede toegang tot de peritoneale caviteit bij magere en obese patiënten. De voordelen van Gelpoint tegenover een zelfgeconstrueerde handschoenpoort waren een kortere installatietijd, gemakkelijker plaatsen van de instrumenten door de trocars, betere ergonomie en een minder fragiele poort.

In hoofdstuk 3 wordt aangetoond dat deze nieuwe hysterectomietechniek via vNOTES ook met behulp van robotchirurgie kan uitgevoerd worden. Het was wereldwijd de eerste keer dat transvaginale robotchirugie in de klinische praktijk beschreven werd. We toonden aan dat transvaginale robotchirurgie mogelijk is en dat dit een nieuw chirurgisch domein is dat, met de hulp van toekomstige ontwikkelingen in robot technologie, hoogstwaarschijnlijk verder zal ontwikkelen om patiënten de combinatie van de voordelen van vNOTES en robotchirurgie aan te bieden.

In hoofdstuk 4 hebben we als volgende stap de 4 verschillende vaginale NOTES hysterectomie technieken gestandaardiseerd: Vaginaal geAssisteerde NOTES Hysterectomie (VANH), Totaal Vaginale NOTES Hysterectomie (TVNH), Robotisch Vaginaal geAssisteerde NOTES Hysterectomie (RVANH) en, Robotische Totaal Vaginale NOTES Hysterectomie (RTVNH).

Na standaardisatie van de nieuwe technieken werd de evidentie voor de voor- en nadelen van een hysterectomie via vNOTES versus conventionele laparoscopie bij vrouwen met goedaardig baarmoederlijden samengevat en kritisch geëvalueerd. De resultaten van deze systematische review met meta-analyse worden weergegeven in hoofdstuk 5. Er werden geen gerandomiseerde gecontroleerde studies gevonden. Na een uitgebreid literatuuronderzoek werden maar twee retrospectieve cohortstudies weerhouden waarvan de methodologische kwaliteit voldoende was. De evidentie toonde dat een hysterectomie via vNOTES minder lang duurt dan een LAVH zonder statistisch significante verschillen voor intra- of postoperatieve complicaties. Er waren geen gegevens over de incidentie van postoperatieve infectie. Er was evidentie voor een statistisch significant verschil ten voordele van vNOTES voor hospitalisatieduur maar de klinische relevantie van dit verschil leek beperkt. Er was geen evidentie voor statistische verschillen tussen vNOTES en LAVH voor pijn VAS scores of analgeticagebruik. Er waren geen gegevens over de ernst of de incidentie van dyspareunie, het seksuele welbevinden of de levenskwaliteit na chirurgie. Eén studie rapporteerde hogere hospitalisatiekosten voor vrouwen die behandeld waren via vNOTES. We concludeerden dat de beperkte evidentie onvoldoende was om de effectiviteit en veiligheid van vNOTES hysterectomie te evalueren. Daarom moest vNOTES hysterectomie gezien worden als een techniek die nog onder evaluatie was: er was nood aan verder onderzoek zoals beschreven in de richtlijnen van de IDEAL samenwerking over het implementeren van nieuwe chirurgische technieken.

Op basis van onze observationele bevindingen met vNOTES hysterectomie en van de resultaten van deze systematische review werd beslist om de IDEAL richtlijnen te volgen en werd een geblindeerde gerandomiseerd gecontroleerde studie opgezet en uitgevoerd om vNOTES hysterectomie te vergelijken met totaal laparoscopische hysterectomie (TLH), de techniek die in België momenteel het meest gangbaar is voor het uitvoeren van een hysterectomie (Fig. 1). Het protocol van de HALON (Hysterectomy by transAbdominal Laparoscopy or NOTES) studie, zoals voorgesteld in hoofdstuk 6, werd geregistreerd bij de National Institutes of Health op ClinicalTrials.gov en werd gepubliceerd in BMJ Open. De resultaten van de HALON studie werden gepubliceerd in BJOG. We concluderen dat vNOTES even werkzaam is als TLH voor het verwijderen van een uterus. De secundaire uitkomsten tonen aan dat vNOTES resulteert in een kortere operatieduur, dat meer vrouwen het ziekenhuis binnen de 12 uur na de operatie verlaten, dat de hospitalisatieduur korter is, dat er minder complicaties gedurende de eerste 6 postoperatieve weken zijn, dat het analgeticagebruik lager is en dat er lagere pijnscores gedurende de eerste 7 dagen zijn. Er was geen verschil tussen beide technieken in de prevalentie en ernst van dyspareunie op 3 en 6 maanden na een hysterectomie.

