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VaNoLaH trial: a study protocol—a multinational randomised controlled trial including two identical substudies comparing vaginal versus vNOTES (vaginal natural orifice transluminal surgery) hysterectomy or laparoscopic versus vNOTES hysterectomy

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ABSTRACT

Introduction Hysterectomy is one of the most common surgeries performed in women. Minimally invasive methods are on the rise globally as they have been shown to decrease surgical morbidity compared with abdominal hysterectomy. Hysterectomy by vaginal natural orifice transluminal endoscopic surgery (vNOTES) is the latest innovation. It combines the vaginal approach and endoscopy via the vagina. Large pragmatic randomised controlled trials (RCTs) are lacking comparing outcomes after vNOTES, vaginal hysterectomy (VH) and laparoscopic hysterectomy (LH).

Methods Multicentre pragmatic RCT aiming to recruit 1000 women aged 18–75 years undergoing hysterectomy for benign disease. The RCT includes two identical substudies (groups A and B). If VH is considered safe and feasible, the patient will be randomised within group A (VH vs vNOTES). If VH is not considered safe or feasible, patients will be randomised within group B (LH vs vNOTES).

Analysis Primary outcome is the proportion of women leaving the hospital within 12 hours after surgery. Secondary outcomes are hospitalisation time, conversion rates, duration of the surgical procedure, intraoperative complications, postoperative complications and readmission.

Ethics and dissemination The Ethical Board Committee at Imelda Hospital, Bonheiden, Belgium, has approved the research protocol 230704 (principal investigator). Before including patients, all centres will require local or national ethical approval. The results of the study will be published in international peer-reviewed journals.

Trial registration number NCT05971875.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study is a non-blinded pragmatic randomised controlled trial including two identical substudies (groups A and B) with the aim to compare vaginal natural orifice transluminal endoscopic surgery hysterectomy with vaginal hysterectomy and laparoscopic hysterectomy.
⇒ The pragmatic design will generate generalisable results in real-life settings.
⇒ All surgeons are proficient in all three surgical techniques.
⇒ Due to the differences in the healthcare systems of the participating centres, no cost analysis will be performed. This could be considered a weakness of the study.

INTRODUCTION

Hysterectomy is the most commonly performed gynaecological surgical procedure worldwide.[1] Minimally invasive techniques for hysterectomy have evolved the last 30 years and include vaginal hysterectomy (VH), laparoscopic hysterectomy (LH), robot-assisted laparoscopic hysterectomy (RH) and vaginal natural orifice transluminal endoscopic surgery (vNOTES).[1]

The vaginal entrance to the abdomen is considered the most minimally invasive, and despite being associated with the lowest incidence of complications, lowest surgical time and quickest postoperative recovery, the incidence of VH is declining worldwide to the benefit of laparoscopic techniques.[1–3] A retrospective cohort study has recently[4] shown benefits of LH over VH, with lower intraoperative bleeding, potentially due to the direct visualisation of the bleeding vessels during laparoscopic surgery.

vNOTES is the latest development within gynaecological surgery and is a combination of a traditional vaginal approach together with endoscopy through a GelPort via the vagina. The technique offers the benefits of a vaginal, scarless entrance to the abdomen together with endoscopic overview of the surgical field.[5]

Only one randomised controlled trial (RCT) comparing vNOTES with LH has been published; the HALON trial was a parallel group 1:1 RCT demonstrating that vNOTES was not inferior to conventional laparoscopy for a successful benign hysterectomy.[5] Same-day discharge was more common after vNOTES hysterectomy than after LH. Furthermore, surgical time, postoperative pain and postoperative complications were lower after vNOTES hysterectomy compared with LH. The HALON trial was a single-centre trial including only a small number of participants (n=70). There was only one surgeon that had advanced expertise beyond learning curve in ideal (=experimental) conditions.

Hence, the findings and conclusions of HALON cannot be generalised.

In a systematic review with meta-analysis[6] published in 2020 comparing vNOTES to total laparoscopic hysterectomy (TLH) including six studies: the HALON RCT and five observational studies. The pooled analysis of two subgroups demonstrated that vNOTES, compared with laparoscopy, was equally effective to successfully remove the uterus. vNOTES showed significantly lower operation time (mean difference in operation time of 16.73 min (−16.73 (95% CI −21.04 to −12.40)) and length of hospital stay (mean difference of 0.58 days (95% CI −0.71 to −0.45)) and estimated blood loss (mean difference −98.87 mL; 95% CI −126.67 to −71.07)). There were no significant differences between both treatment arms for several outcomes, including intraoperative or postoperative complications, readmission rates, 24 hours postoperative pain scores and haemoglobin drop on day 1 postoperatively. The available evidence suggests that vNOTES hysterectomy may be an effective alternative approach. Since there is only one small conventional exploratory RCT, more good quality evidence is warranted, hence the design of a multicentre pragmatic RCT comparing hysterectomy by vNOTES versus LH for benign gynaecological disease. The absence of a direct comparison between VH and vNOTES hysterectomy was a commonly addressed criticism following the publication of the HALON trial. The current trial therefore also includes a second direct comparison; vNOTES versus VH.

