



# Clinical relevance of vaginal natural orifice transluminal endoscopic surgery (vNOTES) in gynecology

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This study reviews the progress and recent advances in vaginal natural orifice transluminal endoscopic surgery (vNOTES) as a minimally invasive gynecologic procedure. The proposed advantages of vaginal natural orifice transluminal surgery include enhanced cosmesis due to a scarless procedure, better exposure compared with the pure vaginal approach, tolerable pain scores, fewer perioperative complications, and a shorter hospital stay. Recent advances in surgical instrumentation and technology have improved the feasibility of vNOTES as an innovative treatment option for gynecological conditions. However, technical challenges and training issues must be overcome before its widespread use. As a promising surgical innovation, further randomized comparative studies are required to clarify the safety and effectiveness of vNOTES in gynecology.

**Keywords:** Gynecology; Laparoscopy; Minimally invasive surgical procedures; Natural orifice endoscopic surgery

## Introduction

Natural orifice transluminal endoscopic surgery (NOTES) is a minimally invasive procedure that uses the natural orifices of the human body to access the abdominal cavity. Utilizing natural orifices to reach internal organs via the transgastric, transurethral, transanal, and transvaginal routes spares the abdominal wall from incisions. Therefore, the proposed benefits of NOTES include fewer surgical site infections, hernias, scars, and postoperative pain and improved cosmetic results [1]. Since the first preclinical trial in a porcine model by Kalloo [2], surgical innovations have been made to safely and successfully apply NOTES to various procedures.

Among the several entry sites for NOTES, the vaginal approach through the vaginal fornix has gained special interest because colpotomy has been used widely in gynecologic surgery and has proven to be a safe and feasible entry port [3]. Historically, culdoscopy has been regarded as the first natural orifice procedure according to the definition of pure NOTES, allowing access to and adequate visualization of the abdominal cavity while avoiding abdominal incisions [4]. Therefore, vaginal NOTES (vNOTES) is gaining increasing interest in the field of gynecology for its utility in adnexectomy, hysterectomy, myomectomy, sacrocolpopexy, and recently, in cancer surgery [5,6].

Although vNOTES is gaining popularity as a minimally invasive procedure, the complexity of its technical skills limits its wider adoption compared with conventional laparoscopy. The learning curve of NOTES was reported to be rapid in the initial 20 cases; however, previous studies have suggested 100 cases to acquire competency [7,8]. The main difficulty of vNOTES is the space restriction caused by the conflict between instruments inside a single port. In addition, owing to the different orientations of view compared with convention-

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al laparoscopy, specific skills are needed to implement this new surgical concept safely. Nonetheless, the application of vNOTES is increasing in benign and malignant gynecological conditions. However, the evidence is largely limited to case series, cohort studies, and a few randomized clinical trials with small sample sizes. Moreover, there is a lack of surgical standardization owing to the novelty of the technique and heterogeneity among studies. Therefore, this report reviews current advances in applying vNOTES in various gynecologic procedures.

## vNOTES in benign gynecologic conditions

### 1. Adnexectomy

The first gynecological vNOTES was an adnexal procedure performed in 2012. Lee et al. [9] described 10 cases of adnexal surgery, including tubal sterilization, salpingectomy, and ovarian cyst enucleation. Another case series was reported in the same year by Ahn et al. [10] with broader indications, including ovarian cystectomy, salpingostomy, oophorectomy, and paratubal cystectomy, without complications. Although involving a few cases, vNOTES for adnexal masses was feasible without any postoperative complications and reported a high level of cosmetic satisfaction [11-15]. Early reports on vNOTES adnexectomy were mainly conducted in Taiwan and Korea and subsequently in Belgium, China, and other countries. In 2016, Wang et al. [13] performed a case-matched study to compare the surgical outcomes of vNOTES (n=34) and conventional laparoscopic ovarian cystectomy (n=243). The outcomes were similar regarding feasibility and safety, suggesting that vNOTES was comparable to conventional laparoscopy. The most recent and first randomized controlled trial (RCT) of benign adnexectomy (NOTABLE trial) was conducted by Baekelandt et al. [16]. Sixty-seven patients were randomly assigned to the vNOTES (n=34) or conventional laparoscopy (n=33) group, stratified by adnexal size. The contraindications for vNOTES were a history of rectal surgery, suspected rectovaginal endometriosis or malignancy, pelvic inflammatory disease or active lower genital tract infection, virginity, and pregnancy. There were no limitations regarding ovarian size, body mass index (BMI), parity, or previous mode of delivery. All the patients were treated with the allocated intervention without converting to other procedures. The

