Adnexectomy by vaginal Natural Orifice Transluminal Endoscopic Surgery versus laparoscopy: results of a first randomised controlled trial (NOTABLE trial)

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Running title

NOTABLE study

ABSTRACT

Objective:

To compare adnexectomy by vaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES) versus laparoscopy.

Design:

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

Setting:

Belgian teaching hospital

Population:

Women regardless of age and parity scheduled to undergo an adnexectomy for an adnexal mass assessed to be benign on ultrasound by applying the IOTA criteria.

Methods:

Randomisation to laparoscopy (control group) or vNOTES (experimental group). Stratification according to adnexal size. Blinding of participants and outcome assessors by sham incisions.

Main Outcome Measures:

The primary outcome measure was adnexectomy by the allocated technique. Secondary outcomes included duration of surgery, pain scores and anlagesics used, and spilling in endobag.

Results:

We randomly assigned 67 participants (34 to the vNOTES group and 33 to the laparoscopy group). The primary endpoint was always reached in both groups: there were no conversions. A sensitivity analysis for the primary outcome, assuming one conversion in the vNOTES group and no conversions in the laparoscopy group still demonstrated non-inferiority for vNOTES.

The secondary outcomes demonstrated a shorter duration of surgery, lower pain scores, lower total dose of analgesics and a lower rate of spilling in the endobag for the vNOTES group.

Conclusions:

vNOTES is non-inferior to laparoscopy for a successful adnexectomy without conversion. vNOTES allowed shorter operating times, less postoperative pain and less spilling in an endobag.

Funding:

No funding by any third party.

Keywords

Adnexectomy, salpingo-oophorectomy, vNOTES, laparoscopy, randomised controlled trial

INTRODUCTION

Minimally invasive surgery aims to reduce the surgical morbidity and mortality. After the evolution from laparotomy to laparoscopy, this evolution was continued with single site surgery (SILS or LESS) and natural orifice transluminal endoscopic surgery (NOTES) with or without robotic assistance. Different natural orifices can be used to perform NOTES: transvaginal NOTES (vNOTES), transgastric NOTES (gNOTES), transrectal NOTES (rNOTES), and transurethral NOTES (uNOTES).[1]

vaginal Natural Orifice Transluminal Endoscopic Surgery(vNOTES) enables surgeons to perform minimally invasive abdominal and pelvic surgery through a colpotomy without making any abdominal incisions. In 2018 our group published the results of a first randomised controlled trial (HALON trial) comparing vNOTES with laparoscopy for hysterectomy.[2] Simultaneously we performed a second RCT comparing vNOTES with laparoscopy for adnexectomy.[3] To the best of our knowledge this is the second RCT on vNOTES and the first one on vNOTES for adnexal surgery.

The study objective was to compare vNOTES with laparoscopy for adnexectomy. Our study hypothesis was that the new approach (vNOTES) was non-inferior to the established technique (laparoscopy) for performing a successful adnexectomy, while being superior for one or several secondary outcomes predefined in the study protocol (Appendix S1)

METHODS

Trial design and study analysis

The NOTABLE (vNOTes Adnexectomy for Benign indication versus Laparoscopic Excision) study is a single-centre parallel-group double blinded (patient and outcome assessor) randomised trial performed at the Department of Gynaecology of the Imelda Hospital in Bonheiden, a 596 bed non-universitary teaching hospital in Belgium. The study was approved by the local IRB (REF no B689201526268) and conducted in compliance with the ICH Good Clinical Practice guideline and the Belgian Law of May 7th 2004 relating to experiments on humans. The study protocol was prospectivel registered as NCT02630329 and published in BMJ Open Access. [3]

All women regardless of age and parity, with a symptomatic or asymptomatic adnexal mass presumed to be benign based on ultrasound examination by applying the IOTA rules[4] were eligible provided they had no contraindications. The exclusion criteria were the following contraindications for vNOTES surgery: a history of rectal surgery, suspected rectovaginal endometriosis, suspected malignancy, pelvic inflammatory disease (PID), active lower genital tract infection, virginity or pregnancy. There were no limitations with respect to ovarian size, body mass index (BMI), parity or previous mode of delivery. We used stratification according to adnexal size. Women were randomly allocated to laparoscopy (control) or vNOTES (intervention). Participants and outcome assessors were blinded by making sham incision in the intervention group. Women were evaluated on day 0-7, and at 3 and 6 months. The primary outcome measure was the proportion of women successfully treated by removing one or both adnexa as allocated by randomisation without conversion. Secondary outcomes were: proportion of women hospitalized on the day of surgery; postoperative pain scores measured twice daily from day 1-7; total dosage of pain killers used from day 1-7; hospital readmission during the first six weeks; dyspareunia and sexual wellbeing at baseline, 3 and 6

months using a validated questionnaire(SSFS scale); health-related quality of life at baseline, 3 and 6 months after surgery using an validated questionnaire (EQ-5D-3L); duration of surgical intervention; infection or other surgical complications.direct costs up to 8 weeks following surgery For the primary outcome measure, a one-sided 95% confidence interval of the difference in the proportions of women with a successful removal of the uterus by the randomised technique was estimated. Non-inferiority was concluded when 15% (percentage points) was above the upper limit of the 95% CI.