Samenvattend beantwoorden we de vier grote onderzoeksvragen van dit proefschrift:

1. *Het gebruik van een voor deze techniek nog niet gevalideerde toegangspoort voor vNOTES evalueren.*

   We toonden aan dat het Gelpoint advanced access platform geschikt is voor gebruik in een vNOTES hysterectomie.

2. *Evalueren of een vNOTES hysterectomie robotisch kan uitgevoerd worden.*

   We voerden wereldwijd de eerste transvaginale robotchirurgie uit en toonden aan dat robotische vNOTES hysterectomie mogelijk is via twee verschillende technieken: RVANH en RTVNH.

3. *De huidige wetenschappelijke evidentie voor hysterectomie via vNOTES samenvatten en kritisch evalueren.*

   We voerden een systematische review met meta-analyse uit en concludeerden dat de beperkte evidentie ontoereikend is en dat er nood is aan verder vNOTES onderzoek. We volgden vervolgens de IDEAL richtlijnen om vNOTES hysterectomie verder te onderzoeken.

4. *De doeltreffendheid en kortetermijnveiligheid van vNOTES hysterectomie in vergelijking met TLH onderzoeken.*

   We voerden prospectief een geblindeerde gerandomiseerd gecontroleerde studie uit waarin we vNOTES hysterectomie vergeleken met TLH. De resultaten werden samengevat in de vorige paragraaf.

We concluderen dat we met succes de vier grote onderzoeksvragen van dit proefschrift beantwoord hebben en dat vNOTES hysterectomie inderdaad een veelbelovende nieuwe techniek is. In de handen van een ervaren vNOTES chirurg kan hij belangrijke voordelen bieden tegenover andere hysterectomie technieken: operatie zonder zichtbare littekens, kortere operatieduur, meer vrouwen die het ziekenhuis verlaten op de dag van de operatie, kortere hospitalisatieduur, lagere pijn scores en minder complicaties. Deze gegevens moeten verder bevestigd worden in de handen van andere chirurgen in multicentrum gerandomiseerd gecontroleerde studies.

Appendices

1. Publications
2. Presentations
3. Curriculum Vitae
4. Dankwoord

Appendix 1 Publications

NOTES adnexectomy for benign pathology compared to laparoscopic excision (NOTABLE): a randomised controlled trial (study protocol).

J. Baekelandt, P.A. De Mulder, I. Le Roy, C. Mathieu, A. Laenen, P. Enzlin, S. Weyers, B.M.J. Mol, J.J.A. Bosteels.

BMJ Open 2018 Jan;10:8(1):e018059. doi: 10.1136/bmjopen-2017-018059.

Transvaginal Natural Orifice Transluminal Endoscopic Surgery: a new approach to ovarian cystectomy.

J. Baekelandt.

Fertil Steril. 2018 Feb;109(2):366. doi: 10.1016/j.fertnstert.2017.10.037. Epub 2017 Dec 13.

Measures to improve the safety of power morcellation in laparoscopic surgery: IMELDA morcellation.

J. Baekelandt, K. Maas, F. Ballaux, C. Bourgain, C. De Rop.

Clin. Exp. Obstet. Gynecol. 2018 XLV;1 doi:10.12891/ceog3737.2018.

Transvaginal Natural Orifice Transluminal Endoscopic Surgery: a new approach to myomectomy.

J. Baekelandt.

Fertil Steril. 2018 Jan;109(1):179. doi: 10.1016/j.fertnstert.2017.09.009. Epub 2017 Nov 9.

Hysterectomy through the looking glass: iHysterectomy frugal by iPhone.

J. Baekelandt, J. Bosteels.

BMJ Innov 2017;0:1-5 doi:10.136/bmjinnov-2016-000132.