vNOTES group showed a shorter operating time, lower pain scores, and lower use of postoperative analgesics. Although there was no difference in the length of admission or postoperative infection rate, there was a trend toward fewer intraoperative and postoperative events in the conventional laparoscopy group. Intraperitoneal spillage was observed in the vNOTES group. The most common postoperative complication was bleeding, documented in four patients in the vNOTES group and one patient in the laparoscopy group. Only one vNOTES case required revision and re-suturing. Taken together, the authors of this study demonstrated the non-inferiority of vNOTES to laparoscopy, with shorter operating times and less postoperative pain. As noted in previous studies on vNOTES adnexectomy, potential limitations should be considered when applying this surgical technique. As in conventional laparoscopy, intraoperative spillage of ovarian tumors should be avoided whenever possible. The effect of vNOTES on spillage has not yet been compared with that of conventional laparoscopy. Difficulty dissecting adhesions is another limitation due to the different visual orientations of the vNOTES technique, requiring further analysis.

### 2. Hysterectomy

Hysterectomy via the vaginal route is not a new surgical technique in gynecology. However, with the emergence of minimally invasive surgery, vaginal surgery has been less frequently adopted in recent years due to poor visualization, limited surgical space, and the need for extensive surgical training [17]. Therefore, vNOTES hysterectomy was suggested to overcome the limitations of vaginal hysterectomy by utilizing laparoscopic instruments under an endoscopic view [18]. vNOTES has been the most commonly applied hysterectomy among many gynecologic procedures [19]. vNOTES hysterectomy for benign uterine diseases was first reported in 2012 by Su et al. [20]. Sixteen patients underwent vNOTES hysterectomy through posterior colpotomy, and follow-up data at 2 and 6 months showed good wound healing without complications. In a larger study of 137 patients by Lee et al. [21], the mean surgical time was 88.2±4.1 minutes, with a blood loss of 257±23.9 mL. Transvaginal colpotomy failed in five patients due to a narrow vagina, cul-de-sac obliteration, or mass obstruction. Complications, including intraoperative hemorrhage, unintended cystotomy, postoperative urinary retention, and febrile morbidity, occurred in seven patients (5.1%), and all patients recovered with conservative

treatment. This study stressed the importance of transvaginal posterior colpotomy to implement vNOTES successfully. Wang et al. [22] compared the surgical outcomes of vNOTES with those of conventional laparoscopic hysterectomy in a large cohort of 147 patients in 2015. In their cohort, vNOTES was associated with significantly less blood loss, shorter operative times, and shorter hospital stays. The same group reported the learning curve of vNOTES hysterectomy using operative time as a surrogate marker of surgical competency. The authors suggested a minimum of 20 cases for a well-trained laparoscopist to achieve surgical proficiency [8].