Randomisations, blinding, and treatment allocation

Eligible women were counselled about the NOTABLE study by their treating gynaecologist in the department. Women who signed informed consent were randomised to the vNOTES group or the laparoscopic group based on a computer-generated random number list (https://www.randomizer.org). Randomisation was stratified based on the ultrasound size of the ovarian cyst into category A (cyst < 5cm), category B (cyste 5-10cm) or category C (cyst>10cm). The randomisation process was performed by an officer who was not involved in the trial. The day before the surgery, the patients were randomly allocated to the intervention (vNOTES) or the control (laparoscopy) group by opening the opaque sealed envelopes containing the sequentially numbered allocation.

One surgeon (JFB) performed all the procedures in the trial (both vNOTES and laparoscopy). Participants, personnel, nursing staff and the outcome assessor were blinded by making sham skin incisions in the intervention group identical to those in the laparoscopy group. In order to minimize the risk of performance bias standardized intra- and postoperative protocols were used. Data collection and postoperative assessment were done by a second surgeon (JJAB) who was blinded.

Procedures

All operations were scheduled on a Thursday or Friday. Women were admitted to the outpatient department between 07:00 and 07:30 am. The nursing staff administered one dose of vaginal Clindamycin cream on admission. All NOTABLE trial operations were scheduled as first or second case on the OR-list starting at 08:00am. All operations were performed by one surgeon (JFB) who introduced vNOTES in our department in 2013 and had performed more than 200 vNOTES procedures before the start of the trial. In accordance with the hospital protocol 1.5g of Metronidazole and 2 g of Cefazolin were administered by the anaesthesiologist prior to incision.

vNOTES Adnexectomy

In participants allocated to the experimental group a vNOTES adnexectomy was performed.

The woman was positioned in dorsal lithotomy position under general anaesthesia. After disinfecting and draping, a Foley catheter was placed. 3 non-therapeutic sham skin incisions were made to blind women, outcome assessor and nursing staff. These incisions were made in a similar location as those of accessory trocars to be used during an standard laparoscopic adnexectomy. Steristrips and bandages were applied. Access to the peritoneal cavity was created by making a 2.5 cm posterior colpotomy and opening the peritoneum using cold scissors. A Gelpoint Mini Advanced Access Platform (Applied Medical, Rancho Santa Margarita, CA, USA) was used as a vNOTES port. The inner Alexis ring was inserted through the colpotomy into the Pouch of Douglas. Three trocars were inserted into the Gelpoint cap to insert the endoscopic camera and instruments. A 10mm rigid 30° camera was used and two reusable bipolar instruments and cold scissors were used as endoscopic instruments. A pneumoperitoneum was created to a pressure of 15 mmHg. The operating table was tilted to

20° Trendelenburg position. The small intestine was lifted out of the pelvis and the ureter was identified but the retroperitoneal space was not opened.

The ovarian ligament was coagulated and transected followed by the proximal end of the fallopian tube at its insertion into the uterus. Subsequently the infundibulopelvic ligament was coagulated and cut to excise the ovary. When indicated the same steps were repeated on the contralateral ovary. The surgical specimen was placed in an endobag and removed through the Alexis after removal of the Gelpoint cap. For specimens too large to remove in toto the cyst content was drained in the endobag transvaginally through the open end of the endobag. Subsequently the Alexis was removed and the colpotomy was sutured using 3 figure of 8 Vicryl 2/0 sutures. A vaginal pack was inserted into the vagina to be removed with the Foley catheter after 3 hours.

Laparoscopic Adnexectomy

In participants allocated to the control group a vNOTES adnexectomy was performed.

The woman was positioned in dorsal lithotomy position under general anaesthesia. After disinfecting and draping, a Foley catheter was placed. A 1cm vertical incision was made deep in the umbilicus. A Veress needle was introduced into the peritoneal cavity and correct position was check using a Semm test. A pneumoperitoneum was created by insufflating CO_2 to a pressure of 15mmHg. The Veress needle was replaced by a 10mm trocar. 2 additional 5mm trocars were placed in the left iliac fossa and suprapubically. A 10mm rigid 30° camera was used and two reusable bipolar instruments and cold scissors were used as endoscopic instruments. The operating table was tilted to 20° Trendelenburg position and the small intestine was lifted out of the pelvis. The ureter was identified but the retroperitoneal space was not opened. The infundibulopelvic ligament was coagulated using a bipolar grasper and transected using cold scissors. Subsequently the ovarian ligament and the proximal end of the fallopian at

its insertion into the uterus are coagulated and transected. When indicated the same steps were repeated on the contralateral ovary. The adnexa was placed in an endobag and removed through an extended umbilical incision. For specimens too large to remove in toto the cyst content was drained in the endobag transumbilically through the open end of the endobag. The trocars were removed, the umbilical fascia was sutured using a Vicryl-1 running suture and the skin incision were sutured intradermally using a 3/0 Monocryl suture. Steristrips and bandages were applied identically as in the intervention group. A vaginal pack was inserted into the vagina to be removed with the Foley catheter after 3 hours.