Postoperative outcomes and quality of life following hysterectomy by natural orifice transluminal endoscopic surgery (NOTES) compared to laparoscopy in women with a non-prolapsed uterus and benign gynaecological disease: a systematic review and meta-analysis.*

J. Baekelandt, P.A. De Mulder, I. Le Roy, C. Mathieu, A. Laenen, P. Enzlin, S. Weyers, B.M.J. Mol, J.J.A. Bosteels.

European Journal of Obstetrics, Gynecology, and Reproductive Biology 1/2017;208:6-15.

IMELDA transvaginal approach to ectopic pregnancy: Diagnosis by transvaginal hydrolaparoscopy and treatment by transvaginal natural orifice transluminal endoscopic surgery

J. Baekelandt, J. Vercammen.

Fertil Steril. 2017 Jan; 107(1):e1-e2.doi:10.1016/j.fertnstert.2016.09.024. Epub 2016 Oct 25.

HALON-hysterectomy by transabdominal laparoscopy or natural orifice transluminal endoscopic surgery: a randomised controlled trial (study protocol).*

J. Baekelandt, P.A. De Mulder, I. Le Roy, C. Mathieu, A. Laenen, P. Enzlin, S. Weyers, B.M.J. Mol, J.J.A. Bosteels.

BMJ Open 8/2016;6(8):e011546.

Uterine Smooth Muscle Tumors of Uncertain Malignant Potential: Analysis of diagnoses and therapies illustrated by two case reports.

N. Peeters, S. Hulsbosch, F. Ballaux, **J. Baekelandt.**

European Journal of Gynecological Oncology (2016) 37;3:367-73.

GelPOINT (Applied Medical) is a suitable port for transvaginal NOTES procedures.*

J. Baekelandt, D. Cavens.

Journal of Gynecologic Surgery 2016;32(5). DOI:10.1089/gyn2016.0013.

Robotic vaginal NOTES hysterectomy: Two new surgical techniques.*

J. Baekelandt.

Journal of Gynecologic Surgery 2016;32(5). DOI:10.1089/gyn2016.0020.

New Hysterectomy Techniques via NOTES (Book Chapter).*

J. Baekelandt, J Bosteels.

http://www.avidscience.com/wp-content/uploads/2016/07/HYST-16-01_June-02-2016.pdf

Robotic vaginally assisted NOTES hysterectomy: the first case series demonstrating a new surgical technique.*

J. Baekelandt.

Gynaecological Surgery 2016;13(1):57-62.

Response to "Total Vaginal Natural Orifice Transluminal Endoscopic Surgery Hysterectomy".

J. Baekelandt.

Journal of Minimally Invasive Gynecology 2016;23(3):459.

Squamous cell carcinoma in situ lining the uterine cavity.

J. Anthuenis, **J. Baekelandt,** C. Bourgain, C. De Rop.

European Journal of Gynecological Oncology 2016;37(1):135-8.

Adnexectomy by poor man's transvaginal NOTES.

A. Reynders, **J. Baekelandt.**

Gynaecological Surgery 08/2015;12(3):207-211.

Natural orifice transluminal endoscopic surgery (NOTES) salpingectomy for ectopic pregnancy: a first series demonstrating how a new surgical technique can be applied in a low-resource setting.

S. Van Peer, **J. Baekelandt.**

Gynecological Surgery 07/2015; DOI:10.1007/s10397-015-0904-6.

Total Vaginal NOTES Hysterectomy (TVNH): A new approach to hysterectomy via Natural Orifice Transluminal Endoscopic Surgery.

J. Baekelandt.

Journal of Minimally Invasive Gynecology 2015;22(6):1088-94.

Low-cost total laparoscopic hysterectomy by single-incision laparoscopic surgery using only reusable standard laparoscopic instruments.

A. Reynders, **J. Baekelandt.**

Gynecological Surgery 2015;12(2):101-105.

Response to letter to the Editor regarding "Laparoscopic Hysterotomy For A Failed Termination of Pregnancy: A First Case Report With Demonstration Of A New Surgical Technique".

J. Baekelandt, J. Bosteels.

Journal of Minimally Invasive Gynecology 2015;22(5):919.

Laparoscopic Hysterotomy For A Failed Termination of Pregnancy: A First Case Report With Demonstration Of A New Surgical Technique.

J. Baekelandt, J Bosteels.

Journal of Minimally Invasive Gynecology 2015;22(4):544.

Poor Man's NOTES: Can It Be a Good Approach for Adhesiolysis? A First Case Report With Video Demonstration.