The first RCT of vNOTES was reported by Baekelandt et al. [23] in 2019 in women with benign uterine diseases. Interestingly, the intervention group was planned to undergo vNOTES hysterectomy with four superficial non-therapeutic skin incisions identical to those in the control group (conventional total laparoscopic hysterectomy, TLH). There was no conversion of vNOTES to TLH, while the operative time was significantly shorter in the vNOTES group ( $41\pm 22$  minutes vs.  $75\pm 27$  minutes). Due to the increasing number of studies, a recent systematic review and meta-analysis reported the surgical outcomes of vNOTES hysterectomy compared with laparoscopic hysterectomy for benign indications [19]. The results of five retrospective cohort trials and one RCT showed that vNOTES was equally effective for hysterectomy as conventional laparoscopy. In addition, vNOTES was associated with a significantly shorter operative time, blood loss, and length of stay. Intra- and postoperative complications, readmission rates, and pain scores at 24 hours post-surgery did not significantly differ between the two surgical methods. The pain profiles of vNOTES compared to those of single-site or multiport laparoscopic surgery vary among small studies and are largely unknown. In a prospective randomized pilot study, Park et al. [24] measured abdominal and vaginal pain until 48 hours after vNOTES or laparoscopic single-site hysterectomy. While the surgical time was shorter in the vNOTES group, postoperative abdominal pain intensity did not differ between the two groups. However, the vNOTES group reported higher vaginal pain than the single-port laparoscopy group at 16 and 24 hours postoperatively (numerical rating scale: 3 vs. 1 and 2 vs. 0, respectively) while on patient-controlled analgesia. The authors suggested further investigation into postoperative pain differences among different routes of hysterectomy, paying attention to factors such as the detailed steps of the surgical technique, use of vessel-sealing devices

versus conventional suture and ligation, presence of vaginal laceration, and use of local analgesic infiltration or patient-controlled analgesia.

Notably, quality of life (QOL) measurements were reported in only a single randomized trial by Baekelandt et al. [23]. There were no differences between the vNOTES and laparoscopic hysterectomy arms regarding the severity of dyspareunia, sexual well-being, or health-related QOL at 3 and 6 months postoperatively. Although a meta-analysis on the comparative financial cost could not be performed due to the heterogeneity in the pooling of the data, the findings of two studies implied higher total hospital charges for vNOTES due to the higher cost of disposable devices [22] and no difference in the direct health-related cost, including the bill up to 6 weeks postoperatively [24]. Cost issues and QOL are areas requiring further investigation in the future, considering various health insurance systems. Evidence on vNOTES in gynecology is largely limited to case series, cohort studies, and only a few randomized clinical trials with small sample sizes (Table 1).

### 3. Myomectomy

Transvaginal myomectomy may be technically challenging compared with other modes of surgery owing to the restricted operative field. Two studies have reported the application of vNOTES in uterine myomas. In 2018, Baekelandt [25] reported eight patients with different positions of the vNOTES port according to the location of the myoma. Anterior and posterior myomas were resected through an anterior and posterior colpotomy (approximately 2.5 cm), respectively. There were no complications, and the authors suggested that the vNOTES technique could be applied to the International Federation of Gynecology and Obstetrics type 3-7 myomas. Liu et al. [26] described the removal of a 6-cm anterior myoma with anterior colpotomy. In their experience, the vNOTES approach was more advantageous for larger uteri as the flexibility of the vaginal canal provided an enhanced extension of the colpotomy incision and subsequently allowed the laparoscopic instruments to reach the deeper pelvic area. In this case, the age and parity of the patient were critical surgical indications.

### 4. Sacrocolpopexy

A few retrospective and prospective studies have shown that sacrocolpopexy and uterosacral ligament suspension using

**Table 1.** Characteristics of randomized controlled trials on vaginal natural orifice transluminal endoscopic surgery in gynecology

Study	Study design	Patients evaluated	Surgery type	Inclusion criteria	Exclusion criteria	Indication for surgery (n)	Age (yr)	BMI (kg/m <sup>2</sup> )	Operation time (minutes)	Uterus weight (g)	Hemoglobin change (g/dL)	Postoperative hospital stay (days)
Baekelandt et al. [23] (2019)	Prospective, single center, double arm randomized controlled study	35 (vNOTES), 35 (TLH)	Hysterectomy	Age 18-70, benign disease such as symptomatic uterine fibroids, adenomyosis, high-grade cervical dysplasia, treatment-refractory dysfunctional uterine bleeding, atypical endometrial hyperplasia, BRCA-positive women 45 years or older	History of rectal surgery, suspected rectovaginal endometriosis, suspected malignancy, PID, active lower genital tract infection, virginity, pregnancy	Myoma (17), adenomyosis (6), cervical dysplasia (4), treatment resistant uterine bleeding (5), endometrial hyperplasia (2), BRCA-positive breast cancer (1)	46 (24-65)	27 (18-44)	41 (22)	206 (44-788)	NI	0.8 (0.77)
Park et al. [24] (2021)	Prospective, single center, double arm randomized controlled study	13 (vNOTES), 13 (LESS)	Hysterectomy	Women of age 19 years or more and under the age of 80 years; suitable for endoscopic surgery evaluated by the ASA classification 1 or 2	Age of less than 19 years or over the age of 80 years, pregnant or breastfeeding, no history of sexual intercourse, suspected of pelvic malignancy; women who have received three or more cesarean sections,	Myoma (7), cervical intraepithelial neoplasia 3 (3), adenomyosis (2), endometrial hyperplasia (1)	54 (35-77)	23.8 (21.32-27.6)	55 (25-105)	238 (40.8-40)	Post hemoglobin result: 11.6 (7.8-13.8)	4 (4-4)

