

Postoperative outcomes and quality of life following hysterectomy by Natural Orifice Transluminal Endoscopic Surgery (NOTES) compared to conventional laparoscopy in women with benign gynaecological disease: a protocol for a systematic review of the literature.

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ADMINISTRATIVE INFORMATION

Title

Identification

Postoperative outcomes and quality of life following hysterectomy by Natural Orifice Transluminal Endoscopic Surgery (NOTES) compared to conventional laparoscopy in women with benign gynaecological disease: a protocol for a systematic review of the literature.

Update

Not applicable.

Registration

We registered the protocol of the systematic review in accordance with the PRISMA-P 2015 guidelines (1, 2) with the International Prospective Register of Systematic Reviews (PROSPERO) on 10 January 2016. Last update on 7 April 2016 (registration number CRD42016033023).

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Contributions

JBO, JBA and SW drafted the protocol and contributed to the development of the eligibility criteria, the risk of bias assessment strategy and the data extraction criteria. JBO and JBA developed the search strategy. AL provided statistical expertise. PDM and IL provided expertise on anaesthesiology. PE provided expertise on the measurement of sexual health. CM

and BWM have expertise on clinical practice research and scientific conduct of trials. All authors read, provided feedback and approved the final draft of the protocol.

Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and a justification.

Support

Sources of support

CEBAM, the Centre for Evidence-based Medicine, Cochrane Belgium provides support from a Biomedical Librarian for peer review of the search strategy.

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Role of sponsor

Not applicable.

INTRODUCTION

Rationale

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

NOTES is a technique that uses the natural orifices of the human body (mouth, vagina, urethra and rectum) as an access route to the peritoneal cavity for performing endoscopic surgery. Its application was described for the first time in 2004 in a porcine model by researchers at the Johns Hopkins University (3). The feasibility of NOTES has been demonstrated in general surgical procedures, such as transgastric appendectomy (4) and cholecystectomy (5). Several observational studies reported less postoperative pain, a shorter length of hospital stay and less complications. The improved cosmetic results due to scar-free surgery in combination with reduced wound (trocar) complications, tends to support the increasing use of this new surgical technique.

NOTES has gained popularity amongst general surgeons, urologists and gastroenterologists over the past few years and its feasibility and safety have been reported (6). Although it can be performed via various entry approaches the majority of NOTES procedures in women have used the vagina as this allows direct access to the peritoneal cavity (7). Culdotomy has been used widely for several surgical procedures involving extraction of large specimens: it has been reported as a safe access that is easy to close afterwards (8, 9). In hybrid NOTES the surgical procedure is performed through a natural body orifice with transabdominal assistance, whereas the term pure NOTES refers to procedures that involve only transluminal access.

Hysterectomy using a transvaginal NOTES approach was described for the first time in a human patient by Su et al. in 2012 (10). The present systematic review aimed to summarise and critically appraise the body of evidence on the effectiveness and safety of the NOTES approach for doing a hysterectomy in women with a non-prolapsed uterus and benign gynaecological disease compared to alternative techniques. We aimed to design and conduct a randomised controlled trial (RCT) if no RCTs were retrieved.

Objectives

The aim of this systematic review is to retrieve studies that have evaluated the effectiveness and harms of NOTES for doing hysterectomy in women with a non-prolapsed uterus and benign gynaecological disease compared to the laparoscopic technique. Both randomised and non-randomised comparative studies are eligible for inclusion. To this end, the proposed systematic review will aim to answer the following clinically relevant questions:

1. Is the NOTES technique at least as effective compared to the laparoscopic approach for successfully removing a uterus without the need for conversion to any alternative approach?
2. Are women treated by NOTES less frequently hospitalized when admitted to the day care unit compared to treatment by laparoscopy?
3. Do women treated by NOTES suffer less pain compared to women treated by laparoscopy in the postoperative period?
4. Is the removal of a uterus by NOTES faster compared to laparoscopy?
5. Does NOTES cause more pelvic infection or other surgical complications compared to the use of the laparoscopic approach?
6. Does the use of the NOTES approach result in more hospital readmissions following surgery compared to laparoscopy?

7. Does the use of the NOTES technique result in more women reporting dyspareunia, less sexual wellbeing or any decrease in quality of life in the longer term when compared to women treated by laparoscopy?
8. What are the comparative economic costs of both techniques?

METHODS

Eligibility criteria

We will select studies according to the following criteria.

Study designs

We will include randomised controlled trials (RCTs), controlled (non-randomised) clinical trials (CCTs) and prospective/ retrospective cohort studies. We will exclude all other types of study designs that do not allow a direct comparison of NOTES compared to laparoscopy (e.g. case series, case reports, letters to the editor,...).