We plan to conduct an RCT including two identical substudies, comparing vNOTES (intervention) with either VH or with LH (control groups).

Multiple countries and centres are participating in the study. The different centres have slightly different antibiotic regimens, surgical instruments and routines regarding Foley catheters and suture types. Our pragmatic trial is designed to evaluate the different surgical techniques in real-life routine practice conditions, producing results that can be generalised and applied in routine practice. The pragmatic approach also illustrates how the surgical techniques work in different healthcare settings.

Surgical innovation is an important part of surgical practice. Its assessment is complex because of idiosyncrasies related to surgical practice but necessary so that introduction and adoption of surgical innovations can derive from evidence-based principles rather than trial and error. We decided to follow the principles and guidelines established by IDEAL.[7] On four occasions between 2007 and 2009, invited international experts gathered at Balliol College, Oxford, to explore potential solutions concerning quality, innovation and evaluation in surgical practice and research. The conclusions and guiding principles were published in *The Lancet* in 2009.[7] Surgery lacks regulatory authorities that require studies of efficacy before a new procedure can be offered to patients. Nevertheless, there is little difference between operations and other complex treatments delivered by individuals within teams. In each instance, the skill, experience and judgement of the surgeon should be recognised, and outcomes are affected by the patient and the team. There was agreement between the experts that none of these factors is beyond the design of a clinical trial. The central concept in the IDEAL framework is that surgeons are regularly innovating and improving their craft. Because the point at which an innovation evolves into a novel procedure might not be obvious at the time, prospective open registration of new procedures and early ethical approval are encouraged. Evolution and evaluation can then occur simultaneously. The framework recognises that at different stages of innovation, different study designs will be appropriate. According to the IDEAL framework,[7] the vNOTES approach is entering stage 3 (assessment) given that the technique of vNOTES has been described (stage 1, ideal) and the main technical aspects have been worked out (stage 2a, development) and the results of the HALON trial have been published (stage 2b, exploration). It is important now to assess this technique in a randomised trial in the hands of multiple surgeons in multiple centres and in a larger group of patients to assess whether the promising results of the HALON trial can be confirmed outside its strict single centre single surgeon setting (stage 3). The assessment of long-term uncommon outcomes after vNOTES surgery (stage 4) has been and can continued to be assessed with data from the international NOTES society complication database.[8] Furthermore, the HALON trial only compared vNOTES and LH and it is of equal importance to compare vNOTES with conventional VH.

Limitations to the study include the difficulties performing a cost analysis due to the different countries' healthcare organisations. As there are not enough surgeons that master all four minimally invasive techniques for hysterectomy (VH, LH, vNOTES and RH), it is not feasible to include a robotic arm for comparison. Also, the majority of surgeons participating in the study are more experienced in VH or LH than vNOTES and have recently passed their learning curve for vNOTES.

This discordance in experience leads to a potential advantage for the outcomes associated with non-vNOTES hysterectomies.

METHODS AND ANALYSIS

Study design

Two arm, parallel group, multicentre pragmatic RCT. The RCT includes two identical substudies (group A: vNOTES vs VH and group B: vNOTES vs LH).

Study population

All women aged 18–75 years regardless of parity with a benign indication for hysterectomy. Hysterectomies due to stage II+ prolapse as part of vaginal prolapse repair or due to endometriosis will be excluded. Women with clinically relevant comorbidities or other conditions that require inpatient postoperative care or surveillance for more than 12 hours will be excluded. Other criteria for exclusion are subtotal hysterectomy; history of rectal surgery; suspected rectovaginal endometriosis; suspected malignancy; suspected obliteration of the pouch of Douglas following severe pelvic inflammatory disease (PID) or other causes; active lower genital tract infection; pregnancy; failure to provide written informed consent prior to surgery.