J. Baekelandt.

Journal of Minimally Invasive Gynecology 2015;22(3):319.

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T.Marynissen, D. Timmerman, J.Bosteels, **J. Baekelandt**.

Belgisch tijdschrift voor geneeskunde (2010) 66;12:571-581.

A case of didelphic uterus and blind hemivagina with renal dysplasia and ectopic ureter presenting with vulvodynia and recurrent fever.

E. Stevens, **J. Baekelandt**, L. Lemmens, E. Dufraimont, A. Valcke, M. De Bruyn, J. Bosteels.

Gynaecological Surgery 2010;7:279-283.

Niche in een sectiolitteken.

I. Segaert, **J. Baekelandt**, J Bosteels.

Gunaikeia. 2009 Nov;14(9):305.

Laparoscopic endopelvic sacral implantation of a Brindley controller for recovery of bladder function in a paralyzed patient.

M. Possover, **J. Baekelandt**, A. Kaufmann, V. Chiantera.

Spinal Cord. 2008 Jan;46(1):70-3. Epub 2007 Apr 10.

Anatomy of the sacral roots and the pelvic splanchnic nerves in women using the LANN technique.

M. Possover, V. Chiantera, **J. Baekelandt.**

Surg Laparosc Endosc Percutan Tech. 2007 Dec;17(6):508-10.

The laparoscopic implantation of neuroprothesis – LION technique – to control intractable abdomino-pelvic neuralgia.

M. Possover, **J. Baekelandt**, V. Chiantera.

Neuromodulation 2007;10:18-23.

Laparoscopic neurolysis of the sacral plexus and the sciatic nerve for extensive endometriosis of the pelvic wall.

M. Possover, **J. Baekelandt**, C. Flaskamp, D. Li, V. Chiantera.

Minim Invasive Neurosurg. 2007 Feb;50(1):33-6.

The laparoscopic approach to control intractable pelvic neuralgia: from laparoscopic neurosurgery to the LION procedure.

M. Possover, **J. Baekelandt**, V. Chiantera.

Clin J Pain. 2007 Nov-Dec;23(9):821-5.

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* Presented in this thesis

Appendix 2 Presentations

TVH 2.0 – vNOTES (Surgical tutorial: vaginal hysterectomy with large uterus)

AAGL Global Congress, Las Vegas, 11/2018

Current status of vNOTES

International vNOTES Summit, Las Vegas, 11/2018

Future of vNOTES

International vNOTES Summit, Las Vegas, 11/2018

Windows on the future of hysterectomy

Grand rounds, Haifa Technion University, Rambam Health Care Campus, Haifa, 10/2018

First 1000 vNOTES operations: prospective complication data

ESGE 27th Annual Congress, Vienna, 10/2018 **(Best oral presentation award)**

Why vNOTES: surgical technique and rationale for a new approach to gynaecologic surgery

ESGE 27th Annual Congress, Vienna, 10/2018

Future of vNOTES

International vNOTES Summit, Vienna, 10/2018

Vaginal surgery and vNOTES

International vNOTES Summit, Vienna, 10/2018

Hysterectomy: what does the future bring?

VVOG Annual Congress, Mechelen, 10/2018

Is my smartphone screen the future of gynaecologic surgery: iHysterectomy frugal by iPhone

Beyond Gynecologic Surgery (AAGL-ESGE-APAGE conference), Clermont-Ferrand, 4/2018

HALON trial: Hysterectomy by transabdominal Laparoscopy or vNOTES

Beyond Gynecologic Surgery (AAGL-ESGE-APAGE conference), Clermont-Ferrand, 4/2018

Is there evidence for the benefits of transvaginal NOTES over laparoscopy

Global Congress of Natural Orifice Transluminal Endoscopic Surgery, Guangzhou, China, 4/2018

vNOTES: a paradigm shift in gynaecological surgery

Aristotle University Thessaloniki, Invited lecture, 1/2018

vNOTES - history, surgical techniques and current data

International vNOTES Summit, National Harbor, Washington DC, 11/2017

HALON (Hysterectomy by transabdominal Laparoscopy or vNOTES) a randomized controlled trial

AAGL Global Congress, National Harbor, Washington DC, 11/2017

Therapy reduction in gynaecological cancer: is it feasible? Debate Moderator

Pentalfa video conference, Bonheiden, Belgium, 11/2017

Transvaginal Natural Orifice Transluminal Endoscopic Surgery: a new approach to myomectomy

ESGE 26th Annual Congress, Antalya, 10/2017

HALON: a randomized controlled trial. Hysterectomy by transabdominal laparoscopy or vNOTES

ESGE 26th Annual Congress, Antalya, 10/2017

Transvaginal robotic treatment for endometrial cancer: first feasibility study.