**Table 1.** Characteristics of randomized controlled trials on vaginal natural orifice transluminal endoscopic surgery in gynecology (Continued)

Study	Study design	Patients evaluated	Surgery type	Inclusion criteria	Exclusion criteria	Indication for surgery (n)	Age (yr)	BMI (kg/m <sup>2</sup> )	Operation time (minutes)	Uterus weight (g)	Hemoglobin change (g/dL)	Postoperative hospital stay (days)
Baekelandt et al. [16] (2021)	Prospective, single center, double arm randomized controlled study	34 (vNOTES), 33 (laparoscopy)	Adnexectomy	All women with an intact uterus regardless of age and parity presenting with a symptomatic or asymptomatic adnexal mass presumed to be benign based on ultrasound examination by applying the IOTA rules <sup>a)</sup>	History of rectal surgery, suspected rectovaginal endometriosis, suspected malignancy, pelvic inflammatory disease, active lower genital tract infection, virginity or pregnancy	Randomization based on the ultrasound size of the ovarian cyst; category A (cyst <5 cm), category B (cyst 5-10 cm), category C (cyst >10 cm)	52 (8.5)	27 (5.8)	24 (8)	NI	NI	Discharge day 0: 94%

Values are presented as mean±standard deviation or median (range).

BMI, body mass index; vNOTES, vaginal natural orifice transluminal endoscopic surgery; TLH, total laparoscopic hysterectomy; BRCA, BRCA1/2 gene; PID, pelvic inflammatory disease; NI, no information; LESS, laparoscopic single-site surgery; ASA, American Society of Anesthesiologists Physical Status; IOTA, International Ovarian Tumor Analysis.

<sup>a)</sup>IOTA rules: the rules introduced by the IOTA group comprised five ultrasonographic features (shape, size, solidity, and results of color Doppler examination) to predict a malignant tumor and five to predict a benign tumor.

vNOTES appears feasible and safe [5,7,27]. Also, the vNOTES approach seems to be a reasonable option for patients who desire excellent cosmetic results through a minimally invasive approach. Liu et al. [28] reported a pilot study of 23 successful vNOTES sacrocolpopexy procedures for stage II-IV pelvic organ prolapse, with improvement in prolapse recovery and QOL. However, three cases were converted to single-incision abdominal laparoscopy. The rationale for safer access to the sacrum via the vaginal route is that extraperitoneal access to the sacrum can be achieved through the vNOTES route so that the mesh goes along the access to the presacral region without affecting the intraperitoneal organs [18]. In addition, Jallad and Walters. [5] showed that sacrocolpopexy via NOTES allowed improved visualization, leading to safe access to the sacrum and a tendency to apply more accurate tension to the mesh. The extraperitoneal approach decreases the risk of ureteral injury owing to adequate ureteral exposure and safe stitch placement. However, the vNOTES approach for vault suspension procedures requires training, and surgical performance is reportedly achieved in a short period [29].

