Sacrospinous hysteropexy versus vaginal hysterectomy with uterosacral ligament suspension in women with uterine prolapse stage two or higher: a multicentre randomised non-inferiority trial

Journal:	*BMJ*
Manuscript ID:	BMJ.2015.025142
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	30-Jan-2015
Complete List of Authors:	Detollenaere, Renée; Isala, Obstetrics and Gynaecology den Boon, Jan; Isala, Obstetrics and Gynaecology Stekelenburg, Jelle; Medical Centre Leeuwarden, Obstetrics and Gynaecology IntHout, Joanna; Radboud university medical center, Radboud Institute for Health Sciences Vierhout, Mark; Radboud university medical center, Obstetrics and Gynaecology Kluiver, Kirsten; Radboud university medical center, Obstetrics and Gynaecology van Eijndhoven, Hugo; Isala, Obstetrics and gynaecology
Keywords:	uterine prolapse, hysterectomy, hysteropexy, randomised controlled trial

Sacrospinous hysteropexy versus vaginal hysterectomy with uterosacral ligament suspension in women with uterine prolapse stage two or higher: a multicentre randomised non-inferiority trial

Renée J Detollenaere *research fellow and resident in obstetrics and gynaecology*[1 2], Jan den Boon *urogynaecologist*[1], Jelle Stekelenburg *gynaecologist*[3], Joanna IntHout *medical statistician*[2], Mark E Vierhout *professor and urogynaecologist*[2], Kirsten B Kluivers *urogynaecologist*[2], Hugo WF van Eijndhoven *urogynaecologist*[1]

[1]Isala Department of Obstetrics and Gynaecology, PO Box 10400, 8000 GK Zwolle, The Netherlands; [2] Medical Centre Leeuwarden Department of Obstetrics and Gynaecology, PO Box 888, 8901 BR Leeuwarden, The Netherlands; [3] Radboud university medical center, Radboud Institute for Health Sciences, PO Box 9101, 6500 HB Nijmegen, The Netherlands; [4] Radboud university medical center Department of Obstetrics and Gynaecology, PO Box 9101, 6500 HB Nijmegen, The Netherlands

Correspondence to: r.j.detollenaere@isala.nl

Word count

Abstract 287 words

Manuscript 3756 words

ABSTRACT

OBJECTIVE To investigate whether vaginal sacrospinous hysteropexy is non-inferior to vaginal hysterectomy with uterosacral ligament suspension in surgical treatment of uterine prolapse.

DESIGN A multicentre randomised controlled non-blinded non-inferiority trial (SAVE U) with 1:1 treatment allocation.

SETTING 4 Dutch non-university teaching hospitals

PARTICIPANTS 208 healthy women with uterine prolapse stage two or higher requiring surgery, without a history of prior pelvic floor surgery.

INTERVENTIONS Treatment with sacrospinous hysteropexy or vaginal hysterectomy with uterosacral ligament suspension. The predefined non-inferiority margin was an increase in surgical failure rate of 7%.

MAIN OUTCOME MEASURES Primary outcome was recurrent prolapse stage two or higher of the uterus or vaginal vault (apical compartment) evaluated by Pelvic Organ Prolapse Quantification examination in combination with bothersome symptoms or repeat surgery for recurrent apical prolapse at 12 months follow-up. Secondary outcomes were overall anatomical recurrences, functional outcome, complications, hospital stay, post-operative recovery, and sexual functioning.

RESULTS Sacrospinous hysteropexy was non-inferior regarding anatomical recurrence of the apical compartment with bothersome symptoms or repeat surgery (n=0, 0%) compared to vaginal hysterectomy with uterosacral ligament suspension (n=4, reduction of 3.9%; 95% CI for difference -0.7 to 8.6, p=0.06). A benefit was observed for sacrospinous hysteropexy with regard to duration of surgery (59 minutes SD 13 vs 72 minutes SD 21; p<0.01). There were no statistically significant differences in overall anatomical recurrences, functional outcome, quality of life, complications, hospital stay, measures on post-operative recovery and sexual functioning between the two groups. Five serious adverse events were reported during hospital stay. None of the events was assumed to be related to the type of surgery.

CONCLUSIONS Uterus preservation by sacrospinous hysteropexy was non-inferior to vaginal hysterectomy with uterosacral ligament suspension regarding surgical failure of the apical compartment at 12 months follow-up.

TRIAL REGISTRATION trialregister.nl Identifier: NTR1866.

Introduction

Pelvic organ prolapse is one of the most common benign gynaecological disorders with an increasing incidence due to ageing and increased obesity rates. About 40% of the women over 45 years of age are affected and the lifetime risk for prolapse surgery is 11-20%. [1–3] Pelvic organ prolapse has negative influence on women's quality of life and is associated with physical, psychological, and sexual distress.

The standard surgical care worldwide for patients with symptomatic uterine prolapse is vaginal hysterectomy[4–6] It is a matter of debate whether or not the uterus should be removed in case of uterine prolapse as the descent of the uterus may be a consequence and not a cause of pelvic organ prolapse. Vaginal hysterectomy may cause surgical injury to the innervation and vascularisation of the pelvic floor muscles and even more disrupt supportive structures of the pelvic floor, making woman at an increased risk for stress-incontinence and recurrence of prolapse.[7,8] To prevent future prolapse, additional support of the vaginal apex after hysterectomy is recommended and in experts opinion hysterectomy alone is an inadequate treatment for uterine prolapse. [9,10]

Several cohort studies are available but randomised trials comparing uterus preservation with hysterectomy are limited. Prospective non-randomised and retrospective cohort studies have shown that vaginal sacrospinous hysteropexy was as effective as vaginal hysterectomy with a similar rate of recurrence and repeat surgery but with shorter operating time, less blood loss, faster recovery, and fewer complications.[11-13] One randomised controlled trial (RCT) found a higher rate of recurrences of the apical compartment after sacrospinous hysteropexy after 12 months (21% vs. 3% in patients with vaginal hysterectomy with uterosacral ligament suspension), however recurrence rate was only a secondary endpoint.[14] Another RCT found no differences in sexual functioning after six months but did not report on anatomical outcome.[15] A Cochrane review on pelvic organ prolapse surgery concluded that data from randomised trials are currently insufficient to guide practice.[16] The SAVE U trial was designed to test the hypothesis that sacrospinous hysteropexy was non-inferior to vaginal hysterectomy with uterosacral ligament suspension regarding surgical failure after 12 months follow-up. Secondary outcomes were overall anatomical outcome, functional outcome, quality of life, hospital stay, post-operative recovery, complications, and sexual functioning.

Methods

Study Design

A detailed version of the SAVE U trial protocol has been published previously.[17] In short, all women with pelvic organ prolapse quantification (POP-Q) stage two or higher uterine prolapse requiring surgery were asked for participation. Participants were randomly assigned to sacrospinous hysteropexy or vaginal hysterectomy with uterosacral ligament suspension in a non-blinded multicentre randomised controlled non-inferiority trial. Patients with co-existing anterior and/or posterior vaginal wall prolapse were allowed to participate as well as patients with cervical elongation. Concomitant repair of anterior and/or posterior vaginal prolapse was allowed including anti-incontinence surgery. Patients with previous pelvic floor or prolapse surgery, known malignancy or abnormal cervical smears, a wish to preserve fertility, language barriers, presence of immunological or haematological disorders interfering with recovery after surgery, abnormal ultrasound findings of the uterus or ovaries, or abnormal uterine bleeding, and those who were unwilling to return for follow-up were excluded.

All participating centres (n= 4) were large non-university teaching hospitals. Centres had to offer both treatment modalities and were asked for participation if they were known to perform the interventions in the same standardized manner. All gynaecologists were experienced and performed a minimum of 20 procedures of each intervention before the start of the trial. As the participating hospitals were teaching hospitals, residents were allowed to perform procedures under direct supervision of the gynaecologist. Gynaecologists and residents of the participating centres assessed eligibility of patients. Written patient information was provided and informed consent prior to randomisation was obtained. The trial was approved by the medical ethical committee of the Isala hospital (MEC 09-625) and the local ethical committees of the participating centres, in accordance with the Declaration of Helsinki. Patients were randomly allocated in a 1:1 ratio using a web-based application with computer-generated randomization tables with a block size of 4, stratified by hospital and POP-Q stage. The trial was non-blinded as it was impossible to blind the surgeon and patient for the surgical procedure to which the patient was allocated. An independent physician who was not in any way involved in the treatment carried out follow-up after 12 months.

Outcome measures

Surgical failure at 12 months follow-up was the initial primary outcome. As outcome definitions to evaluate prolapse surgery were improved after start of this trial, during enrolment and before data analysis the primary outcome was changed into the following composite outcome measure: recurrent prolapse POP-Q stage 2 or higher in the apical compartment (uterus or vaginal vault) with bothersome prolapse complaints or repeat surgery for recurrent apical prolapse at 12 months follow-up. The medical ethical committee approved this change and during enrolment the protocol was published in an open access online journal.[17]

The original primary outcome, overall anatomical failure (prolapse POP-Q stage two or higher in any compartment) was evaluated as secondary outcome together with two additional definitions of surgical failure/success: (I) composite outcome of success defined as no prolapse beyond the hymen, no bothersome bulge symptoms and no repeat surgery or pessary use for recurrent prolapse within 12 months follow-up and (II) overall surgical failure: prolapse POP-Q stage two or higher, pessary use or repeat surgery for recurrent prolapse in any compartment within 12 months.[18] Other secondary outcomes were functional outcome, quality of life, complications, hospital stay, post-operative recovery, and sexual functioning.