Randomisation

Randomisation will be performed based on a two-step clinical decision. Based on surgical judgement, parity, volume of the uterus and accessibility, the surgeon will decide prior to randomisation if a classical vaginal hysterectomy is feasible and safe. If a vaginal hysterectomy is considered feasible and safe, eligible women will be randomly allocated within comparison group A (vNOTES vs VH). If vaginal hysterectomy is not considered feasible or safe, women be randomised within comparison group B (vNOTES vs LH). Figure 1 shows the enrolment flowchart. Several clinical practice guidelines from different societies for counselling women on the preferred technique of hysterectomy for benign disease have been published.[9–13] The recommendations of these guidelines can be used as a guide/tool for counselling women on the preferred technique. If patients were randomised freely, in one step, between the three techniques, surgeons

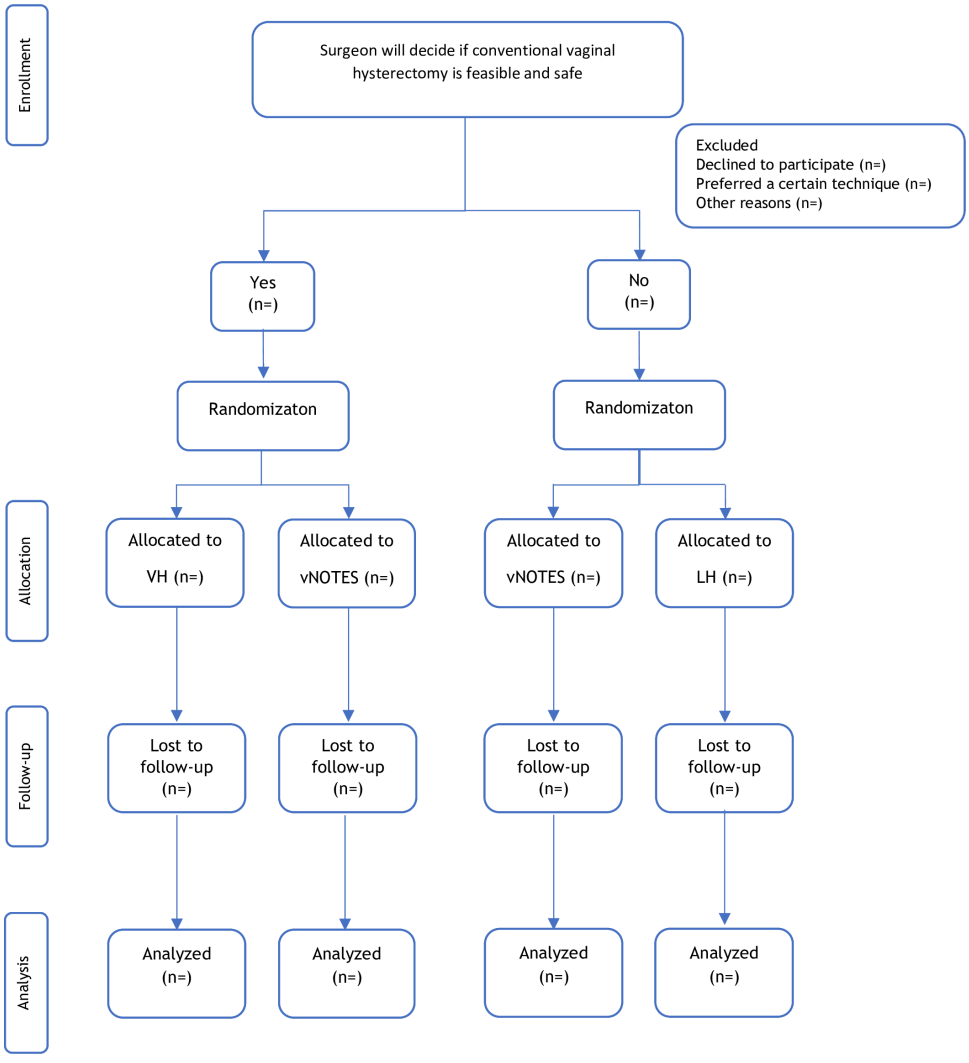

Figure 1 Flowchart of the VaNoLaH trial.

would be forced to perform a VH on larger uteri than they would feel comfortable with. This would be unethical to both the patient and the surgeon and lead to complications. Therefore, the larger uteri will probably, in most centres, be randomised to the laparoscopic group, and among these, 50% will be randomised to vNOTES.

Permuted block randomisation via REDCap software will be used. Women will be treated by a surgeon who is not blinded to the treatment allocation. The RCT includes two identical substudies (groups A and B), and the results will be analysed separately in the two cohorts. Pooled analysis of vNOTES versus VH/LH will be analysed in the same matter as a secondary endpoint.

vNOTES is the intervention arm in both groups A and B. Stratified randomisation within group A or B will be used, according to uterus size (under/over a longitudinal length of more than 15 cm), previous caesarean section (CS) (no/yes) and body mass index (BMI) (under/over 35).

Whether or not to offer an opportunistic salpingectomy[14] at the time of hysterectomy will be decided according to the clinical practice of the surgeon of the participating centre. The aim of the study is to compare hysterectomy and not adnexal surgery, and the consideration to perform an opportunistic salpingectomy should not influence the decision on what surgical technique to use for hysterectomy.

Recruitment of patients for the study started in 2024, with the aim of 10–20 participating centres and countries. The study is expected to end in 2026.