9th Annual SERGS meeting on Robotic Gynaecological Surgery, Lille, 6/2017

Is there a place for robotics in transvaginal surgery?

ESGE 25th Annual Congress, Brussels, 10/2016

Study protocol NOTABLE study: NOTES Adnexectomy for Benign indication versus Laparoscopic Excision.

ESGE 25th Annual Congress, Brussels, 10/2016

Study protocol HALON study: Hysterectomy by transabdominal laparoscopy or NOTES.

ESGE 25th Annual Congress, Brussels, 10/2016

iHysterectomy: Frugal by iPhone (poster presentation)

Presentations

ESGE 25th Annual Congress, Brussels, 10/2016 **(Best poster presentation award)**

IMELDA morcellation: improving the safety of power morcellation in laparoscopic surgery (poster presentation)

ESGE 25th Annual Congress, Brussels, 10/2016

Needlescopic surgery

ESGE 25th Annual Congress, Brussels, 10/2016

Frugal Innovations in Minimally Invasive Surgery.

Global Health Economics Summit, Berlin, 7/2016

Transvaginal Robotic Hysterectomy: Two different approaches.

8th Annual SERGS meeting on Robotic Gynaecological Surgery, Barcelona, 6/2016

Natural Orifice Transluminal Endoscopic Surgery

iPodium, Bonheiden, Belgium 6/2016

Outpatient Laparoscopic Hysterectomy.

ISGE 25th Annual Congress, Croatia, 5/2016

Arguments against medical treatment of myomas.

Post Universitary Study Day. Leuven, 5/2016

NOTES innovations and the merits of vaginal hysterectomy over laparoscopic hysterectomy.

ESGE 24th Annual Congress. Budapest, 10/2015

Transvaginal laparoscopy and its role in ectopic pregnancy.

ESGE 24th Annual Congress. Budapest, 10/2015

NOTES Adnexectomy: A new approach to adnexectomy via Natural Orifice Transluminal Endoscopic Surgery.

ESGE 24th Annual Congress. Budapest, 10/2015

NOTES Hysterectomy: A new approach to hysterectomy via Natural Orifice Transluminal Endoscopic Surgery. (poster presentation)

ESGE 24th Annual Congress. Budapest, 10/2015

vNOTES: the future of gynaecological surgery? An overview of 5 different procedures performed by pure vNOTES: Salpingectomy – Adhaesiolysis – Adnexectomy – Cystectomy - Hysterectomy.

ESGE 24th Annual Congress. Budapest, 10/2015

Transvaginal Robotic Surgery: The first case reports of Robotic NOTES Hysterectomy.

7th Annual SERGS Meeting on Robotic Gynaecological Surgery. Istanbul, Turkey, 06/2015

Live Surgical Tutorial: Total Laparoscopic Hysterectomy via Poor Man's SILS Technique.

European Society of Gynaecological Endoscopy 23rd annual congress, Brussels 24-27 September 2014

Left Upper Quadrant

VVOG Spring Conference, Gent, Belgium, March 2014

Surgical Video presentation: Laparoscopic Hysterotomy after failed TOP at 18 weeks gestation: a first case report

ESGE 22nd Annual Congress, Berlin, October 2013

Hormones, Total Hysterectomy and Pelvic Floor. Debate Moderator

Pentalfa video conference, Bonheiden,Belgium, 2011

Myomectomy: surgical techniques.