Interventions

A detailed description of the study interventions was used to warrant a uniform technique amongst surgeons.[17] Sacrospinous hysteropexy was performed unilaterally to the right sacrospinous ligament. Two permanent sutures (Prolene 1.0, Ethicon, Somerville, NJ, USA) were placed under direct vision at least 2 cm from the ischial spine and attached to the posterior part of the cervix. Vaginal hysterectomy was performed with additional vault suspension by uterosacral ligament suspension. With uterosacral ligament suspension, the vaginal cuff was reattached to the proximal uterosacral ligaments without plicating the uterosacral ligaments or obliterating the cul-de-sac.[19] Concomitant anterior and/or posterior vaginal wall repair and anti-incontinence surgery were performed if indicated. All women received perioperative antibiotics, thrombosis prophylaxis and a bladder catheter according to local hospital protocol. Analgesics were given post-operatively in accordance with local hospital protocol. All patients were advised to abstain from heavy physical work for a period of 6 weeks.

Measurements and Procedures

Gynaecological examination prior to surgery included pelvic ultrasound to exclude uterine or ovarian disease, PAP-smear and vaginal inspection in 45° semi-upright position for staging pelvic organ prolapse by a POP-Q examination.[20] Patients came to the hospital for follow-up and POP-Q examination at baseline and 6 weeks, 6 months and 12 months after surgery and completed validated health-related and disease-specific quality of life questionnaires: Short Form-36 (SF-36), Euroqol 5D (EQ5-D), Urogenital Distress Inventory (UDI), Defecatory Distress Inventory (DDI), and Incontinence Impact Questionnaire (IIQ). [21–24] The presence of subjective prolapse symptoms after surgery was defined as a positive answer to any of the following two questions from the UDI: '' do you experience a sensation of bulging or protrusion from the vagina?'' and ''do you have a bulge or something falling out that you can see in the vagina?'' in combination with a response 'somewhat bothered' to 'very much bothered' to the question ''how much does this bother you?'' To assess sexual functioning the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12), translated from the validated questionnaire but not validated for Dutch language, was used.[25]

During hospitalisation and the first 6 weeks after surgery patients kept a diary to evaluate post-operative pain (range 0-10) measured by the validated Visual Analogue Scale, pain medication, and post-operative recovery measured with the validated Recovery Index-10 (RI-10). [26]

Data were entered and registered using a web-based application facilitated by the Dutch consortium for studies in women's health and reproductivity (www.studies-obsgyn.nl).

Statistical Analysis

The sample size for this trial was estimated for the primary objective, i.e. to evaluate whether sacrospinous hysteropexy was non-inferior to vaginal hysterectomy regarding surgical failure of the apical compartment after 12 months. The expected failure rate was based on outcomes of the gold standard (vaginal hysterectomy) in a previous study. [12, 27] A difference in failure rate larger than 7% was expected to be clinically relevant. Assuming an absolute recurrence rate of 3% in both groups and a two-sided α risk of 0.05, with two groups of 94 patients the trial had 80% power with a pre-specified non-inferiority margin of 7% to assess non-inferiority of sacrospinous hysteropexy. Considering a 10 percent loss to follow-up, 104 women per arm were needed and in total 208 women.

Study outcomes were assessed by intention-to-treat (ITT) analysis. In case of missing data on anatomical outcome at 12 months we applied two strategies: first the last observation carried forward (LOCF) ITT approach using data of the six months follow-up visit if available. If 6-month data were not available, patients were left out of the ITT-LOCF analysis. For the second ITT analysis we applied conservative imputation for all patients with missing data at 12 months (worst case scenario, i.e. failure). In case of a missing questionnaire, the presence or absence of prolapse symptoms was obtained from the 12 month follow-up visit. Also a per protocol (PP) analysis was carried out on the primary and secondary outcomes regarding anatomic and surgical failure. This analysis included patients who completed the entire treatment protocol as originally planned with availability of POP-Q score at 12 months and absence of major protocol deviations.

All statistical analyses were performed with SPSS for windows (version 22.0.0.1). We compared proportions and continuous variables between the groups using Fisher's exact tests and Mann-Whitney U tests. 95% Confidence intervals (CIs) for differences in proportions were calculated using the Agresti-Coull method.[28]

Exploratory logistic regression analyses were performed to identify possible risk factors for failure. Considered risk factors were age, parity, body mass index, smoking, operating time, blood loss, length of hospital stay, primary surgeon (gynaecologist or resident), and a history of vaginal operative delivery. For each risk factor the analysis was adjusted for centre, preoperative POP-Q stage, and randomisation outcome. Adjusted odd ratios (ORs) for the possible risk factors were estimated with corresponding 95% CI. Two-sided p values below 0.05 were considered statistically significant.

Results

Between November 27, 2009, and March 12, 2012 208 women were randomly assigned to sacrospinous hysteropexy (n=103) or vaginal hysterectomy (n=105). Figure 1 shows the flow diagram.

Fourteen protocol deviations occurred: two patients received sacrospinous hysteropexy instead of vaginal hysterectomy due to technical difficulties during surgery (crossovers). In one patient allocated to vaginal hysterectomy, laparoscopic cystectomy prior to vaginal hysterectomy showed intra-abdominal adhesions and an abdominal hysterectomy was performed. In two women an exclusion criterion was ignored before randomisation: one patient had previous pelvic floor surgery (repair of posterior vaginal wall prolapse)

and another patient suffered from primary sclerosing cholangitis with thrombocytopenia. Three patients who were assigned to sacrospinous hysteropexy had abnormal PAP smears and were treated with electrosurgical excision (n=2) during prolapse surgery and/or follow-up. In six patients (6 of 102, 6%) apical suspension after vaginal hysterectomy was performed by a Mc Call culdoplasty instead of uterosacral ligament suspension. In the other patients uterosacral ligament suspension was performed (96 of 102, 94%). According to the ITT principle, we included these patients in the ITT analysis and all patients were analyzed in their group as randomised. In the PP analysis these patients were excluded, except for the crossovers (n=2) as the primary outcome was related to efficacy and these women had no other protocol deviations and patients with abnormal PAP smears (n=3) were included as well as this was regarded as minor protocol deviation.

Baseline characteristics were similar between the groups (table 1) and no differences at baseline were found regarding pelvic measurements and characteristics (table 2). Intra- and postoperative details are shown in table 3. Five serious adverse events (SAEs) during hospital stay were reported: two after hysterectomy and three after sacrospinous hysteropexy. One patient after vaginal hysterectomy developed a paralytic ileus. She experienced this problem also after previous orthopaedic surgery. Unfortunately she aspirated gastric content eight days after surgery, developed aspiration pneumonia and died because of multi-organ failure. The other SAEs were: 1. atrial fibrillation which required cardioversion (vaginal hysterectomy), 2. stroke two days after surgery; full recovery without any loss of function (sacrospinous hysteropexy), 3. postoperative pneumonia (sacrospinous hysteropexy) and 4. anaphylactic reaction on prophylactic antibiotics prior to the surgical procedure (sacrospinous hysteropexy); in this patient the surgical procedure was postponed until several months later, without any problems. None of the SAEs were judged to be related to the type of surgery.

In table 4 results on the primary outcome are presented. Sacrospinous hysteropexy was non-inferior to vaginal hysterectomy regarding anatomical recurrence of the apical compartment with bothersome prolapse symptoms or repeat surgery for recurrent apical prolapse: sacrospinous hysteropexy n=0, 0% versus vaginal hysterectomy n=4, 3.9% (95% CI for difference -0.7 to 8.6, p=0.06) for the ITT-LOCF approach. The ITT analysis with conservative imputation and the PP analysis also resulted in non-inferiority of sacrospinous hysteropexy. There were also no significant differences in overall anatomical or surgical failure between the interventions.

After 12 months there were no significant difference in functional outcome and quality of life between the groups (Table 5). Post-operative recovery was similar after both interventions with comparable

RI-10 scores at 1, 2, 4 and 6 weeks after surgery. VAS pain scores did not notably differ between both interventions except for day 14 in favour of hysterectomy. In eight out of nine patients who experienced buttock pain, a typical complaint after sacrospinous hysteropexy, the pain resolved (VAS<2) spontaneously within the first 6 weeks. One patient underwent suture cutting and vaginal hysterectomy after four months because of persistent pain localised at the place of the sacrospinous hysteropexy sutures. After this procedure she was free of symptoms. Among the patients who completed the PISQ-12 before and after surgery, there was significant improvement in PISQ-12 scores in both the sacrospinous hysteropexy ($p<0.01$) and vaginal hysterectomy group ($p<0.01$) and there was no significant difference regarding improvement between both interventions.