Primary study outcome

1. The proportion of women leaving the hospital within 12 hours based on their own preference, when the local hospital discharge criteria are met and the absence of complications is verified.

Secondary outcomes

1. Hospitalisation time.
2. Conversion rates: the proportion of women treated by any other approach than the allocated technique as randomised.
3. The duration of the surgical procedure; defined as the time from the placement of the Foley catheter to the last stitch.
4. Intraoperative complications, that is, any adverse event before the end of the surgical intervention including but not limited to visceral injury, for example, to the bladder, ureter, bowel or vessels.
5. Postoperative complications: major bleeding or pelvic haematoma requiring transfusion, infections of the vaginal cuff, abdominal wall wound, urinary tract infection, chest or febrile episodes/unspecified infections, thromboembolism, postoperative ileus or wound dehiscence, classified according to the Clavien-Dindo[15] classification detected during the first 6 weeks after surgery.
6. Readmission requiring hospitalisation for any adverse event with a causal relationship to the gynaecological intervention during the first 6 weeks after surgery.
7. Patient-reported outcome measures. Short Female Sexual Function Index. Questionnaire will be sent out automated by REDCap 3 months postoperatively to the patients via email.

Surgical procedures

The treating surgeons of all participating centres are beyond their learning curves for the three techniques (VH, LH and vNOTES). Treating surgeons have a minimum of 3 years of experience as an independent vaginal and laparoscopic surgeon and have performed a minimum of 50 vNOTES cases. The surgeons will not be blinded to the allocated technique. The surgeons that include patients in the trial have been selected mainly by their registration of patients in the iNOTES registry. To include patients in the iNOTES registry and be certified vNOTES surgeon, the surgeon sends in a video of his or her 10th vNOTES hysterectomy for surgical feedback. The surgeons including patients are experienced vaginal surgeons, and we therefore approximate a somewhat higher prevalence of VH than in a traditional clinical setting, with 40–50% of the patients will be included in group A (VH vs vNOTES). The different surgeons have slightly different expertise and some centres will include more patients in group A: VH/vNOTES and some centres will include more patients in group B: (LH/vNOTES). When 500 patients per group/substudy have been included, this substudy will be terminated awaiting full inclusion of 500 patients in the other group/substudy. All patients will be operated, regardless of mode of hysterectomy, with the start of surgery before 12:00.

Sample size

The aim of this study is to reproduce previously observed results in a larger sample. A total sample size of 1000 patients (500 in group A and 500 in group B) is considered feasible. The power was calculated for the primary outcome. In the HALON trial, 27 out of 35 (77%) patients were discharged within 12 hours in the vNOTES arm compared with 15 out of 35 (43%) in the TLH arm. With similar results, we would reach a power >99%, considering a two-sided χ^2 test and adopting a 5% significance level. However, the power will still be >80% for much smaller effect sizes, for example, assuming 77% in the vNOTES arm versus 65% in the control arm (VH or LH), implying an effect size of 12% which would be considered clinically relevant.

Statistical analysis

A two-sided Cochran-Mantel-Haenszel test will be used for the primary outcome analysis and for binary secondary outcomes, with strata as defined in the randomisation process (uterus size, CS, BMI). A 5% significance level will be adopted. Results will be presented as relative risks

with 95% CIs. Additionally, group proportions and overall proportion differences will be reported with 95% CIs.

Fisher's exact test will be used in case of rare events (cell frequencies <5).

Continuous secondary outcomes will be analysed using analysis of variance with study arm and randomisation strata as factors. Results will be presented as least squares means and mean differences with 95% CIs. Distributional assumptions will be evaluated by visual inspection of histograms. In case of severe deviation from normality, transformation of the response variable will be considered. A 5% significance level will be adopted for all secondary outcomes.

Analysis will be performed on an 'intention to treat' basis in the first instance, as recommended in the CONSORT (Consolidated Standards of Reporting Trials) statement.[16] A 'per protocol' analysis will also be performed, and a sensitivity analysis will be done to test the robustness of the study data.

Descriptive statistics on the baseline characteristics of the patients enrolled in the two comparison groups will be reported to ensure that randomisation has produced comparable groups of participants.

Proposed frequency of analyses

The follow-up period of this multicentre pragmatic trial has been limited to 6 weeks postoperatively. No interim analysis is planned.

Ethics and dissemination

The ethical board at the main centre, Imelda Hospital, Belgium, has given ethical agreement (dated 4 July 2023). The ethical board in Sweden, Croatia, Switzerland and Israel has given ethical agreement at the time of publication of the protocol. We expect to include 10–20 centres/countries. Before inclusion of patients, all centres must have an approved ethical agreement from their hospital or country. Results will be submitted for publication in a peer-reviewed journal.

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