Participants

We will include studies examining the target adult female population (aged 18 to 70 years) bound to undergo surgical removal of a non-prolapsed uterus with or without removal of one or both adnexa for benign gynaecological disease. We will exclude genital prolapse or gynaecological malignancy as the primary indication for surgical treatment.

Interventions

Hysterectomy using the Natural Orifice Transluminal Endoscopic Surgery (NOTES) technique is the intervention of interest. We will exclude studies on Single Incision Laparoscopic Surgery (SILS) as the experimental (but not control) intervention. We will also exclude abdominal or vaginal hysterectomy as the experimental intervention.

Comparators

Laparoscopy assisted vaginal hysterectomy or total laparoscopic hysterectomy using the umbilicus as the primary entry site using single (SILS) or multiple ports will be the comparator of interest. We will exclude abdominal hysterectomy or vaginal hysterectomy as comparators. We will use the definitions for the different types of hysterectomy as presented in a recent Cochrane review (11).

Outcomes

The following outcomes are of primary interest:

- The successful removal of the uterus by the intended technique without the need for conversion to any other technique of hysterectomy
- The proportion of women hospitalized after surgery
- Postoperative pain scores
- The amount and the duration of use of analgesics taken after surgery
- Postoperative infection
- Intra- or postoperative complications
- Readmission to hospital after discharge
- Frequency and intensity of dyspareunia
- Sexual wellbeing
- The duration of surgery
- Quality of life
- Amount of money spent for the use of either technique

Timing

Studies will be selected for inclusion based on the length of follow-up of outcomes. The following will be used as a guide for all study designs:

- For postoperative pain scores and the amount/duration of analgesics used, studies should report a follow-up time of at least one week.
- Postoperative infection, any surgical complication or readmission to hospital after discharge, should be reported between 6 weeks and 3 months of follow-up.
- Dyspareunia, sexual wellbeing and quality of life, should be reported between 3 months and 1 year of follow-up.

Setting

There will be no restrictions by type of setting.

Language

We will include articles reported in English. We will include manuscripts in other languages if they can be adequately translated using Google translate due to resource limits. A list of possibly relevant titles in other languages that cannot be translated will be provided as an appendix

Information sources

We will develop a literature search strategy using a combination of medical subject headings (MeSH) and text words related to NOTES. Two reviewers (JBO and JBA) will independently search MEDLINE (PubMed interface, 1950 onwards), EMBASE (Embase.com interface, 1974 onwards) and the Cochrane Central Register of Controlled Trials (Wiley interface, current issue). The literature search will be limited to the English language and human subjects.

The electronic database search will be supplemented by searching for trial protocols in ClinicalTrials.gov (<https://clinicaltrials.gov/>) and the WHO ICTRP search portal (<http://apps.who.int/trialsearch/>). We will also search Web of Science (interface Thomson Reuters), the Centre for Reviews and Dissemination (<http://www.crd.york.ac.uk/CRDWeb/>) and LILACS (<http://lilacs.bvsalud.org/en/>). We will search the grey literature in Open Grey (<http://www.opengrey.eu/>). To ensure literature saturation we will hand-search the ESGE peer-reviewed journal Gynaecological Surgery because this journal has no citation index. We will scan the reference lists of the included studies or relevant reviews identified through the search. We will circulate a bibliography of the included articles to the systematic review team as well as to experts in gynaecological NOTES procedures identified by the team.

Search strategy

We will search for comparative quantitative studies using no study design or date limits. We will use language limits (only English) but we will include eligible studies in languages other than English that can be adequately translated using Google translate due to time and resource limits. Two authors (JBO and JBA) will develop the specific search strategy for MEDLINE with input from the systematic review team. The draft will be presented for review by a Health Sciences librarian at the 2 Bergen Biomedical Library of the KU Leuven, not associated with the project. The MEDLINE search strategy is included in Appendix 1. The final MEDLINE strategy will be adapted to the syntax and the subject headings of the other databases.

The International Clinical Trials Registry Platform Search Portal and ClinicalTrials.gov will be searched for ongoing or recently completed trials, and PROSPERO will be searched for ongoing or recently completed reviews. As relevant studies are identified, the reviewers will be alert for identifying additional relevant cited and citing articles by setting up e-mail alerts for each search when possible. The search will be updated towards the end of the review, after being validated to ensure that the MEDLINE strategy has enough sensitivity to retrieve a high proportion of eligible studies found through any means but indexed in MEDLINE.