Only body mass index was significantly associated to failure (OR 1.12, 95% CI 1.02 to1.24, $p<0.01$). Table 6 shows adjusted ORs with 95% CIs for each of the possible predictors for failure.

In the sacrospinous hysteropexy group three procedures (3%) and in the vaginal hysterectomy group 19 procedures (18%) were performed by residents. No statistically significant difference was found in overall surgical failure rate (recurrent prolapse, pessary use or repeat surgery) in patients who underwent surgery by either gynaecologist or residents (91 failures out of 180 procedures (50.6%) versus nine failures out of 19 procedures (47.4%), $p=0.81$). In one patient after sacrospinous hysteropexy (1.0%) endometrial cancer was diagnosed during follow-up and a laparoscopic hysterectomy was performed. Urinary retention, which was defined as more than 150 ml urine retention after removal of the catheter, was similar between groups: 15 of 103 (14.6%) versus 12 of 105 (11.4%). These women received a transurethral catheter or were instructed to perform clean intermittent self-catheterisation. In all women spontaneous micturition was achieved after a maximum length of catheterisation of 40 days (median 5.0 days, range 1 - 40 days). After 12 months, 1 of 102 (1.0%) after sacrospinous hysteropexy versus 4 of 102 (3.9%, $p=0.37$) after vaginal hysterectomy had undergone subsequent surgical treatment for stress urinary incontinence.

Discussion

The SAVE U trial shows that treatment with sacrospinous hysteropexy is non-inferior to vaginal hysterectomy with uterosacral ligament suspension regarding surgical failure of the apical compartment neither in the intention to treat nor in the per protocol analysis. We found no significant differences in overall

anatomical and surgical failure, functional outcome, quality of life, complications, post-operative recovery, hospital stay and sexual functioning between the interventions. A benefit was observed for sacrospinous hysteropexy with regard to duration of surgery. Patients after sacrospinous hysteropexy reported more buttock pain after surgery but VAS pain scores were low and pain resolved within 6 weeks in the majority of cases.

Strengths and limitations of the study

Major strength of this study is the randomised multicentre design and sufficiently large study population. This is to our best knowledge the first randomised trial that compared uterus preservation with hysterectomy on a large scale using clinically relevant outcome measures.

The study also has some limitations. First, our report is on a relatively short follow-up period of 12 months. Women gave consent for follow-up till 60 months after surgery and these data will be further analyzed.

After vaginal hysterectomy the ligatures of the uterosacral ligaments was sutured to the vaginal cuff to aid in long-term vaginal support. However in six patients the protocol was ignored and Mc Call culdoplasty was performed instead of uterosacral ligament suspension. During a McCall procedure, the uterosacral ligaments are plicated in the midline, incorporating the cul-de-sac peritoneum and posterior vaginal cuff. [29] Both procedures rely on the uterosacral ligaments for support of the vaginal apex but are considered different treatment modalities which could have led to treatment differences. As far as we know, in literature there is no strong evidence on the best technique for vault suspension after vaginal hysterectomy and a recent published trial found similar outcomes after uterosacral ligament suspension and sacrospinous fixation for apical prolapse.[30] In the PP analysis these patients were excluded but this did not alter the conclusions.

Another limitation might be that residents were allowed to perform sacrospinous hysteropexy or vaginal hysterectomy under direct supervision of a gynaecologist because of their training position. Surgery by residents may have led to variation in treatment. More procedures were performed by residents in the vaginal hysterectomy group. No statistically significant difference was found in surgical failure rate in patients who underwent surgery by either gynaecologist or resident. Surgery performed by residents seem to improve the generalisability of the trial findings as their involvement in treatment of POP is common in the Dutch urogynaecological practice.

Comparison with other studies

The anatomical outcome after sacrospinous hysteropexy in our study is overall in line with previous studies [12,31] although the only previous randomised study showed opposite results: Dietz et al. have found a higher rate of anatomical recurrence of the apical compartment after sacrospinous hysteropexy (7 of 34 [21%] versus 1 in 31 [3%] after vaginal hysterectomy, p=0.03) after 12 months follow-up. Possible explanations for this difference might be differences in surgical protocol or skills, precise definition of the recurrence outcome, and sample size. The primary outcome in the study reported by Dietz et al. was recovery time instead of anatomical outcome. They considered a POP-Q stage two or higher of the uterus or vaginal vault as a recurrence. Recurrent prolapse was defined in our study as prolapse of the apical compartment POPQ stage two or higher in combination with bothersome symptoms or repeat surgery for recurrent apical prolapse. In our opinion, this composite outcome measure is more clinically relevant than outcome in terms of objective POP-Q scores alone. Barber et al. reported on different definitions of success after pelvic organ prolapse surgery in 2009.[18] Treatment success varied widely depending on the definition used, but all definitions that included the absence of vaginal bulge symptoms had the strongest relationship with the patients assessment of overall improvement and treatment success. They furthermore concluded that the hymen is an important cut-off point for symptom development. As new trials probably will use these updated outcome definitions, we also analyzed our data using the hymen as anatomical threshold and also used their composite outcome measure, making this trial in the future comparable to others.

Although the presence of posterior vaginal wall prolapse in both groups was similar prior to surgery, more posterior vaginal wall repairs were performed in the vaginal hysterectomy group. The surgeons were free to decide on concomitant surgery and in general this was decided intra-operative. One explanation might be that the surgeons felt that the more dorsal axis of the vagina after sacrospinous hysteropexy already protected against a recurrent posterior vaginal wall prolapse. Despite the higher number of posterior colporrhaphies significantly more anatomical recurrences of the posterior compartment were found after hysterectomy with uterosacral ligament suspension, which supports this vision. The risk for recurrent anterior vaginal wall prolapse after sacrospinous hysteropexy is often discussed. We found a trend towards more anatomical anterior vaginal wall prolapse although this finding was not significant (p=0.06). This is in line with previous studies: a retrospective study by Smilen et al. demonstrated that the occurrence of anterior vaginal wall prolapse was not altered by the performance of a sacrospinous hysteropexy and the randomized study

performed by Dietz and co-workers did not find more cystoceles after sacrospinous hysteropexy compared with a vaginal hysterectomy after one year.[12, 32]

Reoperation rates for (recurrent) pelvic organ prolapse did not differ. Two patients after uterine preservation ended up undergoing hysterectomy. Endometrial carcinoma was found in 1 patient during follow-up (1%). A previous retrospective analysis of pathology findings after prolapse surgery with hysterectomy showed premalignant or malignant abnormalities in 17 of 644 patients (2.6%).[33] In that study, 2 patients (0.3%) had endometrial cancer diagnosed. Because of the low incidence and the early diagnosis of endometrial cancer due to blood loss we believe that future risk of malignancy should not be regarded as a valid reason to remove the uterus.

Clinical implications and future research

Uterus preservation has gained popularity during the last years among gynaecologists and patients.[4, 34–36] A recent trial among 213 women from multiple study sites throughout the United States showed that 36% of the women preferred uterus preservation, 20% of the women preferred hysterectomy and 44% had no preference, assuming equal outcomes after both procedures.[35] Another preference study among 100 women showed that 60% would decline hysterectomy in case an equally efficacious alternative was available.[36] This trial provides evidence that sacrospinous hysteropexy is such an alternative and therefore this study has implications for clinical practice. Women who prefer uterus preservation or do not have an obvious preference can be reassured that sacrospinous hysteropexy was found to be equally effective after short-term follow-up. However longer follow-up is necessary and also randomized controlled trials comparing other uterus preserving procedures are needed.

Conclusions

Based on the analysis after 12 months follow-up, we conclude that sacrospinous hysteropexy is non-inferior to vaginal hysterectomy with uterosacral ligament suspension regarding recurrent prolapse of the apical compartment with bothersome complaints or repeat surgery for recurrent apical prolapse. There were no statistically significant differences regarding overall anatomical outcome, functional outcome, hospital stay,

complications, post-operative recovery, and sexual functioning with the benefit of a shorter duration of surgery.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Uterine prolapse is a very common health problem with increasing incidence due to ageing and increased obesity rates
- Vaginal hysterectomy is the standard treatment for uterine prolapse but uterus preservation is gaining popularity. No large randomised trials are available to compare both treatment options.

WHAT THIS STUDY ADDS

- Sacrospinous hysteropexy was non-inferior to vaginal hysterectomy with uterosacral ligament suspension regarding recurrent prolapse of the apical compatment with bothersome symptoms or repeat surgery and no differences were found in overall anatomical outcome, quality of life, subjective outcome, hospital stay, recovery, complications and sexual functioning after 12 months follow-up
- Sacrospinous hysteropexy showed evidence of shorter duration of surgery

Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Detollenaere, den Boon, Vierhout, Van Eijnhoven
Acquisition of data: Detollenaere, den Boon, Stekelenburg, van Eijndhoven
Analysis and interpretation of data: Detollenaere, den Boon, Stekelenburg, IntHout, Vierhout, Kluivers, van Eijndhoven
Drafting of the manuscript: Detollenaere, den Boon, Stekelenburg, IntHout, Vierhout, Kluivers, van Eijndhoven
Critical revision of the manuscript for important intellectual content: Detollenaere, den Boon, Stekelenburg, IntHout, Vierhout, Kluivers, van Eijndhoven
Statistical analysis: Detollenaere, IntHout, Kluivers.
Obtained funding: Detollenaere, van Eijndhoven
Administrative, technical, or material support: Detollenaere, den Boon, van Eijndhoven
Study supervision: Detollenaere, van Eijndhoven

Funding/Support: The SAVE U trial received an unrestricted grant from the Isala research foundation.