## 5. vNOTES in gynecologic malignancy

Data concerning vNOTES in gynecologic malignancies are scarce compared with those concerning benign surgical indications. Lee et al. [21] described their experience with three cases of surgical staging in patients with early-stage endometrial cancer in 2014. In this short communication, lymphadenectomy was performed using vNOTES, followed by hysterectomy and bilateral salpingo-oophorectomy. This innovation has broadened the indications for vNOTES in oncology by demonstrating the feasibility of dissecting the lymph nodes around the external iliac vessels, hypogastric vessels, and obturator nerves. The same group published an update on 15 patients with stage 1, grade 1-2 endometrial cancer in 2022 [30]. Eighty percent (12/15) of the patients underwent sentinel lymph node (SLN) biopsy under indocyanine green guidance, and the rest (3/15) underwent pelvic lymph node dissection. Patients without sexual debut or with a narrow vagina, history of multiple abdominopelvic surgeries, BMI >42 kg/m<sup>2</sup>, history of deep endometriosis surgery, or suspicious cul-de-sac obliteration were excluded. The mean operative time was 231 minutes, with an estimated blood loss of 122 mL. One patient with bladder injury required conversion to conventional laparoscopy. Despite the feasi-

bility of vNOTES for early endometrial cancer staging, the authors described the limitations of this new approach. For those specific to oncology vNOTES, it is difficult to identify the paravesical and pararectal spaces and skeletonization of vessels for lymphadenectomy due to unfamiliarity with the different surgical views. Moreover, they noted that the edge of the vaginal ring retractor could obscure the caudal or distal sides of the paravesical space. Therefore, lymph node assessment can be challenging in vNOTES, mainly due to the difficulty in approaching the relevant anatomical spaces, especially the obturator space at the pelvic level. Another technical challenge of vNOTES for staging surgery is the visualization and approach to the para-aortic space [31]. Therefore, full lymphadenectomy of the para-aortic space above the inferior mesenteric artery will be incredibly challenging with the current vNOTES approach unless longer and more flexible endoscopic instruments and a more comprehensive camera are used [30,32]. Another option to overcome such obstacles is the use of a retroperitoneal approach through a paracervical incision in the vaginal lateral fornix [33]. This approach provides optimal exposure to the entire retroperitoneal space, including the caudal obturator space, iliac vessels, sacral plexus, and lower para-aortic region. Further validation is required for this new retroperitoneal approach, which has only been reported twice to date [33,34].

Regarding other gynecological malignancies, only one case report has been published regarding vNOTES SLN biopsy in early-stage cervical cancer [35]. Similar benefits have been observed in sentinel node biopsies for endometrial cancer staging. However, the need for radical hysterectomy for cervical cancer limits the completion of pure vNOTES. Therefore, retroperitoneal vNOTES for cervical cancer could be a valuable tool for integrating a two-step approach to cervical cancer treatment with reduced surgical morbidity.

## 6. vNOTES in special situations

### 1) Virgin patients

Nulens et al. [36] recently published a feasibility study of vNOTES hysterectomy in virgin patients. The virgin state and narrow vagina were common exclusion criteria for many studies, and this was the first feasibility study involving nine patients. The authors attempted vaginal access using a modified Lord's procedure, used for anal dilatation in hemorrhoid surgery [37]. The vaginal introitus was gradually dilated with

fingers to prevent mucosal tears. The surgical technique itself was not different from that of sexually active patients, and the mean age of the cohort was 39 years (range, 30-62). However, the main difference was the need for firm cervical traction during colpotomy due to reduced vaginal accessibility.

## 2) Obese patients

vNOTES in patients with obesity was described in a recent study by Kale et al. [38] for benign and malignant gynecological conditions. Surgical outcomes of 81 patients with class 2 or 3 obesity were reviewed retrospectively. The mean BMI of the 22 patients with class 3 obesity was 41.5 kg/m<sup>2</sup>, and they were receiving treatment for early-stage endometrial carcinoma. Postoperative pain was tolerated, and conversion to conventional laparoscopy or open surgery was not required.