A standardised anaesthetic and pain protocol was developed by the anaesthesiologists involved in the trial (PDM and ILR) and was used identically in both groups. A standardised nursing protocol was written by a senior nurse in the outpatient department and was used identically in both groups. At 18:00 on the day of the surgery the blinded outcome assessor (JJAB) evaluated the condition of the treated women. After a clinical examination and checking the vital parameters, he asked the participantswhether they preferred to leave the outpatient department to return home or preferred to be admitted to the hospital for the night. Women received a discharge letter for their family physician as well as a phone number to call in case of any adverse event. All participants were asked to keep a standardised diary for analgesics an pain scores during the first postoperative week. Follow-up visits were done by the same outcome assessor at days 7 and 42. Questionnaires were sent at 3 and 6 months postoperatively. For a detailed description of the follow up as well as the trial interventions, we refer to the published trial protocol. [3]

Outcome measure

The primary outcome was the proportion of women successfully treated by removing one or both adnexa by the allocated technique as randomised. The secondary outcomes were the

proportion of women hospitalised on the day of surgery based on their own preference, postoperative pain scores measured using a Visual Analogue Scale (VAS)[5] twice daily during the first postoperative week, the total dosage of analgesics used, postoperative infection, intra- and postoperative complications, readmissions, sexual wellbeing and dyspareunia, quality of life, duration of surgery and, health care cost. In the study protocol we predefined health care cost by using the hospital bill as the parameter for all direct costs related to the surgical intervention up to 6 weeks following treatment.

The occurrence and severity of pelvic and vaginal pain and dyspareunia were assessed using a standardised questionnaire and VAS score before surgery and at 3 and 6 months after the surgery. A two-part EQ-5D3L questionnaire (descriptive and VAS) was used with permission of the EuroQol Research Foundation to measure the quality of life at baseline and at 3 and at 6 months after adnexectomy. The following adverse events were measured: hospital readmissions, complications during and in the first 6 weeks after surgery, and postoperative infections. All deviations –symptomatic or not- from the normal postoperative course were considered to be a complication in accordance with the 2004 modified Clavien-Dindo classification for surgical complications.[6]

Sample size calculation

The NOTABLE trial was set up as a non-inferiority study. We hypothesised that women would accept a higher conversion rate of 15% in the vNOTES group based on their preference to avoid visible scars. Non-inferiority was concluded when the upper limit of the one-sided 95% confidence interval for the difference in proportion of women who had their adnexa removed by the allocated technique was below 15%. The calculations before the onset of the trial demonstrated that we would need to include 54 participants to demonstrate non-inferiority of vNOTES when compared to laparoscopy for the primary outcome (power 80%,

alpha error 5%). The sample size was set at 64 participants (32 per group) to account for a potential drop-out of 15%.

Statistical Analysis

We have added the statistical analysis plan (SAP) as Supporting Information Appendix S2. All analyses were performed on the intention-to-treat principle. Data analysis was done by a professional biostatistician who was otherwise not involved in the daily conduct of the trial or data collection (AL). Summary statistics are presented as means and standard deviation (SD)/ medians and interquartile range (IQR) for continuous or ordinal variables and as frequencies and percentages for categorical variables. We conducted a non-inferiority analysis for the primary endpoint only (successful removal of one or both adnexa without conversion to another technique) by estimating the one-sided 95% upper confidence limit for the difference in the conversion rates between both comparison arms. For all secondary endpoints superiority analysis and two-sided tests were applied. For secondary outcomes measured cross-sectionally, we performed comparisons between the two treatment arms by using the Fisher exact test for categorical variables, or Mann-Whitney U test for continuous or ordinal variables. Survival analysis methods were used to analyse time to reach 0 VAS pain score. A Kaplan-Meier curve was constructed, and a Cox proportional hazards model was applied to compare both surgical techniques. For longitudinal measurements on the VAS pain score, analysis was performed using linear mixed models. The best fitting random-effects structure, considering the intercept for patient and linear or quadratic slope in time was selected based on the Akaike information criterion (AIC). For dichotomous outcome measurements (dyspareunia No/Yes) we used logistic regression analysis, where for VAS dyspareunia and quality of life scores a log-normal model was applied, both analyses using generalized

estimating equations to account for the longitudinal structure of the data. In all longitudinal analyses, the fixed-effect structure included a time by treatment interaction, with time modelled as a categorical variable. In the absence of a significant interaction, main effects for treatment and time were modelled. The distribution of the residuals of linear models were graphically checked using histograms. All data analyses have been performed by the author biostatistician of the NOTES RCT team (AL) using SAS software (version 9.4 SAS® System for Windows, Tervuren, Belgium).

Role of the funding source

Similar to the HALON study, the NOTABLE trial was an investigator-driven trial. The investigators funded the cost of the conduct and the design of the trial. There was no funding from any grant, industry partner or any other third party.

Results

The flow chart of the NOTABLE study is presented in figure 1. We treated 356 women for adnexal pathology between 9 December 2015 and 20 February 2020: 193 women were not eligible for participation in the trial due to one or more exclusion criteria. We counselled 163 potentially eligible women: 76 women had a strong preference for vNOTES technique, 6 women preferred a classical laparoscopic adnexectomy and 14 women declined to cooperate in a research study. The 67 women who gave written informed consent were randomly assigned to vNOTES (*n=34*) or laparoscopy (*n=33*). No women were lost to follow up. There were no statistically significant differences between both comparison arms for the baseline characteristics (Table 1). There were no statistically significant differences for age, body mass index (BMI), number of vaginal births or cyst diameter between the vNOTES group, the

laparoscopy group and the group of 96 women that were potentially eligible but not randomised.