Study records

Data management

We will upload the search results to EndNote Web (<https://www.myendnoteweb.com/>), an Internet based software program by Thomson Reuters that facilitates collaboration among reviewers during the study selection process. We will develop and test screening questions and forms based on the inclusion and exclusion criteria. Citation abstracts and full text reports will be uploaded to EndNote Web. Prior to the formal screening process a calibration exercise will

be undertaken to pilot and refine the screening questions. We will remove duplicates by using EndNote Web software.

Selection process

Two reviewers (JBO and JBA) will independently and simultaneously screen the titles and abstracts yielded by the search against the inclusion criteria. We will make a long list of potentially eligible studies by removing the publications that are obviously irrelevant for the research question of the present systematic review. We aim to obtain full text reports for all those titles that appear to meet the inclusion criteria or where there is any uncertainty. The two reviewers will then screen the full text reports and decide whether these meet the inclusion criteria. We will seek additional information from study authors where necessary to resolve questions about eligibility. We will resolve disagreement through discussion and seek arbitration by a third reviewer (SW) when needed. We will record the reasons for excluding trials. A short list of eligible studies is made. Neither of the review authors will be blinded to the journal titles or to the study authors or institutions as suggested by the Cochrane Handbook for Systematic Reviews of Interventions (12).

Data collection process

Using standardized data extraction forms two reviewers (JBO and JBA) will extract data independently and in duplicate from each eligible study from the short list. To ensure consistency across the two reviewers, we will pilot calibration exercises before starting the review. Data extracted will include demographic information, study design, characteristics and data of patients, interventions, comparators, length of follow-up and outcomes. Reviewers will resolve disagreements by discussion and arbitration by a third reviewer (SW) will be sought when needed to adjudicate unresolved disagreements. We will contact study authors to resolve any uncertainties. Any unresolved disagreement in the selection or data collection process will

be reported in the final review and its implications on the results and interpretation of the findings will be subjected to multiple sensitivity analyses.

Data items

We will extract the following items:

- Study design: RCT, CCT, prospective cohort, retrospective cohort.
- Characteristics of the study population: age, parity, BMI, any prior abdominal surgery or PID.
- A detailed description of the NOTES procedure: technique and instrumentation, duration of surgery, type and dosage of antibiotics for prophylaxis, type and dosage of analgesics, the follow-up on the recovery/day care unit/ in hospital surgery ward, nursing protocol.
- A detailed description of the comparator intervention: technique and instrumentation, duration of surgery, type and dosage of antibiotics for prophylaxis, type and dosage of analgesics, the follow-up on the recovery/day care unit/ in hospital surgery ward, nursing protocol.
- Key outcomes and at which time point and by which method/tool these were assessed: the proportion of women with successful removal of the uterus by the intended NOTES technique without the need for conversion to any other technique of hysterectomy, the proportion of women hospitalized after surgery, postoperative pain scores, the dosage, route of administration and the duration of use of analgesics taken after surgery, postoperative infection, intra- or postoperative surgical complications, readmission to hospital after discharge, frequency and intensity of dyspareunia, sexual wellbeing, the duration of surgery, quality of life and amount of money spent for the use of either technique.

Whenever possible we will use results from an intention to treat analysis. If effect sizes cannot be calculated, we will contact the study authors for clarification.

Outcomes and prioritisation

Primary outcomes

The proportion of women successfully treated by removing the uterus by the intended approach without conversion to any other technique of hysterectomy, measured at the end of the surgical intervention as a dichotomous outcome.

Secondary outcome measures

Secondary outcomes are as follows: 1. The proportion of women hospitalized after surgery, measured at one time point as a dichotomous outcome; 2. Postoperative pain scores measured as an ordinal outcome using a validated tool (VAS scale) at several time points in the immediate postoperative period with a follow-up of at least one week; 3. The total use of analgesics taken in the period following surgery measured as dichotomous and ordinal outcome at several time points in the immediate postoperative period with a follow-up of at least one week; 4. Postoperative infection, defined by lower abdominal pain with fever $> 38^{\circ}\text{C}$ and positive clinical signs or laboratory findings, measured at one time point as a dichotomous outcome with a follow-up of at least 6 weeks to 3 months duration ; 5. Intra- or postoperative complications, classified according to the Dindo- Clavien classification (13), measured at several time points as a dichotomous outcome with a follow-up of at least 6 weeks to 3 months duration; 6. Readmission to hospital after discharge, measured at several time points as a dichotomous outcome with a follow-up of at least 6 weeks to 3 months duration ; 7. Frequency and intensity of dyspareunia, measured as a dichotomous (frequency) and ordinal outcome, measured at several time points using a validated questionnaire and tool (VAS scale) with at least 3 months to 1 year duration for follow-up; 8. Sexual wellbeing, measured as an ordinal outcome using a disease specific validated tool at several time points with at least 3 months to 1 year duration

for follow-up ; 9. The duration of surgery in minutes, as a continuous outcome measured at the end of the surgical procedure; 10. Quality of life, measured as an ordinal outcome using a generic validated tool at several time points with at least 3 months to 1 year duration for follow-up ; 11. Comparative economic costs measured as a continuous outcome at one time point with at least 3 months to 1 year duration for follow-up.