## 3) Repeat vNOTES procedure

A retrospective cohort study involving 11 repeat vNOTES procedures was conducted by the same group in Belgium [39]. The median interval between primary (adnexectomy) and repeat (hysterectomy) vNOTES was 15 months (range, 0.8-37), and colpotomy followed by entrance into the peritoneal cavity was technically feasible in all patients. There were no serious complications or conversions to other surgical methods. Although severe pelvic adhesions have been regarded as a relative contraindication for vNOTES, whether a previous colpotomy complicates future repeat surgeries in the context of vNOTES remains unclear. The findings of this small study showed that a previous colpotomy does not seem to increase complications related to adhesions or scar formation during repeat surgeries.

## 4) Pregnancy outcome after vNOTES

The first retrospective observational study on pregnancy outcomes after vNOTES in women aged <43 years who had previously undergone fertility-preserving vNOTES (adnexal surgery and myomectomy) was reported by Tavano et al. [40]. A cohort of 125 patients over 5 years was reviewed, and 18 pregnancies were diagnosed within a year of vNOTES. No pregnancy-related complications related to the mode of delivery or perineal rupture were observed. These preliminary data showed that vNOTES had no adverse effects in women of reproductive age and that posterior colpotomy itself was

not an indication for surgical delivery.

## 7. Adverse effects of vNOTES

Despite the many advantages of vNOTES, several issues, including postoperative pelvic infections, vaginal pain, and changes in sexual function, need to be addressed. Since the vNOTES procedure necessitates a non-sterile vaginal entry, vaginal infection and ascending pelvic inflammation are potential adverse events. Tolcher et al. [3] reported that of 220 patients, six had grade 2 postoperative infections following vNOTES tubal sterilization, including vaginal cuff cellulitis, bacterial vaginosis, yeast vaginitis, and lower urinary tract infection, all manageable with oral antibiotic treatment. In addition, Lee et al. [21] described five postoperative morbidities in 137 patients who underwent hysterectomy using vNOTES. Four patients had fever, and one had urinary tract infections; however, no additional wound infections were reported. A recent systematic review and meta-analysis comparing vNOTES hysterectomy with laparoscopic-assisted vaginal hysterectomy (LAVH) did not show any significant increase in the incidence of Clavien-Dindo grade 2 wound infection in vNOTES [19]. Therefore, vNOTES does not seem to significantly increase postoperative wound infection, according to the current literature.

Regarding postoperative pain, Baekelandt [25] confirmed a significantly lower visual analog scale (VAS) score in the vNOTES group regarding postoperative pain than in the total laparoscopic hysterectomy group. However, Park et al. [24] reported significantly higher vaginal pain intensity in the vNOTES group in a randomized pilot study that compared the surgical outcomes of vNOTES and laparoendoscopic single-site (LESS) hysterectomy. Postoperative pain was categorized and assessed as abdominal or vaginal, and no significant difference was found regarding abdominal pain between the two groups [23]. Similar results were reported in a systematic review by Housmans et al. [19], who found no mean difference in postoperative day 1 VAS scores between vNOTES hysterectomy and LAVH. Since postoperative pain is expected to be one of the major advantages of minimally invasive surgery, more research is needed on pain intensity according to the surgical entry route.

Patients have concerns regarding vNOTES about changes in sexual function after surgery [41]. Bucher et al. [42] reported that patients had fears regarding postoperative libido and childbirth outcomes related to vNOTES compared with

LESS. Xu et al. [43] assessed and compared the female sexual function index (FSFI) in 130 patients who underwent gynecological surgery (excluding hysterectomy) using vNOTES or transabdominal laparoscopy. There was no statistically significant difference in the total FSFI scores before or at 3 and 6 months postoperatively between the two groups [43].

## 8. Future of vNOTES

The growth and wider adoption of vNOTES depend on developing novel instruments and techniques that can aid surgeons in overcoming the technical difficulties of vNOTES. Several developments have been made, including a transcervical instrument for uterine manipulation described in a video article by Naval et al. [44]. The instrument provided leverage to gain good exposure to all the uterine attachments; therefore, the surgeon's second hand was not required for uterine retraction. The same group introduced a novel gasless technique for vNOTES hysterectomy using a modified vNOTES port made of a silicone face mask and a latex glove [45]. The glove balloon at the tip of the suction irrigator was insufflated with 1 L of CO<sub>2</sub> gas inside the pelvic cavity to push the bowel upward and provide space for a gasless procedure. In addition, in line with the growing use of robotic technology in surgical fields that require basic height, such as the latest minimally invasive surgery, a surgical robot platform for NOTES has been proposed and preliminary testing is being conducted as a future technology [46,47].