Primary outcome

All women were treated by the allocated intervention without need for conversion to another technique. The standard error for the difference in proportions for the primary outcome cannot be determined, hence no confidence interval for the difference between both techniques can be calculated. As a sensitivity analysis, the biostatistician (A.L) performed the planned Farrington-Manning test for non-inferiority, under the assumption of 1 unsuccessful case in the vNOTES group and 0 unsuccessful cases in the laparoscopy group, hence giving the slightest possible disadvantage to the experimental intervention (vNOTES). The Farrington-Manning test for non-inferiority was performed with a 5% significance level and a 15% non-inferiority margin. The one-sided 95% upper limit for the differences in proportions of conversion was estimated as 13%, which is below the predefined non-inferiority margin. We performed a second sensitivity analysis excluding the data from two participants for reasons of unblinding: participants A21 and A 23 had a bleeding in the immediate postoperative period that was treated by the outcome assessor (JJAB) because the primary surgeon (JFB) was not on call at the moment of the diagnosis of the complication. Applying the same analysis strategy and assumptions as above the one-sided 95% upper limit for the differences in proportions of conversion was estimated as 13.5%, which is below the predefined non-inferiority margin.

Secondary outcomes

Table 2 gives an overview of the secondary outcomes of the NOTABLE trial. Laparoscopic removal of one or both adnexa was on average 15 minutes longer compared with vNOTES

(39 minutes versus 24 minutes; mean difference (MD) + 15 minutes; 95% confidence interval (CI) + 11 to + 19 minutes; P<0.001). There were no statistically significant differences for the proportion of women treated as a day-care procedure (leaving the hospital within 12 hours following surgery) with the laparoscopic technique (88%) compared to vNOTES (94%): the risk difference (RD) was -6%; 95% CI -20% to + 7%; P=0.427). Women treated by laparoscopy used more analgesics to be comfortable compared to women treated by vNOTES (11 units versus 6 units; MD +5; 95% CI +2 to +8; P<0.001). The self-assessed VAS scores measured in the morning and in the evening using a Visual Analogue Scale (VAS) were higher in women treated by laparoscopy compared to vNOTES. We found evidence of an arm by time interaction: the difference in pain scores between both comparison arms varies over time during the first week (P = 0.0049). Details of the estimation of the effect of arm at each time point in the presence of the arm by time interaction can be found in supplementary file S1 (NOTABLE study statistical analysis). We calculated the time to reach VAS 0 for both techniques by survival analysis methods. Cox proportional hazards model demonstrated a hazard ratio (HR) of 5.4 (95% CI 2.3-16; P<0.0001) in favour of vNOTES. The time to reach VAS 0 was shorter following vNOTES compared to laparoscopy as graphically presented in the Kaplan-Meier curve (Figure 2). For the differences in the VAS scores during the first postoperative week by treatment arm and time it was not possible to calculate an overall mean difference with 95% CI since the mean difference should be considered at each time point due to the arm by time interaction. (Figure 3) From the data in supplementary file S1 a clinically relevant MD in VAS scores of at least 1 between laparoscopy and vNOTES could be demonstrated during the first 5 five days following surgery. There were more women who self-reported pelvic pain at 3 months following laparoscopic adnexectomy compared to vNOTES (30% versus 5.9%; RD + 24%; 95% CI +7% to +42%; P=0.006). The VAS scores for pelvic pain at 3 months were higher in the laparoscopic group compared to vNOTES (MD

+ 1.5; 95% CI +0.5 to +2.4; P=0.002). There were no statistically significant differences between both surgical techniques for pain in the vagina at 3 or 6 months or for pain in the pelvis at 6 months, nor for the self-reported VAS scores. There were no statistically significant differences between laparoscopy and vNOTES in the self-reported VAS part of the two-part EQ-5D3L questionnaire for the assessment of quality of life at 3 or 6 months. We found no statistically significant differences between both comparison arms for the total hospital bill for all direct costs up to 8 weeks following surgery. Table 3 presents secondary outcomes that should be considered as adverse events of the surgical intervention. The incidence of intraperitoneal spilling in the NOTABLE trial was very low (1 case out of 67 women (1.5%). The difference in the intraperitoneal spilling rates between laparoscopy and vNOTES were not statistically significant (0% versus 3%; RD -3%, 95% CI -1% to +5%, P=1.000). Spilling of the cyst content in the endobag occurred more frequently with the specimen retrieval following laparoscopy compared to vNOTES (82% versus 26%; RD +55%, 95% CI +36% to +75%, P<0.001). There were no statistically significant differences between both techniques for the outcomes of intraoperative (no cases in both groups) or postoperative complications (6% versus 12%; RD -6%, 95% CI -19% to +8%, P=0.672). The majority of all postoperative complications were bleeding complications (type 2) in the vagina (4 vNOTES) or umbilicus (1 laparoscopy group). Only one patient (A23 in the vNOTES group) required revision and suturing under general anaesthesia. Histopathological examination of the adnexectomy specimen of patient A01 demonstrated a borderline ovarian tumour which was adequately managed by a second intervention. There were no cases of postoperative infection or hospital readmission within 6 weeks following surgery. There were no deaths or lasting disabilities caused by any of the two techniques in the NOTABLE trial.

Discussion

Main findings

The results of this first-ever reported randomised trial comparing vNOTES adnexectomy and laparoscopic adnexectomy show vNOTES not to be inferior to laparoscopy for performing an adnexectomy by the allocated technique without conversion. A sensitivity analysis confirmed with confidence the non-inferiority of vNOTES in a hypothetical even more disadvantaged situation with one conversion in the intervention group and no conversion in the control group. vNOTES was associated with shorter operating times, more specimens being removed in toto without spilling in the endobag, lower pain scores and a lower use of analgesics. There was no evidence of differences in complications, admission time, readmissions or postoperative infection rate.

