# Supplementary Online Content

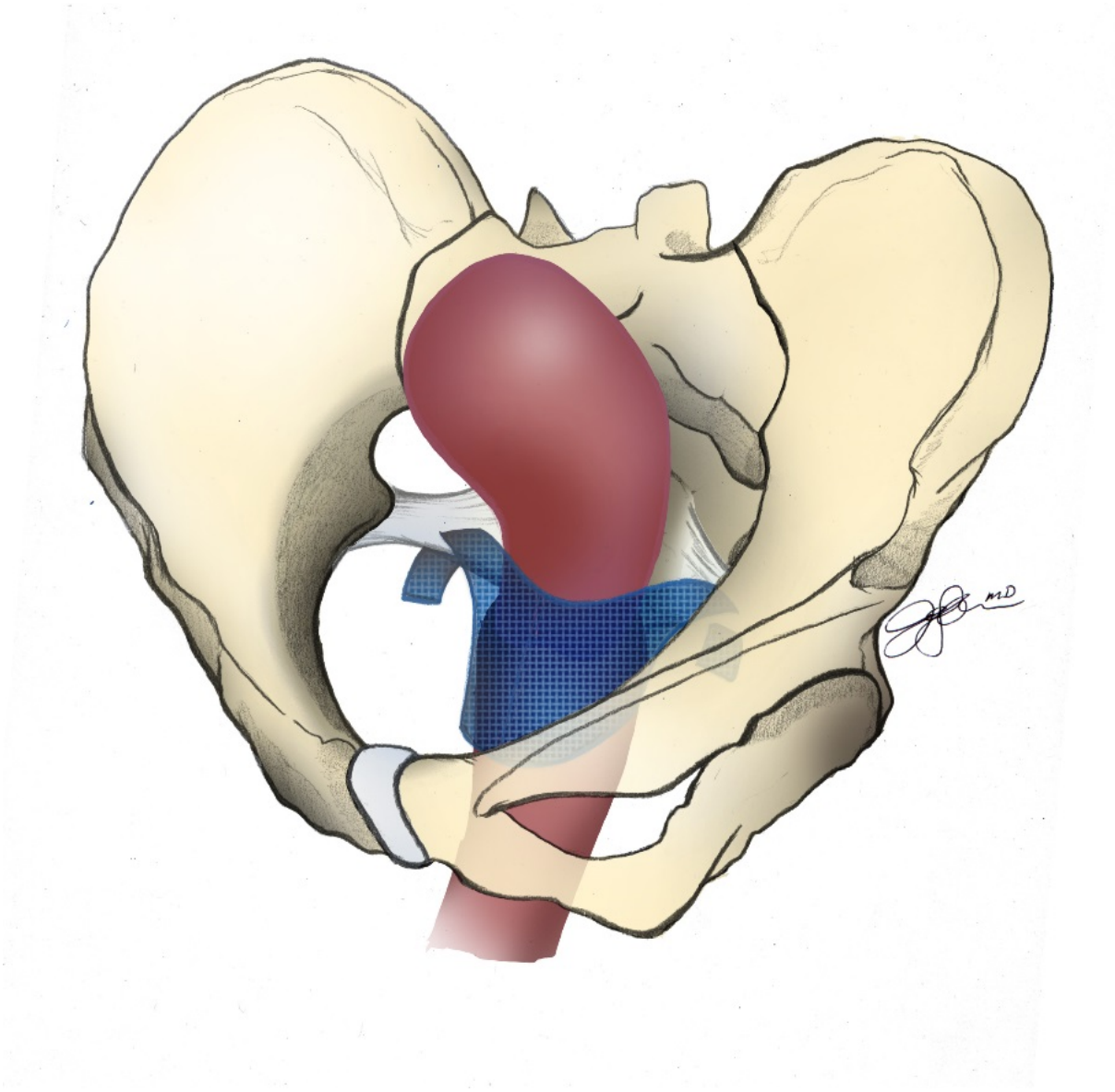
Nager CW, Visco AG, Richter HE, et al. Effect of vaginal mesh hysteropexy vs vaginal hysterectomy with uterosacral ligament suspension on treatment failure in women with uterovaginal prolapse: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2019.12812