Role of the Sponsors: The funding source did not play any role in the design and conduct of the study; in the collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Detollenaere - Nothing to disclose; den Boon - Astellas: Scientific Medical Advisor, writing an e-learning on incontinence for general practioners receiving consulting fee; Stekelenburg - Nothing to disclose; IntHout - Nothing to disclose; Kluivers KB - Nothing to disclose; Vierhout ME- Astellas: Advisory Committee Member receiving consulting fee; Van Eijndhoven - Johnson & Johnson / AMS / BARD: trainer receiving honoraria

Transparency: The corresponding author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; No important aspects of the study have been omitted and any discrepancies from the study as planned have been explained.

Data sharing: No additional data available.

Additional Contributions: We are thankful to the staff at participating centres for their assistance with study enrolment; We greatly appreciate the involvement of N. van Rijn for assistance with data collection and administrative support;

References

1 Slieker-ten Hove MC, Pool-Goudzwaard AL, Eijkemans MJ, Steegers-Theunissen RP, Burger CW, Vierhout ME. The prevalence of pelvic organ prolapse symptoms and signs and their relation with bladder and bowel disorders in a general female population. *Int Urogynecol J Pelvic Floor Dysfunct* 2009;20:1037–45.

2 Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. *Obstet Gynecol* 1997;89:501–6.

3 De Boer TA, Slieker-ten Hove MC, Burger CW, Kluivers KB, Vierhout ME. The prevalence and factors associated with previous surgery for pelvic organ prolapse and or urinary incontinence in a cross sectional study in the Netherlands. *Eur J Obstet Gynecol Reprod Biol* 2011;158:343–9.

4 Detollenaere RJ, den Boon J, Kluivers KB, Vierhout ME, van Eijndhoven HW. Surgical management of pelvic organ prolapse and uterine descent in the Netherlands. *Int Urogynecol J* 2013;24:781–8.

5 Jha S, Moran P. The UK national prolapse survey: 5 years on. *Int Urogynecol J* 2011;22:517–28.

6 Vanspauwen R, Seman E, Dwyer P. Survey of current management of prolapse in Australia and New Zealand. *Aust N Z J Obstet Gynaecol* 2010;50:262–7.

7 Altman D, Granath F, Cnattingius S, Falconer C. Hysterectomy and risk of stress-urinary-incontinence surgery: nationwide cohort study. *Lancet* 2007;370:1494–9.

8 Dällenbach P, Kaelin-Gambirasio I, Jacob S, Dubuisson JB, Boulvain M. Incidence rate and risk factors for vaginal vault prolapse repair after hysterectomy. *Int Urogynecol J Pelvic Floor Dysfunct* 2008;19:1623–9.

9 Kantartzis KL, Turner LC, Shepherd JP, Wang L, Winger DG, Lowder JL. Apical support at the time of hysterectomy for uterovaginal prolapse. *Int Urogynecol J* 2014; doi 10.1007/s00192-014-2474-y.

10 Bulletins-Gynecology ACoP (2007) ACOG practice bulletin No.85: pelvic organ prolapse. Obstet Gynecol 110:717-729. doi:10.1097/01. AOG.0000263925.97887.72.

11 Maher CF, Cary MP, Slack MC, Murray CJ, Milligan M, Schluter P. Uterine preservation or hysterectomy at sacrospinous colpopexy for uterovaginal prolapse? *Int Urogynecol J Pelvic Floor Dysfunct* 2001;12:381–4.

12 Brummen HJ, van de Pol G, Aalders CIM, Heintz APM, van der Vaart. Sacrospinous hysteropexy compared to vaginal hysterectomy as primary surgical treatment for a descensus uteri: effect on urinary symptoms. *Int Urogynecol J Pelvic Floor Dysfunct* 2003;14:350–5.

13 Hefni MA, El-Toukhy TA, Bhaumik J, Katsimanis E. Sacrospinous cervicocolpopexy with uterine conservation for uterovaginal prolapse in elderly women: an evolving concept. *Am J Obstet Gynecol* 2003;188:645–50.

14 Dietz V, van der Vaart CH, van der Graaf Y, Heintz P, Schraffordt Koops SE. One-year follow-up after sacrospinous hysteropexy and vaginal hysterectomy for uterine descent: a randomized study. *Int Urogynecol J Pelvic Floor Dysfunct* 2010;2:209–16.

15 Jeng CJ, Yang YC, Tzeng CR, Shen J, Wang LR. Sexual functioning after vaginal hysterectomy or transvaginal sacrospinous hysteropexy for uterine prolapse: a comparison. *J Reprod Med* 2005;50:669–74.

16 Maher C, Feiner B, Baessler K, Schmid C. Surgical management of pelvic organ prolapse in women. *Cochrane Database Syst Rev* 2013; 30;4:CD004014.

17 Detollenaere RJ, den Boon J, Stekelenburg J et al. Treatment of uterine prolapse stage 2 or higher: a randomized multicenter trial comparing sacrospinous fixation with vaginal hysterectomy (SAVE U trial). *BMC Womens Health* 2011;15;11:4.

18 Barber MD, Brubaker L, Nygaard I et al. Defining success after surgery for pelvic organ prolapse. *Obstet Gynecol* 2009;114:600–9.

19 Cruikshank SH. Preventing posthysterectomy vaginal vault prolapse and enterocele during vaginal hysterectomy. *Am J Obstet Gynecol* 1987:156:1433-40.

20 Bump RC, Mattiasson A, Bo K et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol 1996;175:10–7.

21 Ware JE, Kosinski M, and Keller SD. SF-36 physical and mental component summary measures-a users' manual. 1994. Boston: New England Medical Center, The Health Institute.

22 van der Vaart CH, de Leeuw JR, Roovers JP, Heintz AP. Measuring health-related quality of life in women with urogenital dysfunction: the urogenital distress inventory and incontinence impact questionnaire revisited. *Neurourol Urodyn* 2003;22:97–104.

23 Roovers JP, van der Bom JG, van der Vaart CH, Heintz AP. Prediction of findings at defecography in patients with genital prolapse. *BJOG* 2005; 112:1547–53.

24 Lamers LM, Stalmeier PF, McDonnell J, Krabbe PF, van Busschbach JJ. Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff. *Ned Tijdschr Geneeskd* 2005;149:1574–8.

25 Schweitzer KJ, de Jong M, Milani AL: Prolaps en seks: hoe meten we de relatie? *Ned Tijdschr Obst Gyn* 2008;121:79-82.

26 Kluivers KB, Hendriks JC, Mol BW et al. Clinimetric properties of 3 instruments measuring postoperative recovery in a gynecologic surgical population. *Surgery* 2008;144:12–21.

27 Dietz V, Schraffordt Koops S, van der Graaf Y, Heintz P, van der Vaart C. Sacrospinous hysteropexy and vaginal hysterectomy for uterine descent: a randomized study. *Int Urogynecol J* 2008;19:S1-166.

28 Agresti A, Coull B. Approximate is better than 'exact' for interval estimation of binomial proportions. *The American Statistician* 1998;52:119–26.

29 McCall ML. Posterior culdoplasty; surgical correction. *Obstet Gynecol* 1957:10:595.

30 Barber MD, Brubaker L, Burgio KL et al. Comparison of 2 transvaginal surgical approaches and perioperative behavioral therapy for apical vaginal prolapse: the OPTIMAL randomized trial. *JAMA* 2014;311:1023-34.

31 Gutman R, Maher C. Uterine-preserving POP surgery. *Int Urogynecol J* 2013;24:1803–1813.

32 Smilen SW, Saine J, Wallach SJ, Porges RF. The risk of cystocele after sacrospinous ligament fixation. *Am J Obstet Gynecol* 1998;179:1465-1471.