Strengths and limitations

This second randomised controlled trial comparing the short-term safety and efficacy of vNOTES adnexectomy with laparoscopic adnexectomy followed the HALON trial. The HALON RCT compared vNOTES with laparoscopy and had very similar outcomes to this adnexectomy trial. WHAT WERE THESE OUTCOMES

Both trials reported several patient-reported outcome measures (PROMs)[7],[7] and better painscores after vNOTES. PROMs are important in all trials evaluating novel surgical techniques to measure the impact of the operation on the daily life of patients.

There are several limitations to our pilot study. NOTABLE was a small single-centre trial with all interventions done by only one surgeon. This limits the generalizability of the trial findings. Women patients, nursing staff and outcome assessors were blinded by sham incisions in the intervention group. The incisions were made in the same locations in both groups with the same bandages. Despite these measures, blinding in NOTABLE cannot be

guaranteed as in all surgical trials. Two participants (A21 and A 23) needed an assessment in the immediate postoperative period because of bleeding by the outcome assessor (JJAB) because the primary surgeon (JFB) was not on call at the moment of the diagnosis of the complication. Hence both participants and the outcome assessor were no longer blinded. A sensitivity analysis demonstrated that the findings of the NOTABLE trial are robust because inclusion or exclusion of these two cases did not impact on the result for the primary outcome. Despite the use of non-therapeutic skin incisions in the vNOTES group we cannot exclude that other women might have correctly guessed the allocated technique as well. Sutures on the umbilical muscle sheath in the laparoscopy group must cause more pain around the umbilicus. This sensation cannot be mimicked by the use of non-therapeutic superficial skin incisions in the vNOTES group. For the economic outcome we predefined the use of the total hospital bill for all direct costs up to 6 weeks as the parameter in the registered study protocol. We ended up presenting data for the total hospital bill up to 8 weeksdue to new software used for generating invoices for the hospital bill in our hospital.

It should be clear to the reader that the absence of statistically significant differences between vNOTES and laparoscopy for adverse events should not be taken as a definitive proof of safety of one technique over the other. The NOTABLE trial was not powered to detect differences between both comparison arms for adverse events in the longer term. Safety of the new surgical technique should be assessed by long term follow up studies, e.g. prospective cohort studies over a longer follow up period than 6 weeks or prospective complication/adverse event registries; the international NOTES society (iNOTESs) has initiated such a prospective complication database for vNOTES in 2015 where all vNOTES surgeons are invited to prospectively register every vNOTES case they perform (www.notesurgery.org/complication-registry)[8].

The NOTABLE trial, a small single-centre pilot RCT, is only one small step in the first evaluation of safety and effectiveness of vNOTES for adnexal surgery, as outlined by the IDEAL collaboration.[9] More research is needed based on the hypotheses generated by this first experimental proof of concept RCT.

Interpretation (in light of other evidence)

The NOTABLE study findings of non-inferiority for vNOTES versus laparoscopy, shorter operating times, lower pain scores and lower use of analgesics are consistent with the HALON study findings comparing vNOTES hysterectomy with laparoscopic hysterectomy. [2] The results of both studies are consistent with the findings of a systematic review on gastrointestinal surgery (6 RCT's and 21 observational studies) reporting a benefit in favor of NOTES for the outcome of postoperative pain.[10] The biological rationale for the lower pain scores and lower use of analgesics by women treated by vNOTES could be related to the somatic innervation of the abdominal wall. Indeed, early postoperative pain is mostly a combination of sharp somatic nociceptive pain from the trocar site, local visceral nociceptive pain and referred visceral pain. The vNOTES technique is less prone to typical somatic nociceptive pain because the vaginal fornix is neuroanatomically innervated by visceral autonomous fibers from the vaginal plexus and splanchnic nerves, causing more diffuse, deep, dull and difficult to localize visceral pain.[11] Moreover, some pain studies in different surgical models have reported a positive correlation between the severity of postoperative acute pain and the duration of the surgical intervention.[12] A shorter operating time observed in the vNOTES group may therefore have contributed to lower postoperative pain scores and less uptake of analgesics compared to the laparoscopy group.

Importantly, pain was not the primary outcome and this trial was underpowered to evaluate differences in pain intensity between groups. Future research should not only differentiate between pain at rest and movement-evoked pain but should also apply more robust analytical methods involving the estimation of time weighted area under the time effect curve using measures of pain intensity (SPIDx, summed pain intensity difference over x hours) or of pain relief (TOTPARx, total pain relief over x hours).[13] In addition, pain in different localizations should also be documented e.g. shoulder pain related to the pneumoperitoneum.

Conclusion

The NOTABLE trial demonstrates that vNOTES is at least as good as laparoscopy for removal of one or both adnexa for benign gynaecological disease. Besides the obvious aesthetic benefit of avoiding visible scars, vNOTES allows for shorter operating times, more specimens removed in toto, lower postoperative pain scores and a lower use of analgesics. There were no statistically significant differences for adverse events between vNOTES and laparoscopy.

The results of this pilot single-centre RCT are promising for the vNOTES and form a basis to assess this novel technique further in the hands of different surgeons in multi-centre RCT's following the principles of the IDEAL collaboration. The long-term safety of vNOTES should also be monitored in large international registries, such as the iNOTESs database that has been collecting vNOTES complication data since 2015.