The integration of the robotic modality for vNOTES has been recently described in a small number of observational studies. Lowenstein and colleagues reported the first robot assisted vaginal hysterectomy with the Hominis surgical system, which is designed specifically for vaginal robotic NOTES [48]. It was a feasibility study whether this approach may aid surgeons operate vaginally with the known advantages of the robotic platform. All 15 procedures were performed successfully without conversion to other methods. The first case series of vNOTES sacrocolpopexy with robotic assistance was reported in 2021 by Guan et al. [49] using the da Vinci Xi system (Intuitive Surgical, Sunnyvale, CA, USA). The operative times for the two cases were 227 and 257 minutes, respectively, without any complications or laparoscopic/open conversions. Significant advantages of robotic assistance are the use of articulating instruments for better suturing, increased range of motion, and enhanced visualization of the sacral promontory compared to traditional laparoscopy

or the vaginal route. However, the authors pointed out two technical difficulties: one was the decreased range of motion despite the use of the robotic platform if the robotic arm alignment was not completely suited to the center of the patient. Another challenge was that the sacral promontory was not adequately visualized. Therefore, a steep Trendelenburg position before docking the robots and proper bedside assistance through the accessory port are recommended. The most recent robotic vNOTES for deep infiltrating endometriosis surgery was published in a video article by Guan et al. [50]. Resection of endometriosis involving the parametrium and rectum is challenging; however, it is feasible owing to the use of articulating instruments and the 3-dimensional visualization function of the robotic system.

As more studies have reported the outcomes of vNOTES hysterectomy, recent efforts have been made to standardize the procedure [51-53]. In addition, the exponential uptake of this innovative approach necessitated official guidance to ensure the safe implementation of the technique [54]. Therefore, 59 international surgeons from 13 countries participated in setting a consensus-based statement on vNOTES in 2021. A consensus was reached on 50 (89%) out of 56 questions addressing perioperative management, surgical technique, instruments, pelvic anatomy from the vNOTES perspective, vNOTES training, registries and clinical trials, and definitions. However, consensus was not reached on the remaining six questions pertaining to the patient selection domain. Owing to the recency of the vNOTES technique, surgeons are encouraged to use these data to safely implement the procedure until more evidence becomes available.

## 9. Ongoing randomized clinical trials in vNOTES

Several ongoing trials are applying vNOTES in gynecology (Table 2). The largest planned multicenter prospective trial is ongoing in China and aims to address the clinical application of single-port laparoscopy and NOTES in gynecology (GLESS registry, clinical trial: NCT04096872). Although not randomized, this trial will include various procedures for benign conditions, such as adnexal lesions, ectopic pregnancy, genital tract deformities, and malignant gynecologic conditions. The study aims to collect vast data (estimated enrollment: 9,000 participants) on single-site surgery and vNOTES to compare and standardize both techniques. There are several ongoing studies regarding randomized trials, despite the focus only on hysterectomy. A non-inferiority trial is ongoing in France to