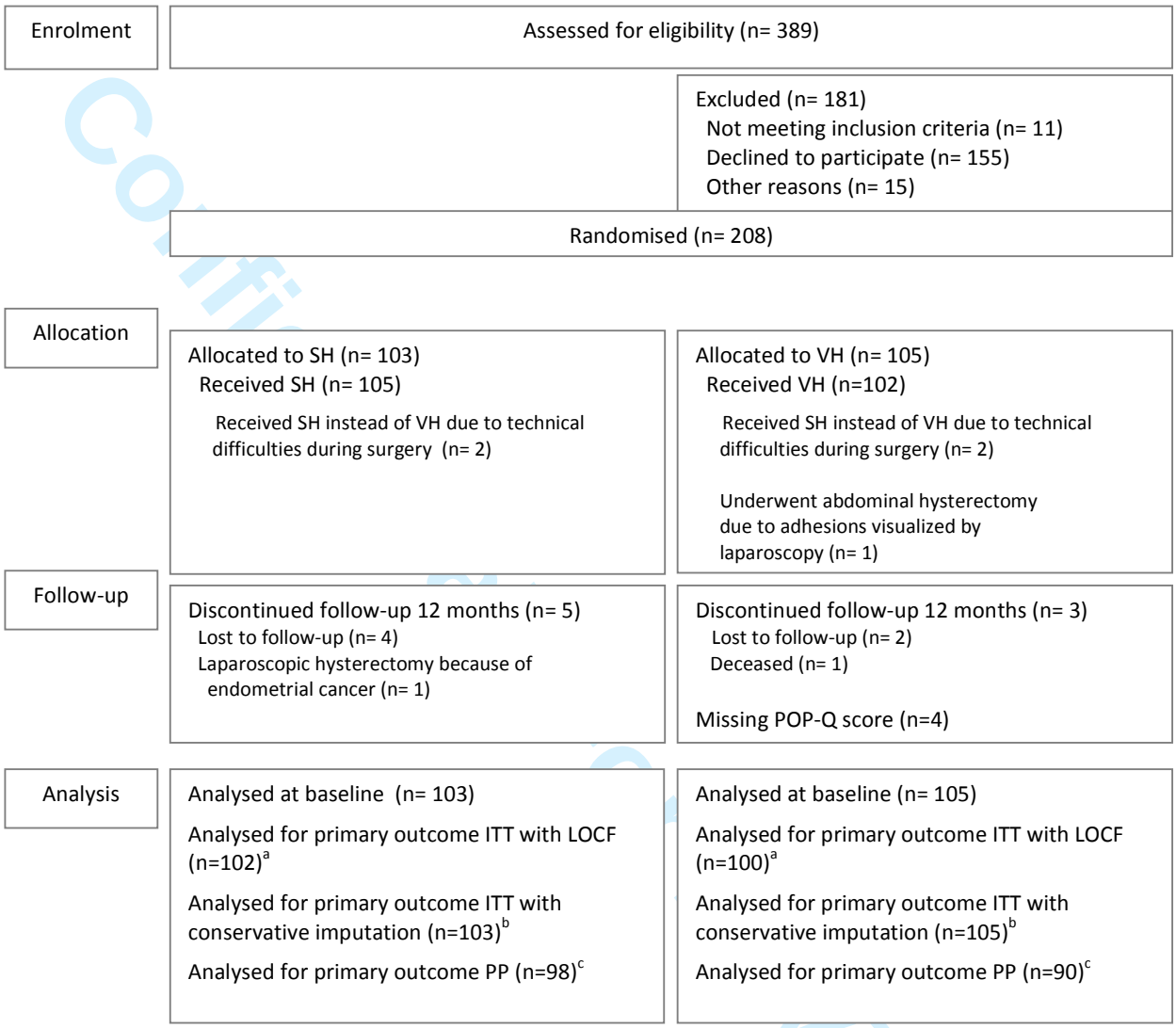
33 Renganathan A, Edwards R, Duckett JR. Uterus conserving prolapse surgery—what is the chance of missing a malignancy? *Int Urogynecol J* 2010;21:819–821.

34 Wu MP, Long CY, Huang KH, Chu CC, Liang CC, Tang CH. Changing trends of surgical approaches for uterine prolapse: an 11-year population-based nationwide descriptive study. *Int Urogynecol J* 2012;23:865–72.

35 Korbly NB, Kassis NC, Good MM, et al. Patient preferences for uterine preservation and hysterectomy in women with pelvic organ prolapse. *Am J Obstet Gynecol* 2013;209:470.e1–6.

36 Frick AC, Barber MD, Paraiso MF, Ridgeway B, Jelovsek JE, Walters MD. Attitudes toward hysterectomy in women undergoing evaluation for uterovaginal prolapse. *Female Pelvic Med Reconstr Surg* 2013;19:103–9.

***Figure 1*. Study flowdiagram SAVE U trial**



ITT= intention to treat; LOCF= last observation carried forward; PP= per protocol; SH=sacrospinous hysteropexy; VH=vaginal hysterectomy;

[a] in the SH group 6 month follow-up data were not available for LOCF in 1 patient; in the VH group LOCF data were not available in 6 patients; 1 patient after VH had a recurrent apical prolapse confirmed by the surgeon but POP-Q was missing, this patient was included in the ITT-LOCF analysis.

[b] missed data imputed as failure

[c] PP analysis: 2 patients allocated to VH received SH and were analysed in the SH group; Excluded PP-analysis: lost for follow-up at 12 months (n=8), POP-Q score was missing or incomplete (n=5) and major protocol deviations (n=9); Two patients met two criteria to be excluded from PP analysis.

***Table 1*. Baseline characteristics**

	SH (n=103)	VH (n=105)
Age in years, median (range)	62.7 (45 to 85)	61.9 (33 to 82)
Highest educational level		
Primary / secondary school	14 (14%)	7 (7%)
High school	78 (77%)	82 (80%)
Bachelor, master or academic degree	9 (9%)	13 (13%)
Comorbidity		
Cardiovascular disease	39 (38%)	32 (31%)
Diabetes mellitus	5 (5%)	5 (5%)
Respiratory disease	3 (3%)	7 (7%)
Current smoker	13 (14%)	9 (10%)
Vaginal deliveries, median (range)	2 (0 to 7)	3 (0 to 7)
Caesarean deliveries, median (range)	0 (0 to 1)	0 (0 to 2)
Body Mass Index (kg/m^2), mean (SD)	26.0 (3.3)	25.9 (3.5)

SH=sacrospinous hysteropexy; VH=vaginal hysterectomy; Data are number of patients (percentage) unless otherwise specified. Percentages were calculated using non-missing data. All patients were analyzed as allocated.

***Table 2*. Pelvic measurements and characteristics at baseline**

	SH (n=103)	VH (n=105)
POPQ stage uterine prolapse (POP-Q point C) [a]		
2	67 (65.0%)	66 (62.9%)
3	28 (28.2%)	29 (27.6%)
4	8 (7.8%)	10 (9.5%)
Anterior prolapse POP-Q stage 2 to 4 (Ba ≥ -1)	94 (94.0%)	95 (92.2%)
Posterior prolapse POP-Q stage 2 to 4 (Bp ≥ -1)	29 (29.0%)	33 (32.0%)
Prolapse beyond the hymen		
Apical (POP-Q C > 0)	48 (48.0%)	43 (41.7%)
Anterior (POP-Q Aa or Ba > 0)	71 (71.0%)	72 (70.0%)
Posterior (POP-Q Ap or Bp > 0)	11 (11.0%)	11 (10.7%)
Overall POP-Q stage prolapse [a]		
2	25/100 (25.0%)	36/103 (35.0%)
3	70/100 (70.0%)	62/103 (60.2%)
4	5/100 (5.0%)	5/103 (4.9%)
Vaginal bulge symptoms		
Any	94/101 (93.1%)	98/103 (95.1%)
Bothersome	93/100 (93.0%)	96/101 (95.0%)
POP-Q value, median (range), cm [b]		
Aa	0·0 (-3.0 to 3.0)	0·0 (-3.0 to 3·0)
Ba	2·0 (-3.0 to 6.0)	2·0 (-3.0 to 8.0)
C	0·0 (-1.0 to 10.0)	0·0 (-1.0 to 10.0)
Ap	-2·0 (-3.0 to 3.0)	-2·0 (-3.0 to 3.0)
Bp	-2·0 (-3.0 to 6.0)	-2·0 (-3.0 to 8.0)
GH	4·0 (2.0 to 7.0)	4·0 (2.0 to 7.0)
PB	3·0 (1.0 to 5.0)	3·0 (2.0 to 6.0)
TVL	9·0 (7.0 to 12.0)	9·0 (6.0 to 10.0)

GH=genital hiatus; PB=perineal body; POP-Q=Pelvic Organ Prolapse Quantification; SH=sacrospinous hysteropexy; TVL= total vaginal length; VH=vaginal hysterectomy;
Data are number of patients (percentage) or mean (standard deviation) unless otherwise specified. Percentages were calculated using non-missing data. All patients were analyzed as allocated.
[a] POP-Q stage 2: uterus/vagina or leading edge of the prolapse is prolapsed between 1 cm above the hymen (-1) and 1 cm below the hymen (+1); stage 3: the uterus/vagina or leadin edge of the prolapse is prolapsed > +1 cm beyond the hymen but not totally everted (> TVL minus 2cm); stage 4: the uterus/ vagina is totally everted. 5 POP-Q scores were missing at baseline.
[b] POP-Q values provided to describe pelvic support. Point Aa, Ba, C, Ap and Bp are measured with respect to the hymen. Points above the hymen are negative numbers, points below the hymen are positive numbers. GH, PB and TVL are measured as positive values. Aa: anterior vaginal wall 3cm proximal to the hymen; Ba: most distal position of the anterior vaginal wall,
[c]: most distal edge of cervix or vaginal vault, Ap: posterior vaginall wall 3 cm proximal to the hymen, Bp: most distal position of the posterior vaginal wall.