	Laparoscopy group (N=33)	**vNOTES group (N=34)**	**Non-randomised group (N=96)**
Age (y) (mean ±SD)	50 (10)	52 (8.5)	52 (11)
Body Mass Index (kg/m²) (mean ±SD)	26 (5.5)	27 (5.8)	26 (5.0)
N vaginal births (mean ±SD)	0.97 (1.1)	1.3 (1.0)	1.5 (1.9)
Prior surgery (n, %)	21 (64 %)	18 (53 %)	NA
Prior Caesarean section (n, %)	11 (33 %)	7 (21 %)	NA
Diameter of cyst (mm) (mean ±SD)	43 (25)	47 (20)	40 (29)
Pain vagina (n, %)	5 (15%)	8 (24%)	NA
VAS pain vagina (median ±IQR)	0 (0 - 0)	0 (0 - 3)	NA
Pain pelvis (n, %)	11 (33%)	4 (12%)	NA
VAS pain pelvis (median ±IQR)	0 (0 -5)	0 (0 – 0)	NA
Quality of life (mean ±SD)	77 (16)	82 (13)	NA

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

* There were no significant differences (P<0.05) between the two groups in any of the baseline characteristics

YOU SHOULD NOT COMPARE THE RANDOMISED LAPAROSCOPY and vNOTES GROUP; YOU CAN ONLY COMPARE THE RANDOMISED

IQR: interquartile range

NA: not available

SD: standard deviation

VAS: Visual Analogue Scale

	Laparoscopy (N=33)	vNOTES (N=34)	Effect size (95%CI)
Duration of surgery (minutes) (mean ±SD)	39 (8)	24 (8)	MD +15 (+ 11 to + 19) ∫
Discharge day 0 (n, %)	29 (88%)	32 (94%)	RD - 6% (-20% to +7%) †
Total use analgesics (units) (mean ±SD)	11 (8)	6 (5.9)	MD +5 (+2 to +8) ‡
Pain vagina at 3 months (n, %)	8 (24 %)	7 (21%)	RD +4% (- 16% to + 24%) **
VAS pain vagina at 3 months (median ±IQR)	0 (0-2)	0 (0-1.5)	MD + 0.10 (- 0.9 to + 1.1) *
Pain vagina at 6 months (n, %)	3 (10%)	6 (18%)	RD – 9% (- 25% to + 8%) **
VAS pain vagina at 6 months (median ±IQR)	0 (0-0)	0 (0-1)	MD – 0.70 (- 1.6 to + 0.2) *
Pain pelvis at 3 months (n, %)	10 (30%)	2 (5.9%)	RD +24% (+7% to + 42%) Δ
VAS pain pelvis at 3 months (median ±IQR)	0 (0-3)	0 (0-0)	MD + 1.5 (+ 0.5 to + 2.4) ‡‡
Pain pelvis at 6 months (n, %)	7 (21%)	4 (12%)	RD +9% (- 8% to + 27) **
VAS pain pelvis at 6 months (median ±IQR)	0 (0-2)	0 (0-0)	MD +0.8 (- 0.2 to + 1.9) *
Quality of life at 3 months (mean ±SD)	82 (15)	83 (11)	MD -1.0 (- 7.3 to + 5.3) *
Quality of life at 6 months (mean ±SD)	83 (14)	88 (9)	MD -5.0 (- 11 to + 0.6) *
Total hospital bill for cost up to 8 weeks in € **(mean ±SD)**	654 (280)	634 (282)	MD 20 (-115 to +155) *

Table 2. NOTABLE trial secondary outcomes

CI: confidence interval

IQR: interquartile range

MD: mean difference

RD: risk difference

SD: standard deviation

VAS: Visual Analogue Scale

∫ P < 0.001 (Mann-Whitney U test)

† P = 0.427 (Fishers Exact test)

‡ P < 0.001 (Mann-Whitney U test)

Δ P = 0.006 (Fishers Exact test)

⁑ P = 0.002 (Mann-Whitney U test)

* 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)

	Laparoscopy (N=33)	vNOTES (N=34)	Effect size (95%CI)
Spilling			
-Intraperitoneal (n, %)	0 (0%)	1 (3%)	RD -3% (- 1% to + 5%) †
- In endobag (n, %)	27 (82%)	9 (26%)	RD + 55% (+36% to +75%) ∫
Complications:			
- Intra-operative (n, %)	0 (0%)	0 (0%)	RD 0% (-6% to +6%) *
- Postoperative (n, %)	2 (6 %)	4 (12 %)	RD – 6% (- 19% to +8%) Δ
	A01: BOT	A21: CD type 2 grade I	
	B14: CD type 2 grade I	A23: CD type 2 grade III b	
		B07: CD type 2 grade I	
		B23: CD type 2 grade I	
Postoperative infection (n, %)	0 (0 %)	0 (0 %)	RD 0% (-6% to +6%) *
Readmission < 6 weeks (n, %)	0 (0 %)	0 (0 %)	RD 0% (-6% to +6%) *

Table 3. NOTABLE trial adverse events

BOT: borderline ovarian tumor on histopathological examination

CD: modified Clavien-Dindo classification

CI: confidence interval

RD: risk difference

† P = 1.000 (Fishers Exact test)

∫ P < 0.001 (Fishers Exact test)

Δ P = 0.672 (Fishers Exact test)

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

A01, A21, A23, B07, B14 and B23 are the study numbers of the involved patients

CONSORT 2010 Flow Diagram NOTABLE trial (NCT02630329)