VVOG Annual Congress, Gent,Belgium, October 2009

Hysterectomy: points for discussion. Debate Moderator

Pentalfa video conference, Bonheiden,Belgium, 2009

The Laparoscopic Supracervical Hysterectomy

Conference on minimal invasive approach to surgery, Bonheiden, Belgium September 2009

New techniques in gynaecological surgery

Presentations

Rijmenam, LOK meeting, Belgium 2009

The use of ultracision in laparoscopic hysterectomy and adnexectomy

J&J symposium, Belgium, 2009

Trends in gynaecologic laparoscopy in 2009

Presentation for general medical staff AZ Imelda, Bonheiden,Belgium, 2009

Video demonstration: laparoscopic paraaortic and pelvic lymphadenectomy

New Year's conference and reception AZ Imelda, Bonheiden, Belgium, 2009

Adjuvant endocrine treatment for breastcarcinoma

Imelda Breast cancer symposium, Bonheiden,Belgium, 2008

The laparoscopic hysterectomy

J&J symposium, Brussels, Belgium, 2008

Indications for laparoscopic surgery in gynaecology anno 2007

iPodium, Bonheiden, Belgium, 2007

New trends in laparoscopy in gynaecology

Somedi, LOK meeting, Belgium 2007

Belgian approach to Hydatiforme Mole and GTN

1st National Meeting of the South African Society of Gynaecologic Oncology, Stellenbosch, South Africa, 2005

Radical Surgery for Cervix Cancer FIGO Stage IB to Stage IIA: Are we too optimistic? An audit of the Pretoria Academic Complex.

32nd National Congress of the South African Society of Obstetricians and Gynaecologists, Drakensberg, South Africa, 2005

Skin metastasis after Radical Hysterectomy with Node Dissection for cervical cancer

Belgian, Dutch, South African Gynaecology Conference, Stellenbosch, South Africa, 2005

The role of Sentinel Node Biopsy in Cervical, Endometrial and Vulvar Cancer

Gynaecology Symposium, Pretoria Academic Hospital, University of Pretoria 2003

Triple Diagnostic in Breast Cancer

Gynaecology Symposium, Pretoria Academic Hospital, University of Pretoria, South Africa 2002

Role of the Sentinel Node in Vulvar Carcinoma

Symposium O&G, UZ Gasthuisberg KULeuven, Leuven, Belgium,2002

Group B Streptococcus Prophylaxis in Labour

Symposium O&G, UZ Gasthuisberg KULeuven, Leuven, Belgium,2001

Pathogenesis of fetal distress in a fetus with omphalocoele.

International Symposium Women's Health, Antwerp, Belgium, 2000

Appendix 3 Curriculum Vitae

Jan Baekelandt was born on May 23 1975 in Deurne, Belgium. He grew up in Hove with his loving parents and sister. He graduated Latin-Sciences at OLV Van Lourdes College in Edegem in 1992. He graduated medical school at the Catholic University of Leuven magna cum laude in 1999. During his medical studies he also combined one year of family and sexology science at the same university, which he graduated cum laude in 1996 during his fourth year of medical school. He graduated as a specialist in gynaecology and obstetrics at the Catholic University of Leuven in 2004. After two months of advanced training in laparoscopy in gynaecological oncology with Professor Possover in Köln (Germany), he continued his fellowship in gynaecological oncology at the University of Pretoria (South-Africa) from October 2004 to January 2006. In March 2006 he returned as a consultant to Köln to continue his fellowship in gynaecological oncology and laparoscopic surgery until May 2007. From June 2007 to present he is a consultant at Imelda Hospital in Bonheiden (Belgium), where he focusses on gynaecologic oncology, robotic and endoscopic surgery, and pelvic floor surgery. Jan is married to Amanda McPhail. They are the proud parents of Wolf (°2008), Max (°2010) and Mary-Grace (°2011).

Appendix 4 Dankwoord

Ik wil iedereen bedanken die meegewerkt heeft aan dit proefschrift. Eerst en vooral dank aan alle patiënten die hebben deelgenomen aan de studies. Dank aan alle verpleegkundigen van het Imelda ziekenhuis die mij gesteund hebben en die in de eerste twee jaar van de ontwikkelingsfase van vNOTES veel geduld gehad hebben. Dank aan alle studenten en assistenten die me bij alle ingrepen geholpen hebben. Dank aan de dienst anaesthesie van het Imeldaziekenhuis. In het bijzonder dank aan Dr. Peter De Mulder en Dr. Ilse Le Roy voor jullie inzet in de HALON studie. Dank aan mijn collega gynaecologen in het Imeldaziekenhuis voor jullie steun bij de studies en om vNOTES zo snel te omarmen. Dank aan alle coauteurs.

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