**Supplement 2.** eFigure 1 Mesh Hysteropexy procedure



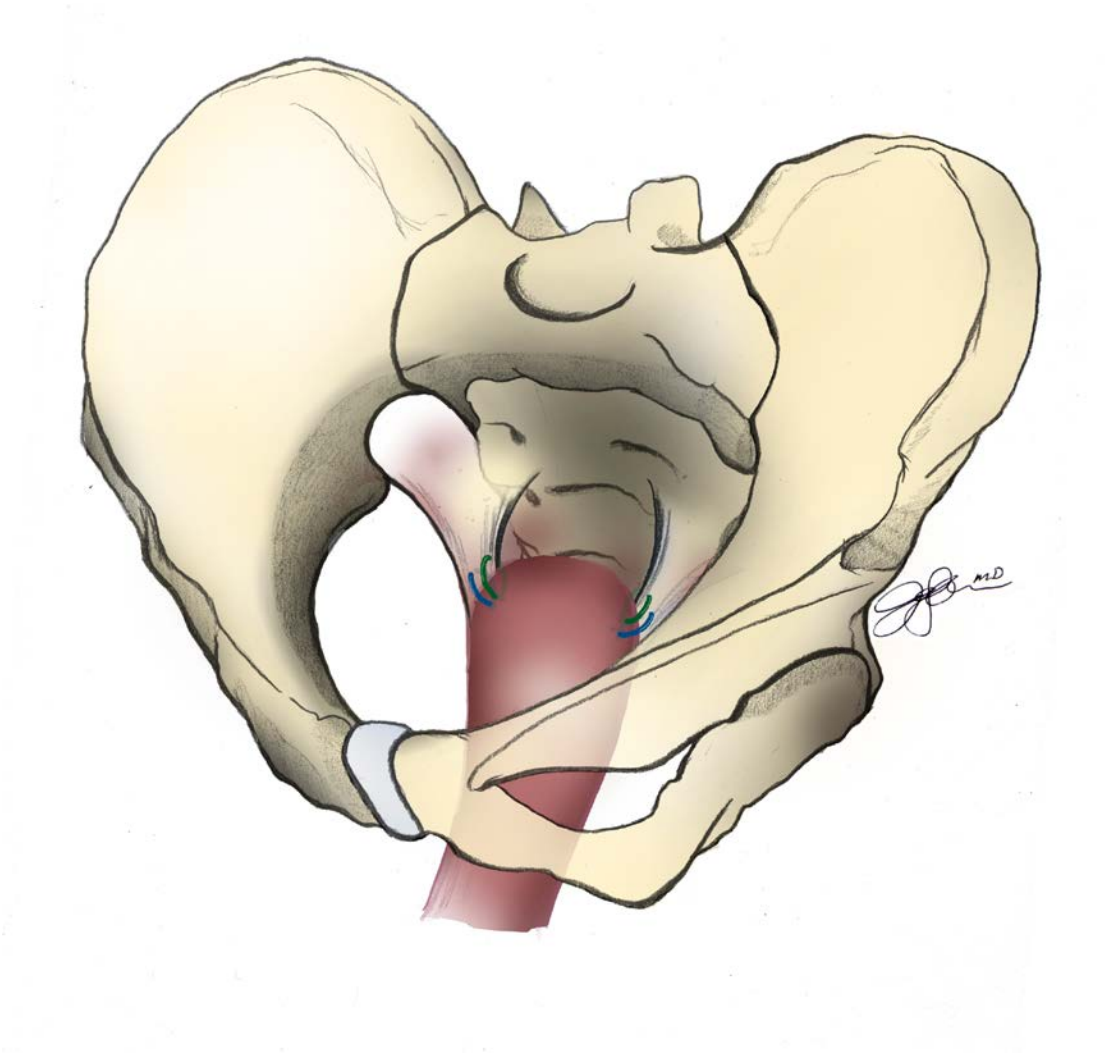
This supplementary material has been provided by the authors to give readers additional information about their work.