We aim to include the primary outcome in a summary of findings table using GRADEPRO GDT software (<http://gradepro.org/>) as well as the following secondary outcomes: the proportion of women hospitalized after surgery, the hospital readmission rate, the rate of postoperative infection and the intra- and postoperative complication rates.

Risk of bias in individual studies

To facilitate the assessment of possible risk of bias for each included RCT, we will collect information using the Cochrane Collaboration tool for assessing the risk of bias (Table 8. 5. a in the Cochrane Handbook for Systematic Reviews of Interventions) (12) which covers the following six items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, selective outcome reporting and other potential sources of bias. For each domain in the tool, we will describe the procedures undertaken for each study, including verbatim quotes. A judgment as to the possible risk of bias on each of the six domains will be made from the extracted information, rated as ‘high risk’ or ‘low risk’. If there is insufficient information reported in the study report, we will judge the risk of bias as ‘unclear’ and the original study investigators will be contacted for further clarification. These judgements will be made independently by two review authors (JBO and JBA) following the guiding principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions Table 8. 5. c (12). Disagreements will be resolved first by discussion and then by arbitration by a third reviewer (SW). Any residual disagreement that cannot be resolved will be assessed as unclear and will be explicitly reported in the final review.

We will draft graphic representations of the risk of bias within and across studies using Review Manager 5 software. We will consider each item in the risk of bias assessment independently without any attempt to collate and assign an overall score.

To assess the risk of bias for each included observational study, we will use the Newcastle-Ottawa scale (NOS). We will resolve any disagreement by discussion and when needed by consulting a third review author (SW) for arbitration. Any residual disagreement that cannot be resolved will be assessed as unclear and will be explicitly reported in the final review.

Data synthesis

Measures of treatment effect

Dichotomous data will be determined by using risk ratio (RR) with 95% confidence interval (CI). The RR is more intuitive than the more mathematically stable odds ratio (OR); OR tend to be interpreted as RR by clinicians, which leads to an overestimate of the true effect size. We will analyse the ordinal outcomes as continuous outcomes. Continuous outcomes will be analysed using mean differences (MD) with 95% CI or weighted standardised mean differences (SMD) with 95% CI if different measurement scales are used. Skewed data and non-quantitative data will be presented descriptively.

Unit of analysis issues

The primary analysis will be per individual woman randomised/treated.

Dealing with missing data

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

Assessment of heterogeneity

We will test the clinical diversity across all included studies by considering the variability in participant factors (for example age or BMI) and study factors (allocation concealment, blinding of outcome assessment, loss to follow-up, treatment type, co-interventions, etc.). Statistical heterogeneity will be tested using the Chi² test (significance level: 0.10) and I² statistic (0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity). If high levels of heterogeneity among the included studies exist (I²≥50% or P<0.10) the study design and characteristics of the included studies will be analysed. We will try to explain the source of heterogeneity by subgroup analysis or meta-regression.

Data synthesis

If studies are sufficiently homogenous in terms of design and comparator, we will conduct meta-analyses. Each outcome will be combined and a summary effect size will be calculated using the statistical software Review Manager 5 according to the statistical guidelines outlined and referenced in the current version of the Cochrane Handbook for Systematic Reviews of Interventions (12). The Mantel-Haenszel method (M-H) will be used for the fixed-effect model for dichotomous outcomes and the Inverse Variance method (IV) will be used for the fixed-effect model for continuous outcomes. If substantial statistical heterogeneity is observed (I²≥50% or P<0.10), the random effects model will be chosen. If heterogeneity is considerable, we will not perform a meta-analysis; a narrative, qualitative summary will be done.

Subgroup analysis and investigation of heterogeneity

We aim to carry out subgroup analyses according to the patient's age, the uterine volume, and the BMI to explore possible sources of heterogeneity only if enough data can be retrieved.