**Table 2.** Ongoing clinical trials of vaginal natural orifice transluminal endoscopic surgery in gynecology

Study identifier	Country	Study title	Study type (estimated enrollment)	Target condition	Primary outcome	Secondary outcomes
NCT04096872	China	Clinical application of laparo-endoscopic single-site surgery and natural orifice transluminal endoscopic in gynecology (GLESS)	Multi-center observational registry (9000)	Cervical cancer, endometrial cancer, endometrial lesion, adnexal lesion, ectopic pregnancy, infertility, pelvic obstructive disorder, and genital tract deformity	Completion time; success rate; recurrence rate; conversion rate	No information
NCT04886791	Netherlands	Vaginal NOTES hysterectomy versus vaginal hysterectomy (VANH)	Single-blinded, multi-center, randomized controlled double arm study (124)	Hysterectomy for benign indications	Percentage of same day discharge	Complications; treatment related outcomes; intended number of salpingectomies in each group; intended number of salpingectomies; performed number of salpingectomies in each group; Recovery Index-10 pre- and postoperative; health- related quality of life (EQ-5D-5L: 5-level EQ-5D version); costs; cost effectiveness
ChiCTR2000036517	China	A randomized controlled study for the efficacy and safety of transvaginal natural orifice transluminal endoscopic surgery (vNOTES) and transumbilical laparo-endoscopic single-site surgery (TU-LESS) for total hysterectomy	Single center randomized controlled trial (140)	Benign and early gynecologic malignant tumors undergoing hysterectomy	Perioperative complications	Duration of operation; intraoperative blood loss; the weight of uterus; the time of postoperative anal exhaust; the time of get out of bed; average length of stay; patient satisfaction; hospitalization expenses; use rate of analgesics; postoperative nausea and vomiting; body image scale/cosmetic scale

**Table 2.** Ongoing clinical trials of vaginal natural orifice transluminal endoscopic surgery in gynecology (Continued)

Study identifier	Country	Study title	Study type (estimated enrollment)	Target condition	Primary outcome	Secondary outcomes
NCT05031182	France	-Tolerance of the vNOTES surgical technique in total hysterectomy for benign lesion -Clinical trial of non-inferiority compared to the laparoscopic Technique (VLAP)	Randomized controlled trial (140)	Benign gynecologic condition	Perioperative and postoperative complications	Measure and quantification of postoperative pain; duration of operation; assessment of quality of life (sexuality, quality of life); duration of work stoppage
NCT05910385	France	TUbal Ligation Per Differe <sup>n</sup> s Endoscopic Routes and Sexuality (TULIPES)	Randomized, controlled, single-blind, two-parallel, bicentric therapeutic trial (140)	Tubal ligation	Quality of sexual life	Duration of operation; postoperative pain; consumption of analgesics; postoperative complications; patient satisfaction; quality of life; number of days of sick leave

NOTES, natural orifice transluminal endoscopic surgery; vNOTES, vaginal natural orifice transluminal endoscopic surgery; TU-LESS, transumbilical laparo-endoscopic single-site surgery.

assess the tolerance of the vNOTES hysterectomy technique to conventional laparoscopic hysterectomy for benign lesions (clinical trial: NCT05031182). Complication rates will be assessed as the primary outcome and other surgical outcomes, along with patient QOL, patient satisfaction, and duration of work stoppage. Another interesting multicenter RCT is ongoing in the Netherlands, comparing the outcomes of vNOTES hysterectomy with traditional vaginal hysterectomy (clinical trial: NCT04886791). The primary outcome is the percentage of same-day discharge, and surgical outcomes, including cost and cost-effectiveness, will also be assessed. Another research subject is the vNOTES versus single-site laparoscopy via the abdominal route, currently being investigated in China, with the primary outcome being perioperative complications (clinical trial: ChiCTR2000036517). To date, no randomized controlled trials for gynecological indications other than hysterectomy and adnexectomy have been published. Therefore, more research is needed for transvaginal NOTES, which should be considered as an innovative technique under evaluation owing to the scarcity of eligible studies to overcome publication bias. The results of ongoing randomized studies will provide crucial evidence for further application and widespread use of vNOTES.

### Conclusion

The available randomized and observational data show that vNOTES is an effective, safe, and innovative technique for women with specific indications eligible for endoscopic surgery. However, technical limitations must be resolved before its widespread use. In addition, surgical standardization with larger multicenter and randomized trials is needed to accurately assess its safety and non-inferiority to conventional laparoscopy, the standard care. Long-term outcomes, including financial and QOL aspects of broader surgical indications, are eagerly awaited.

### Conflict of interest

The authors declare no conflicts of interest.

## Ethical approval

The study did not require Institutional Review Board approval due to its review design.

## Patient consent

Non applicable.

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None.

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