**eFigure1. Mesh Hysteropexy procedure**



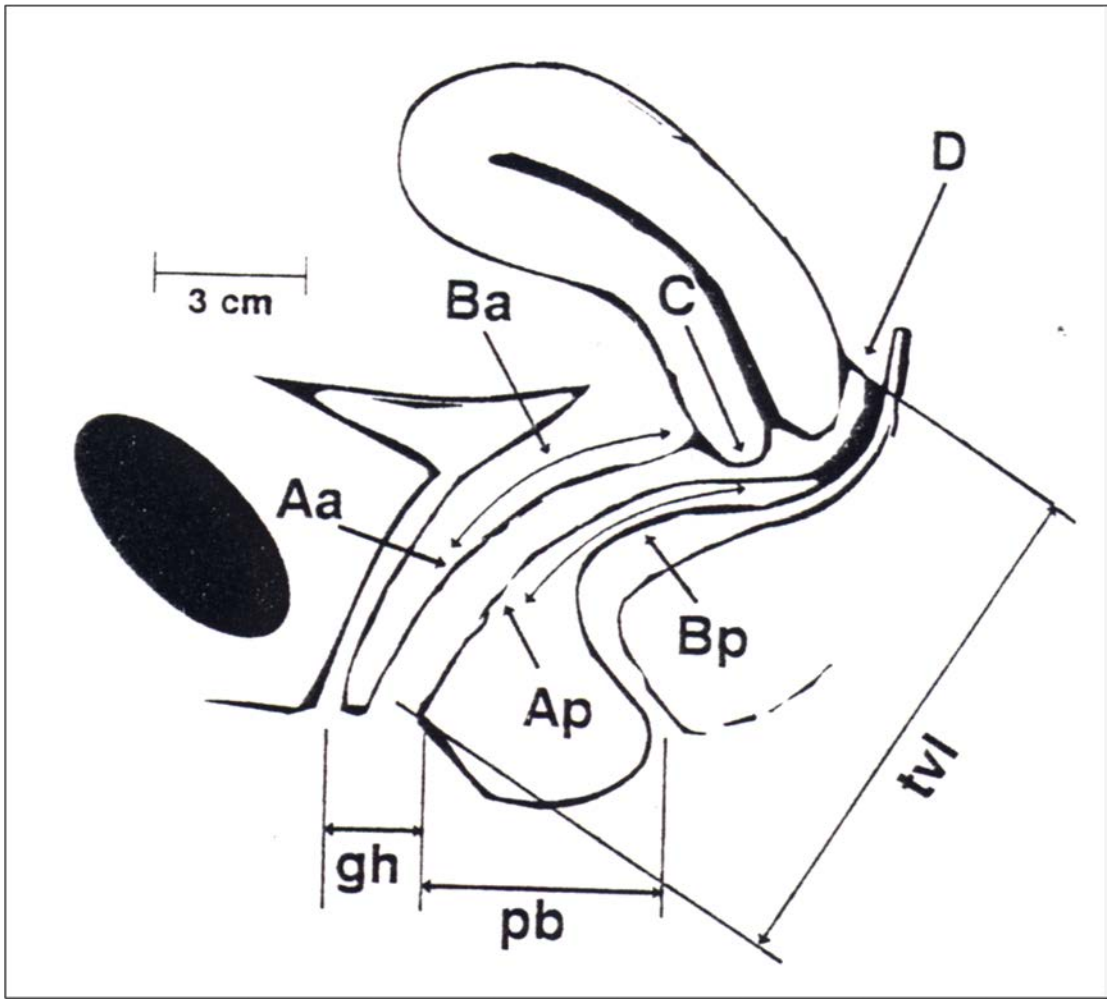
This drawing represents the female bony pelvis and relevant surgical anatomy for the mesh hysteropexy procedure. The upper pink structure depicts the uterus and the lower pink structure is the vagina. The blue hatched area depicts the mesh supporting the cervix and upper anterior vagina by its attachment to both sacrospinous ligaments. (Illustration by Jasmine Tan-Kim, MD)