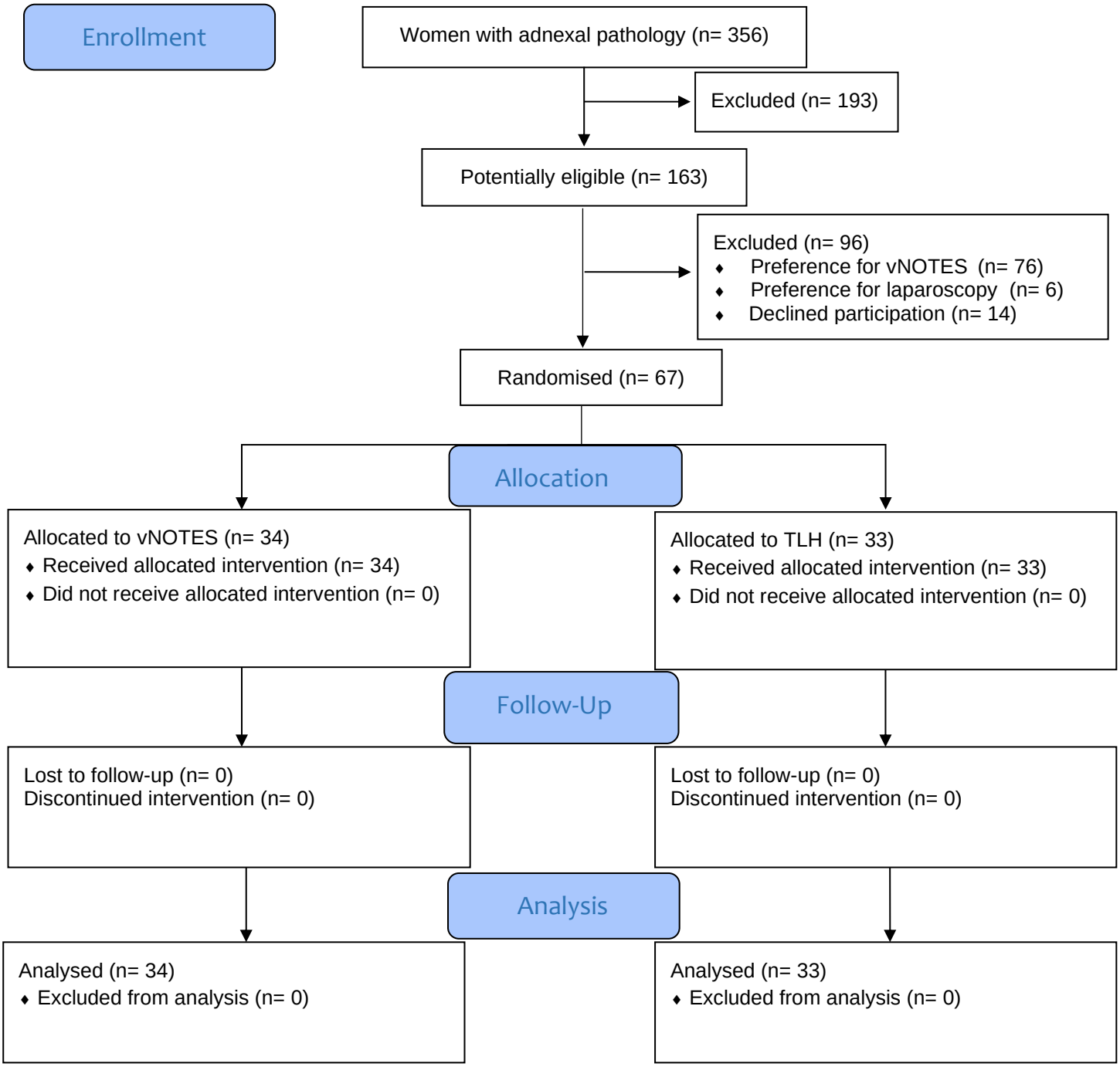

Figure 1. Trial profile

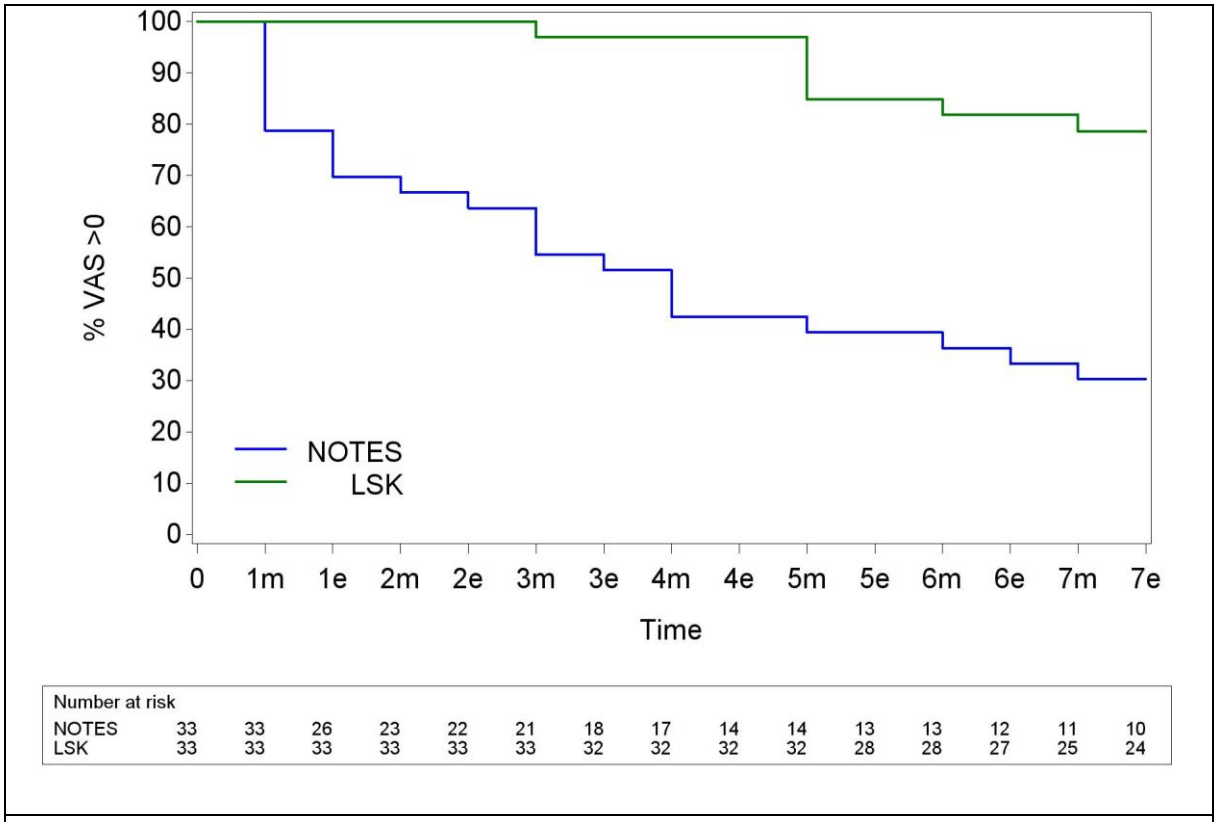

Figure 2. Kaplan Meier curve time to reach VAS 0

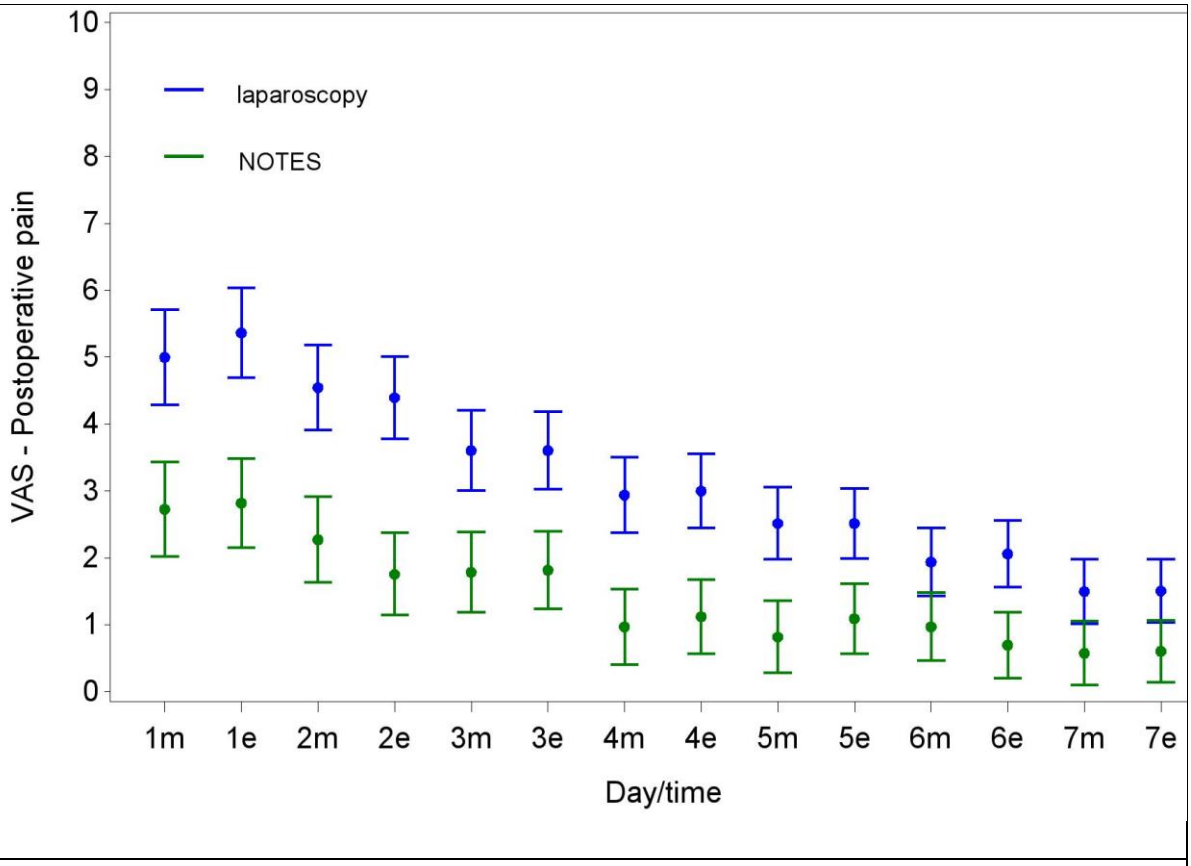

Figure 3. VAS Pain scores.

VAS scores during the first postoperative week by treatment arm and time (+95% CI). The blue dots/ whiskers represent adnexectomy by laparoscopy and the green represent adnexectomy by vNOTES.
Number 1-7: postoperative day 1-7 m: morning e: evening.

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