***Table 3*. Intra- and postoperative details**

	SH (n=103)	VH (n=105)	P value
Intraoperative			
Operating time (min)	59 (13)	72 (21)	**<0.01**
Estimated blood loss (mL)	202 (74)	209 (112)	0.63
Complications			
Related to use antibiotics	1 (1%)	0 (0%)	0.31
Related to surgery	0 (0%)	1 (1%)[a]	0.32
Concomitant surgery			
Anti-incontinence	4 (4%)	4 (4%)	>·99
Anterior colporrhapy	100 (97%)	104 (99%)	0.30
Posterior colporrhapy	30 (29%)	52 (50%)	**<0.01**
Anterior and posterior colporrhapy	30 (29%)	52 (50%)	**<0.01**
Surgeon			
Gynaecologist	98 (97%)	85 (82%)	**<0.01**
Resident	3 (3%)	19 (18%)	**<0.01**
Postoperative			
Length of hospitalisation (days)	3 (1)	3 (1)	0.45
Complications during hospital stay			
Death	0 (0%)	1 (1%)	0.32
Re-operation because of bleeding	0 (0%)	1 (1%)	0.32
Cerebrovasculair accident	1 (1%)	0 (0%)	0.31
Buttock pain	9 (9%)	0 (0%)	**<0.01**
Urinary retention	15 (15%)	12 (10%)	0.50
Infection needing antibiotics	3 (3%)	0 (0%)	0.08
Other			
Endometrial carcinoma	1 (1%)	0 (0%)	0.31

SH=sacrospinous hysteropexy; VH=vaginal hysterectomy. Data are number of patients (percentage) or mean (standard deviation) unless otherwise specified. Percentages were calculated using non-missing data. All patients were analyzed as allocated.

[a] bowel injury during abdominal hysterectomy

Table 4. **Pelvic organ prolapse outcomes and pelvic measurements at 12 months follow-up**

	SH	VH	Difference (95%CI)	P
Recurrent apical prolapse stage ≥2 with bothersome symptoms or repeat surgery for apical prolapse[a]				
ITT analysis with LOCF	0/102 (0.0%)	4/100 (4.0%)	3.9% (-0.7 to 8.6)	0.06
ITT analysis with conservative imputation	6/103 (5.8%)	10/105 (9.5%)	3.6% (-3.9 to 11.2)	0.44
PP analysis	0/98 (0.0%)	3/90 (3.3%)	3.3% (-1.3 to 8.0)	0.11
Overall surgical failure: prolapse POP-Q stage ≥2 prolapse (any compartment) or repeat surgery or pessary use				
ITT analysis with LOCF	52/102 (51.0%)	49/100 (49.0%)	-1.9% (-15.7 to 11.8)	0.89
ITT analysis with conservative imputation	55/103 (53.4%)	54/105 (51.4%)	-1.9% (-15.5 to 11.6)	0.78
PP analysis	51/98 (52.0%)	44/90 (48.9%)	-3.1% (-17.4 to 11.2)	0.77
Composite outcome success: no prolapse beyond the hymen and absence of bothersome bulge symptoms and no repeat surgery or pessary use				
ITT analysis with LOCF	91/102 (89.2%)	83/100 (83.0%)	-6.1% (-15.8 to 3.6)	0.23
ITT analysis with conservative imputation	87/103 (84.5%)	82/105 (78.1%)	-6.2% (-16.9 to 4.5)	0.29
PP analysis	87/98 (88.8%)	75/90 (83.3%)	-5.3% (-15.5 to 4.7)	0.30
Overall anatomical failure: prolapse POP-Q stage ≥2 prolapse (any compartment)[b]	51/101 (50.5%)	44/100 (44.0%)	-6.4% (-20.1 to 7.4)	0.40
Anatomical failure apical compartment	2/102 (2.0%)	7/100 (7.0%)	5.0% (-1.2 to 11.1)	0.10
Anatomical failure anterior compartment	47/101 (46.5%)	33/99 (33.3%)	-12.9% (-26.4 to 0.5)	0.06
Anatomical failure posterior compartment	4/101 (4.0%)	14/99 (14.1%)	10.0% (1.8 to 18.2)	**0.01**
Prolapse beyond the hymen[b]				
Apical (POP-Q C > 0)	0/102 (0.0%)	4/100 (4.0%)	3.9% (-0.7 to 8.6)	0.06
Anterior (POP-Q Ba > 0)	8/101 (7.9%)	6/99 (6.1%)	-1.8% (-9.2 to 5,6)	0.78
Posterior (POP-Q Bp > 0)	0/101 (0.0%)	2/99 (2.0%)	2,0 (-1,9 to 5,9)	0.24
Surgery[b]				
Repeat surgery for recurrent prolapse	1/102 (1.0%)	4/102 (3.9%)	2.9% (-2,0 to 7.8)	0.37
Repeat surgery apical compartment	0/102 (0.0%)	2/102 (2.0%)	1.9% (-1.8 to 5.7)	0.50
Repeat surgery anterior compartment	1/102 (1.0%)	4/102 (3.9%)	2.9% (-2.0 to 7.8)	0.37
Repeat surgery posterior compartment	0/102 (0.0%)	1/102 (1.0%)	1.0% (-2.3 to 4.2)	>.99
Primary surgery different site[c]	0/102 (0.0%)	3/102 (2.9%)	2.9% (-1.3 to 7.1)	0.25
Surgery for non-prolapse conditions				
Anti-incontinence	1/102 (1.0%)	4/102 (3.9%)	2.9% (-2.0 to 7.8)	0.37
Hysterectomy	2/100 (2.0%)	-		
POP-Q value, median (range), cm				
Aa	-2.0 (-3.0 to 2.0)	-2.0 (-3.0 to 3.0)		
Ba	-2.0 (-3.0 to 2.0)	-2.0 (-3.0 to 4.0)		
C	-7.0 (-10.0 to 0.0)	-7.0 (-10.0 to 5.0)		
Ap	-3.0 (-3.0 to 0.0)	-3.0 (-3.0 to 0.0)		
Bp	-3.0 (-3.0 to 0.0)	-3.0 (-3.0 to 3.0)		
GH	3.0 (2.0 to 6.0)	3.0 (2.0 to 6.0)		
PB	3.0 (2.0 to 5.0)	3.0 (2.0 to 5.0)		
TVL	9.0 (6.0 to 11.0)	8.0 (6.0 to 12.0)		

ITT=intention to treat; LOCF= last observation carried forward; POP-Q=Pelvic Organ Prolapse Quantification; PP=per protocol; SH=sacrospinous hysteropexy; VH= vaginal hysterectomy; Data are number of patients (percentage) or mean (standard deviation) unless otherwise specified. Percentages were calculated using non-missing data. P values were calculated using Fisher's exact test; 95% confidence intervals (CI) were calculated using the method of Agresti and Coull.

[a] Primary outcome of this study.

[b] LOCF

[c] reoperation for POP in non-operated compartment

Table 5. **Functional outcome and quality of life after SH and VH at 12 months follow-up.**

	Before surgery		12 months after surgery		
	SH (n=101)	VH (n=104)	SH (n=97)	VH (n=99)	P value*
UDI domain scores [a]					
Overactive bladder	0 (0, 44)	22 (0, 33)	0 (0, 11)	0 (0, 11)	0.34
Urinary incontinence	17 (0, 33)	17 (0, 33)	0 (0, 17)	0 (0, 17)	0.11
Obstructive micturition	8 (0, 33)	17 (0, 33)	0 (0, 0)	0 (0, 0)	0.71
Genital prolapse	50 (33, 67)	67 (33, 67)	0 (0, 0)	0 (0, 0)	0.86
Pain	17 (0, 33)	17 (0, 33)	0 (0, 0)	0 (0, 0)	0.86
DDI domain scores [a]					
Obstipation	0 (0, 17)	0 (0, 17)	0 (0, 0)	0 (0, 0)	0.65
Obstructive defecation	0 (0, 17)	0 (0, 10)	0 (0, 8)	0 (0, 8)	0.85
Pain	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.42
Incontinence	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.38
Flatus	33 (0, 33)	33 (0, 33)	0 (0, 33)	33 (0, 33)	0.20
IIQ domain scores [b]					
Mobility	11 (0, 33)	11 (0, 22)	0 (0, 11)	0 (0, 11)	0.50
Physical	0 (0, 33)	0 (0, 33)	0 (0, 0)	0 (0, 0)	0.81
Social	11 (0, 22)	0 (0, 11)	0 (0, 0)	0 (0, 0)	0.99
Embarrasment	0 (0, 17)	0 (0, 17)	0 (0, 0)	0 (0, 0)	0.12
Emotion	0 (0, 33)	0 (0, 22)	0 (0, 0)	0 (0, 0)	0.56
SF-36 domain scores [c]					
Physical functioning	80 (55, 90)	80 (65, 90)	90 (75, 100)	85 (70, 95)	0.27
Social functioning	94 (75, 100)	88 (75, 100)	100 (88, 100)	100 (75, 100)	0.20
Role limitations physical	75 (6, 100)	100 (50, 100)	100 (100, 100)	100 (75, 100)	0.89
Role limitations emotional	100 (75, 100)	100 (100, 100)	100 (100, 100)	100 (100, 100)	0.78
Mental health	84 (72, 92)	84 (72, 88)	84 (76, 92)	84 (72, 92)	0.57
Vitality	70 (50, 80)	70 (55, 80)	75 (55, 80)	75 (65, 80)	0.39
Bodily pain	78 (59, 100)	80 (67, 100)	100 (67, 100)	100 (78, 100)	0.92
General health perception	75 (55, 85)	75 (61, 85)	75 (60, 90)	75 (60, 90)	0.72
Health change	50 (25, 50)	50 (50, 50)	75 (50, 100)	75 (50, 100)	0.52

DDI: defecatory distress inventory; IIQ: incontinence impact questionnaire; SF-36: short-form 36; UDI: urogenital distress inventory; Data are presented as median (interquartile range). All patients were analyzed as allocated.