**eFigure2. Vaginal Hysterectomy and Uterosacral ligament suspension procedure.**



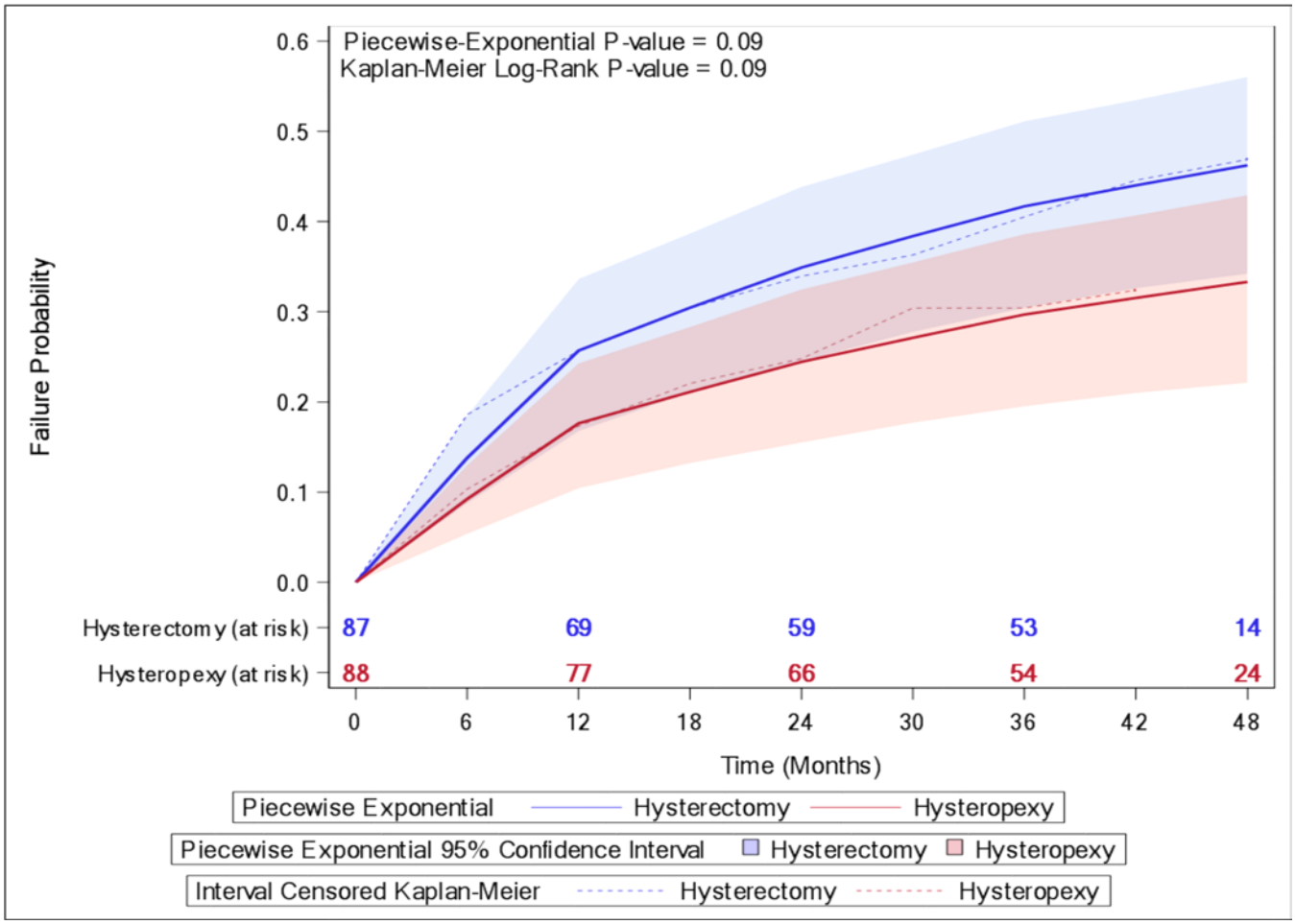
This drawing represents the female bony pelvis and relevant surgical anatomy for the vaginal hysterectomy and uterosacral ligament suspension procedure. The uterus has been removed. The lower pink structure is the vagina. The blue suture represents the permanent suture that is placed during the procedure and the green suture depicts the absorbable suture that attached the upper vagina to both uterosacral ligaments. Eventually this absorbable suture dissolves. (Illustration by Jasmine Tan-Kim, MD)