We aim to do sensitivity analyses for the primary outcome to explore the source of heterogeneity as follows:

- Quality components, including full-text publications versus abstracts, preliminary results versus mature results, published versus unpublished data.
- Risk of bias (by omitting small studies or studies with a high risk of bias).
- Analysis: using odds ratio rather than risk ratio for the summary effect measure or a fixed effect rather than a random-effects as the analysis model.
- Different strategies for dealing with missing data when both available data and ITT data on outcomes have been reported in the primary studies.

If quantitative synthesis is not appropriate, a systematic narrative synthesis will be given with information presented in the text and tables to summarise and explain the characteristics and findings of the included studies. The narrative synthesis will explore the relationship and findings within and between the included studies, in line with the guidance from the Centre for Reviews and Dissemination.

Meta-biases

Publication bias, reporting bias and within-study reporting bias are difficult to detect and correct for. We aim to do the search for eligible studies as comprehensively as possible and by being alert in identifying duplicated reports of trials in order to minimise the potential impact of reporting and publication bias. In order to determine whether reporting bias is present, we will determine whether the protocol of the study was published before recruitment of participants was started. We will screen the Clinical Trial Registers at the International Clinical Trials Registry Platform of the World Health Organisation (<http://apps.who.int/trialsearch/>) and ClinicalTrials.gov (<https://clinicaltrials.gov/>). We will evaluate whether selective reporting of outcomes is present. If a protocol is not available we will cross-examine the methods and results section of the published report. We will compare the fixed-effect estimate against the random effects estimate to assess the possible presence of small study effects in the published literature in which the intervention effect is biased in favour of the smaller studies. In the presence of

small study bias, the random effects estimate of the intervention is more beneficial than the fixed-effect estimate. The potential for reporting bias will be further explored by a funnel plot when ≥ 10 studies are retrieved.

Confidence in cumulative evidence

The quality of the evidence for the primary outcome and some secondary outcomes (the proportion of women hospitalized after of surgery, the hospital readmission rate, the rate of postoperative infection and the intra- and postoperative complication rates) will be judged using the Grading of Recommendations Assessment, Development and Evaluation working group methodology using GRADEPRO GDT software (version 3.2.2.20090501) (<http://ims.cochrane.org/gradepr>). The quality of evidence of the included studies will be assessed across the domains of risk of bias, consistency, directness, precision and publication bias. Quality will be adjudicated as high (further research is very unlikely to change our confidence in the estimate of the effect), moderate (further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate), or very low (very uncertain about the estimate of the effect). The assessment of the quality of the evidence will not include studies that were excluded from meta-analysis.

References

1. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA and PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; 4:1. doi: 10.1186/2046-4053-4-1.
2. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, the PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2014; 349:g7647.
3. Kalloo AN, Singh VK, Jagannath SB, et al. Flexible transgastric peritoneoscopy: a novel approach to diagnostic and therapeutic interventions in the peritoneal cavity. *Gastrointest Endosc* 2004; 60:114-7.
4. Rao GV, Reddy DN, Banerjee R. NOTES: Human experience. *Gastrointest Endosc Clin N Am* 2008; 18: 361–70.
5. Rolanda C, Lima E, Pêgo JM, et al. Third-generation cholecystectomy by natural orifices: transgastric and transvesical combined approach. *Gastrointest Endosc*. 2007; 65: 111-7.
6. Rattner D, Kalloo A. ASGE/SAGES working group on natural Orifice transluminal endoscopic surgery. *Surg Endosc* 2006; 20:329-33.
7. Santos BF, Hungness ES. Natural orifice transluminal endoscopic surgery: progress in humans since white paper. *World J Gastroenterol* 2011; 17:1655–65.
8. Tolcher MC, Kalogera E, Hopkins MR, et al. Safety of Culdotomy as a Surgical Approach: Implications for Natural Orifice Transluminal. *JSLS* 2012; 16:413–20
9. Uccella S, Cromi A, Bogani G, et al. Transvaginal specimen extraction at laparoscopy without concomitant hysterectomy: our experience and systematic review of the literature. *J Minim Invasive Gynecol* 2013; 20:583-90.
10. Su H, Yen CF, Wu KY, et al. Hysterectomy by transvaginal natural orifice transluminal endoscopic surgery (NOTES): Feasibility of an innovative approach. *TJOG* 2012; 51: 217-21.

11. Nieboer TE, Johnson N, Barlow D, Lethaby A, Tavender E, Curr E, Garry R, van Voorst S, Mol BWJ, Kluivers K. Surgical approach to hysterectomy for benign gynaecological disease. *Cochrane Database of Systematic Reviews* 2006, Issue 2. Art. No.: CD003677.

12. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

13. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240: 205–13.

Appendix 1: MEDLINE strategy

* MEDLINE (PubMed interface)

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



PRISMA 2009 Flow Diagram