[a] UDI and DDI: 0=no symptoms or not bothersome and 100=most bothersome symptoms.

[b] IIQ: 0=best quality of life and 100=worst quality of life.

[c] SF-36: 0= worst quality of life and 100= best quality of life.

* P value: Mann-Whitney U test of domain scores of SH vs VH at 12 months follow-up.

Table 6. **Adjusted OR for the risk of failure (overall POP-Q stage 2 or greater or pessary use or repeat surgery)**

Risk factors for failure[a]	No failure		Failure		OR (95% CI)	P value
	N=		N=			
Age (years)	101	62.3 (8.8)	101	62.1 (9.9)	1.00 (0.96 to 1.02)	0.66
Number of children	100	2.8 (1.2)	101	2.9 (1.2)	1.04 (0.83 to 1.31)	0.74
Body Mass Index (kg/m2)	97	25.3 (3.3)	97	26.4 (3.0)	1.12 (1.02 to 1.24)	**<0.01**
Operating time (min)	97	67.2 (20.6)	97	63.9 (17.5)	0.99 (0.97 to 1.00)	0.10
Blood loss (per 100 mL)	98	2.0 (1.0)	101	2.1 (0.9)	1.11 (0.82 to 1.52)	0.50
Length of hospital stay (days)	99	2.3 (1.3)	98	2.3 (0.7)	0.94 (0.70 to 1.26)	0.67
Smoking					1.23 (0.47 to 3.21)	0.68
Yes	9	40.9%	13	59.1%		
No	77	50.7%	75	49.3%		
Type of surgeon					1.14 (0.42 to 3.14)	0.79
Gynaecologist	89	49.4%	91	50.6%		
Resident	10	52.6%	9	47.4%		
History of vaginal operative delivery					0.82 (0.52 to 2.87)	0.65
Yes	14	56.0%	11	44.0%		
No	86	49.1%	89	50.9%		

Data are presented as mean (SD) or (%) as appropriate. OR= odds ratio; POP-Q= Pelvic Organ Prolapse Quantification.
[a] adjusted for randomisation outcome, centre and pre-operative stage of prolapse.

JAMA Reviewer Comments
Reviewer #1 (Remarks to the Author):

This manuscript describes a Dutch non-inferiority trial comparing treatments for uterine prolapse. The non-inferiority margin was not crossed and the authors conclude that SH is non-inferior to VH at 12 months.

While the authors did not include a statistical analysis plan or protocol, the study as described in the manuscript is clear and appropriate. The few statistically significant between group differences may attenuate after adjusting for multiple comparisons. I have only a few minor comments for the authors.

No details about patient recruitment were provided, nor were any details about the 4 centers. However, in the Comments the authors reveal that there one group was disproportionally treated by residents. This should be revealed in the Results, including the details of the analyses alluded to in the Comment. Was skill level, such as number of SH/VH procedures assessed

- We clarified this topic now more extensively in the Methods/Results section. Also data were added to table 3. Exploratory logistic regression did not reveal that the type of surgeon (gynaecologist or resident) was a risk factor for recurrent prolapse (table 2)

Line 118: How was "conflict of interest" determined?
An independent physician carried out follow-up after 12 months, without any conflict of interest related to the assessment undertaken.

- This means that the physician was not the person who did the surgery or the treating gynaecologist. More information is added in the Methods section to clarify the point above.

The study appears to be adequately powered for a non-inferiority margin of 7%.

The study was adjusted for site, but this is not the same as adjusting for clustering, although this should not significantly affect the results.

- The randomization was stratified for centre and stage of prolapse. However the sample size was not large enough to stratify for surgeon.

The primary outcome was surgical failure at 12 months, but patients were assessed at 3 time points and the analyses do not account for repeated measures the way a mixed model would.

- Unfortunately a generalized lineair mixed model did not reach convergence, due to the low number of recurrences during follow-up (zero in the sacrospinous hysteropexy group).

A modified ITT approach was used excluding those who were randomized, but did not receive treatment or dropped out. Missing data were handled by last observation carried forward, which is not ideal as it is a biased method. This affects 2 cases.

To analyze the primary outcome missing data were handled using three different methods
1. ITT analysis with last observation carried forward of 6-month data were available

2. ITT analysis with conservative imputation (worst case scenario)
3. Per protocol analysis

An exploratory logistic regression model was constructed to assess risk factors for failure, but this model was not clearly specified, including varying Ns. It appears as though the authors created a series of models instead of a single multivariate model.

- The models are described in the Methods section. Indeed we have performed analyses for each separate risk factor (adjusted for centre, preoperative POP-Q stage and randomization outcome) since the number of recurrences fell short to use a single multivariate model.

Figure 1 should include the number of patients assessed prior to enrollment.

- The number of patients prior to enrollment is included in Figure 1.

Table 4: It is not clear why the SH group varies in patients.

- In one patient there was an incomplete POPQ score, with data available on apical compartment but missing data on the anterior and posterior vaginal wall.

Line 224: IS this an increase in the odds per 1 unit increase in BMI?

- Yes that is correct

Reviewer #2 (Remarks to the Author):

The authors are to be commended on a major effort to improve surgical decision-making for prolapse surgery. This is an important study and these review comments are intended to strengthen the reporting of this trial.

Abstract (line 47). The authors seem to make the assumption that a vaginal suspension is part of the most common vaginal hysterectomy technique. Regretfully, this is likely untrue. This statement currently is untrue, as simple vaginal hysterectomy is not considered a treatment for reconstruction of the apical support loss. More precise is that vaginal hysterectomy is commonly used as a prelude to reconstruction. (This is true, as shown within the manuscript lines 136-7 where the authors indicate that a separate vaginal vault suspension was performed in the vaginal hysterectomy group.)

- We agree with the reviewer's comment. Since the term VH does not quite cover the performed procedure in the study we have decided to rename the procedure into vaginal hysterectomy with uterosacral ligament suspension.

Abstact (line 48). More precise language would be "assumed to be less morbid" - vaginal surgery with or without hysterectomy is considered similarly "invasive", but the concept of avoiding the potential morbidity of concomitant hysterectomy is an important point.

- The sentence where this comment refers to is removed from the abstract. The issue, which was addressed here, is still included and described on page 3.

Objective: Understates actual aim of study. Simple vaginal hysterectomy is not the comparator. The true comparator is sacrospinous hysteropexy vs. USLS OR McCalls (two different procedures) with concomitant vaginal hysterectomy.

- As commented to reviewer 1: Since the term VH does not quite cover the performed procedure in the study we have decided to rename the procedure into vaginal hysterectomy with uterosacral ligament suspension.

Interventions: Similarly understates the simple vaginal hystectomy arm - see comment above.

Outcomes: Need to state the outcome measure (site of POP) and timing.

- Outcome measure and timing have been described in the abstract and also in the Methods section of the manuscript (page 2 and 5).

Manuscript:

Methods - (minor point) the authors should state whether patients with cervical elongation were eligible for the study. Also, in the tables, not all patients were "bothered" - so clarification is needed about the eligibility criteria of bothersome prolapse.

- Women with cervical elongation were allowed to participate. We have added more information to the Methods section.

- Women with complaints were referred by their general practitioner in case bothersome. Physician interview was in the patient consultation with a gynaecologist or resident. Based on women's complaints, bother and POP-Q/gynaecological examination, women were scheduled for surgical treatment and received information on the study After patients had decided to be operated and consented for participation the questionnaire was provided. This questionnaire could thus differ and was not part in the decision on whether or not surgery was performed.

The role of concomitant anterior/posterior surgery is not stated. This is important because this is an open label trial and readers will need to know whether concomitant surgery was used more/less commonly in these groups. (see subsequent comments regarding reporting outcomes).

- Details on concomitant surgery are described in table 3

Line 146: Adjust language - instead of "consulted the hospital" - were assessed

- We adjusted language

Reference 12 is used to 1) justify the 3% "failure rate of vaginal hysterectomy AND 2) to indicate that there are insufficient prior trials comparing vaginal hysterectomy with uterine preserving techniques. There are several concerns with this - first, the enrollment started in 2009 - prior to the publication of this paper. SAVE-U planning and protocols approvals significantly pre-dated the 2010 publication. Also, this is like a low rate and is supported by

only one reference. Such support for a 3% "gold standard" failure rate is not terribly well supported.

- This study by Dietz and co-workers was published online 16 October 2009. These data were also presented at an International Conference (IUGA 2008 Taiwan).

- Since no other date from other (randomized) trials were available reporting on outcomes after vaginal hysterectomy with USLS for POP after 12 months follow-up we used this 3% golden standard failure rate as the best available evidence.