**eFigure 3. Pelvic Organ Prolapse Quantification (POPQ) Schematic**



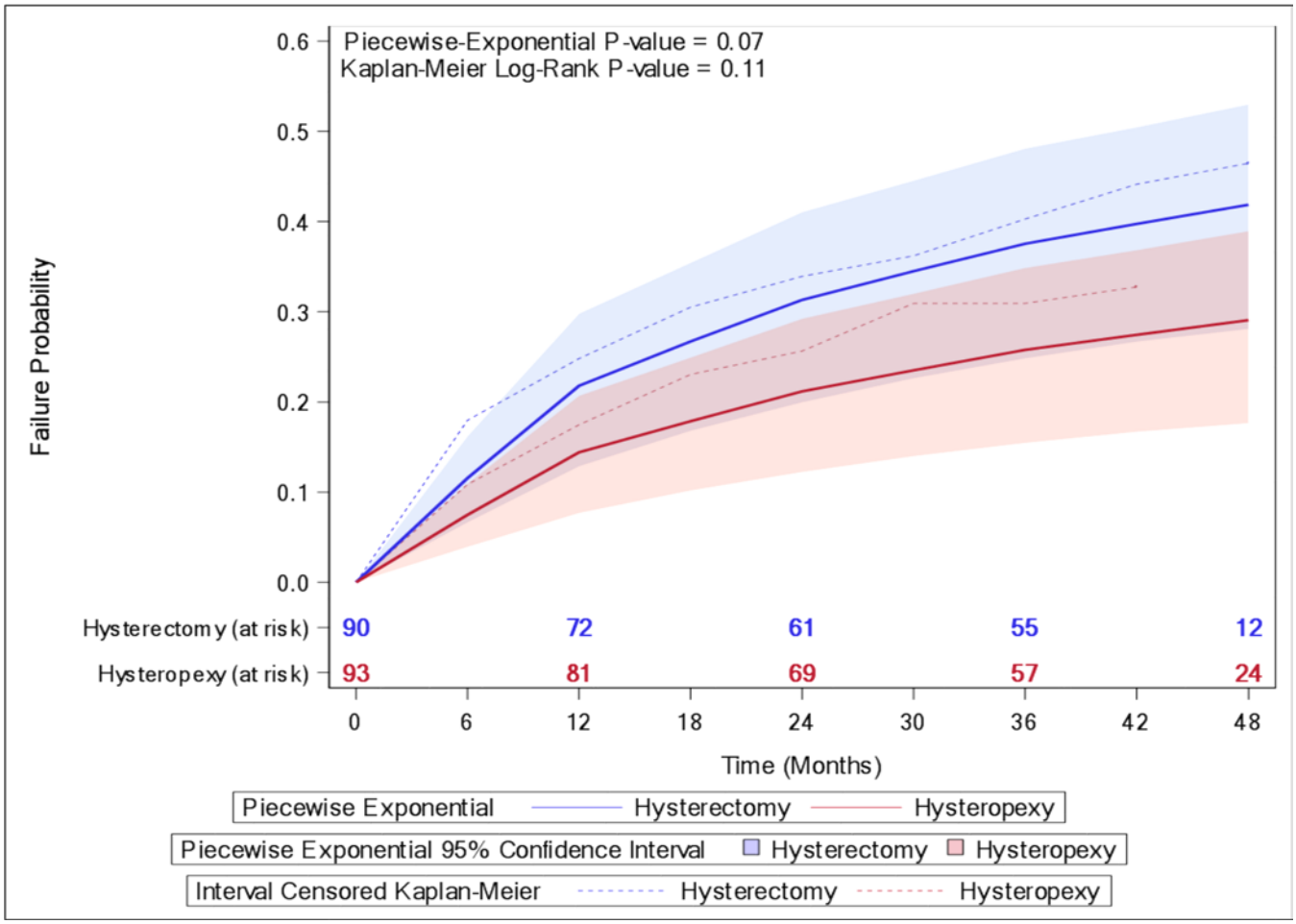

| POPQ Point | Description | Range |
|---|---|---|
| Aa | Anterior vaginal wall 3 cm from hymen | -3 to +3 |
| Ba | Most dependent part of anterior vaginal wall | -3 to +TVL |
| C | Cervix or vaginal cuff | +/- TVL |
| D | Posterior fornix | +/- TVL |
| Ap | Posterior vaginal wall 3 cm from hymen | -3 to +3 |
| Bp | Most dependent part of posterior vaginal wall | -3 to +TVL |
| TVL | Total Vaginal Length | + number |
| gh | Genital hiatus | + number |
| pb | Peineal body | + number |

## eFigure 4. Sensitivity Analysis: Unadjusted Failure Probability for the Composite Primary Outcome Comparing Hysteropexy to Hysterectomy