Line 174 - this suggests that a 6-month outcome was used when 12-month data was not available. This is likely unacceptable in the primary IIT analysis and required more rigorous statistical review and discussion.

- As commented to reviewer 1: It was not possible to perform a mixed model analysis for repeated measurements as in SH group no recurrences were found after one year (primary outcome).
  To handle missing data: We performed 1. an ITT analysis with last observation carried forward using data of 6 month follow-up visit; 2. An ITT with conservative imputation (patients with missing data/POP-Q at 12 months follow-up were considered as failures) and 3. Per protocol analysis.

There are several issues that require further review and clarification in this manuscript:
- although reoperation for prolapse didn't differ, the difference in reoperation (type and number) should be further discussed. Two patients who has uterine preservation ended up undergoing hysterectomy within the year (one for refractory buttock pain and one for cancer). And the authors should discuss why more patients needed subsequent anti-incontinence operations in the hysterectomy+repair group.

- Why was there such a difference in concomitant surgery (more posterior colporrhaphy in the hysterectomy+ repair group)? Was the plan for concomitant surgery pre-specified PRIOR to randomization or determined intraoperatively - and if determined intra-op, what criteria were used.

- Although the presence of posterior vaginal wall prolapse was comparable between the groups prior to surgery, more posterior colporrhaphies were performed in the vaginal hysterectomy group. The operating surgeons were free to decide on concomitant surgery and this was not a part of randomization. In general this was decided intra-operatively and obviously the surgeons felt that the more dorsal axis of the vagina after sacrospinous hysteropexy already protected against a recurrent posterior wall prolapse. Despite that more posterior colporrhaphies were performed, more anatomical recurrences of the posterior compartment were found after hysterectomy with uterosacral ligament suspension, which supports this vision. At this moment a study is performed (by members of our group) comparing MRI scans after sacrospinous hysteropexy and vaginal hysterectomy, which could possibly answer these questions. We explained this comment in the Discussion section.

- The risk of recurrent anterior vaginal wall prolapse after sacrospinous hysteropexy is often discussed. We found a trend towards more anatomical anterior vaginal wall prolapses but this finding was not statistically significant (p=0.06). This is in line with previous studies. A retrospective study by Smilen et al. (AJOG 1998; 179:1465-1471) demonstrated that the occurrence of anterior vaginal wall defects was not found to be altered by the performance of sacrospinous ligament fixation. A randomized study by Dietz et al. (Int Urogyn J 2010 21:209-216) did not find more cystoceles after a sacrospinous hysteropexy compared with a vaginal

hysterectomy after one year.

- Reoperation rate for pelvic organ prolapse did not differ between the groups. Two patients after uterine preservation underwent hysterectomy. More details on uterus preservation and risk of malignancy are provided in the discussion section.

- More patients after hysterectomy needed subsequent anti-continence procedures but this difference was not statistically significant. It has been suggested that hysterectomy may contribute to more post-operative urinary symptoms. However in both groups the UDI domain scores improved and at 12 months follow-up there was no significant difference in domain scores. This is in line with previous research (Roovers, Dietz).

- Could the authors clarify whether the unfortunate dead of the patient who aspirated 8 days following surgery occurred in the hospital - and if so, why was she still in the hospital eight days after surgery? If this is a national norm, then some comment needs to be included in the discussion as this clearly affects the generalizability of these data.

- The patient was still in the hospital because of a persistent paralytic ileus. She experienced this problem also after a previous orthopedic operation (reason unknown). Unfortunately she aspirated gastric content during hospitalisation, developed aspiration pneumonia and died because of multi-organ failure. This extended stay in the hospital is obviously not a national norm. The mean length of hospital stay was 3 days, which can be found in table 3.

- This information is added to the text

Reviewer #3 (Remarks to the Author):

The authors present a multi-center randomized trial of vaginal sacrospinous hysteropexy vs. vaginal hysterectomy for uterine prolapse. The subject is an important one as the role of uterine preservation in uterine prolapse surgery is poorly studied and may offer real safety benefits presuming efficacy is similar.

A few important weaknesses:
1) the length of follow-up is too short (1 year) to really conclude that this approach is non-inferior in terms of treatment success. Additionally, this follow-up is too short to really evaluate the long term risks of uterine preservation during prolapse surgery like development of future uterine pathology; need for future hysterectomy for other gynecologic disease, etc. The findings would be much stronger with longer follow-up.

- We agree this is an intermediate period of follow-up. This is however the first report on this comparison, and until now no large randomized trial have been performed comparing uterus preservation and hysterectomy. Therefore we feel that the presented information is relevant. Many women are treated with hysterectomy although performing hysterectomy is not an evidence-based practice.
  Not only the long term surgical failure is important but also secondary outcomes such as complication rate, postoperative recovery etc. Furthermore data from registry studies suggest that the highest risk for prolapse surgery after hysterectomy is in the first year(s) after surgery (Lykke Int Urogyn 2014; Altman AJOG 2008) Therefore we feel that these one year outcome are relevant to be published.

2) The intervention in the hysteropexy arm is well described but the intervention in the hysterectomy arm is poorly described. As the authors know well, hysterectomy alone is not a treatment for uterine

prolapse; it must be accompanied by an apical suspension of the vagina. The methods indicate that those who received a hysterectomy also received "either a uterosacral ligament suspension or McCall's procedure" but no description of either procedure is described and no information is provided about the proportion who received each of these suspensions in this group. Where there any who got no suspension or a suspension that otherwise would not be considered comparable to the sacrospinous hysteropexy? There is some concern that the hysterectomy group was not an adequate active control for this study.

- A detailed description of the study interventions was used to warrant a uniform technique amongst surgeons (see BMC study protocol). The protocol stated that the ligatures of the uterosacral ligaments was sutured to the vaginal cuff to aid in long-term vaginal support. In addition we have now described both procedures in more detail. In all patients except for 6 ligament plication was the standard treatment. In the other 6 patients the protocol was violated and a Mc Call culdoplasty was performed. This is also described in the Results and Discussion section.

3) Unlike superiority studies, generally, intent to treat analyses are not recommended for non-inferiority studies due to concerns that such analyses bias toward a finding of non-inferiority. For this reason per protocol analyses are preferred non-inferiority and equivalence studies.

- In addition we report on the per protocol analyses on the primary and anatomical outcomes

4) Limiting the anatomic portion of the primary outcome to just the apical compartment rather than any compartment is problematic. Because of concerns about some procedures predisposing for failure in another compartment, recurrence in "any compartment" is a more appropriate anatomic outcome. Several studies, although not all, have suggested that sacrospinous fixation can predispose for prolapse in the anterior compartment.

- We do report on recurrence in all/other compartments (see table 4).

- The suggestion that sacrospinous hysteropexy can predispose for prolapse in the anterior compartment is further discussed in the Discussion section. See also comment above.

Other comments:
- "open-label" seems the wrong term in a surgical trial. "Unblinded" would be preferable.

- We have changed the text in the manuscript as suggested

- The clinical trail registration indicates the primary outcome is "anatomical outcome and recurrence rate assessed by a POP-Q-test at one year follow-up." There is an addendum to the record from November 2014, presumably after the trial had concluded that "Primary outcome should be: Surgical failure, defined as recurrence of prolapse POP-Q stage 2 of the middle compartment and prolapse complaints and/or redo surgery" which seems consistent with the manuscript. Please clarify the discrepancy with the original trial registration.

- As clarified in the Methods section: outcome definitions to evaluate prolapse surgery have

changed (improved) after start of this trial. During enrolment and before data analysis the primary outcome was therefore changed into the following composite outcome measure: recurrent prolapse POP-Q stage 2 or higher in the apical compartment (uterus or vaginal vault) with bothersome prolapse complaints or repeat surgery for recurrent apical prolapse at 12 months follow-up. The medical ethical committee approved this change/improvement and this outcome measure was also published.[17] Unfortunately the addendum was not sent to the trial register, which was done in November 2014.

- The originally primary outcome, overall anatomical failure (prolapse POP-Q stage 2 or higher in any compartment) was evaluated as secondary outcome

- No data is provided about concurrent procedures in each group. The authors should add a table detailing concurrent prolapse and incontinence procedures in each group.

- These details can be found in table 3.

- Where did the 7% non-inferiority margin come from? Some justification should be provided.

- In the study by Dietz et al. the recurrence rate after vaginal hysterectomy was 3% and after sacrospinous hysteropexy 21%, In case sacrospinous hysteropexy would have a recurrence percentage of less than 21% as found by Dietz (i.e.10%%) this was regarded not clinically relevant different from 3%. Therefore, the vaginal hysterectomy recurrence rate was set at 3% and the non-inferiority margin at 7%.

- Overall stage of prolapse (not just apical) should be provided in Table 2

- We have added these data in Table 2.

In Table 2, the range of POPQ value C in the VH group is from -3.0 to 10. This would indicate that at least some of the patients in this group did not meet the inclusion criteria of stage 2 apical prolapse (C >= -1). Please clarify.

- This was erroneously taken from a patient file and has been corrected. Analysis was repeated and gave similar results as previous analysis.