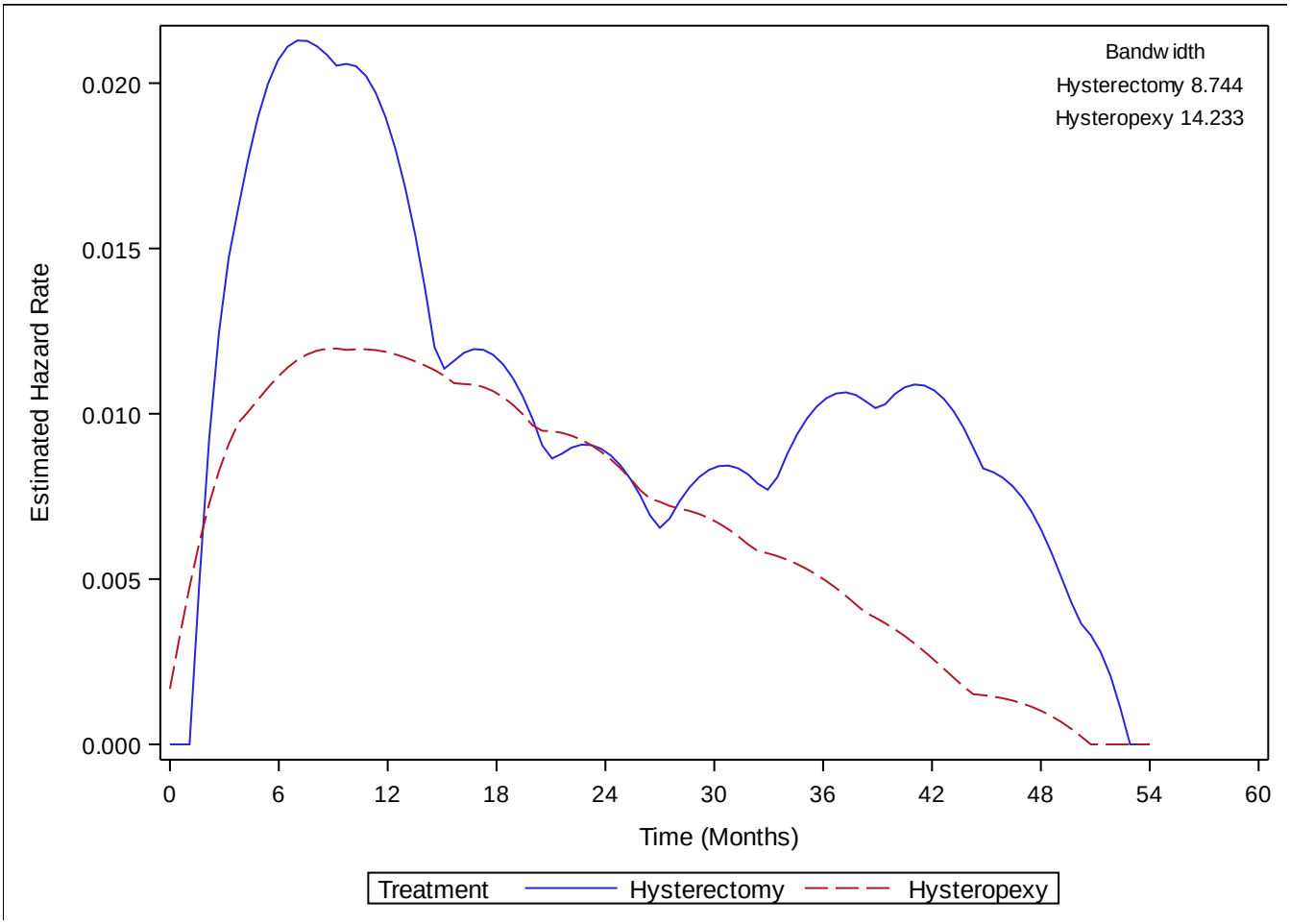

Results from unadjusted survival analysis excluding the 8 ineligible participants was conducted using an interval censored proportional hazard model with an assumed baseline piecewise exponential hazard with four constant-hazard periods: (0 to 12 months, 12 to 24 months, 24 to 36 months, and beyond 36 months). Available follow-up data were included for all participants through the time when the last participant reached 36 months of follow-up. At the time of analysis, 10 participants were censored prior to 36 months (Hysteropexy=7, Hysterectomy=3), 50 participants were censored between [36, 48) months (Hysteropexy=27, Hysterectomy=23), and also 50 participants were censored at or beyond 48 months (Hysteropexy=27, Hysterectomy=23). The overall hazard ratio and 95% confidence interval between hysteropexy and hysterectomy is 0.65 (0.40, 1.07) with the unadjusted estimates for 36 month failure rates and 95% confidence intervals at 0.30 (0.19, 0.39) in the hysteropexy group and 0.42 (0.30, 0.51) in the hysterectomy group. The failure probability from the sensitivity non-parametric interval-censored Kaplan-Meier analysis is also shown. [35]

## eFigure 5. Sensitivity Analysis: Adjusted Failure Probability among all Randomized Participants for the Composite Primary Outcome Comparing Hysteropexy to Hysterectomy




Results from survival analysis for all randomized participants was conducted using an interval censored proportional hazard model with an assumed baseline piecewise exponential hazard with four constant-hazard periods: (0 to 12 months, 12 to 24 months, 24 to 36 months, and beyond 36 months) and controlled for site consistent with study randomization as well as prior prolapse surgery per clinical standards. Available follow-up data were included for all participants through the time when the last participant reached 36 months of follow-up. At the time of analysis, 10 participants were censored prior to 36 months (Hysteropexy=7, Hysterectomy=3), 55 participants were censored between [36, 48) months (Hysteropexy=30, Hysterectomy=25), and 50 participants were censored at or beyond 48 months (Hysteropexy=27, Hysterectomy=23). The overall hazard ratio and 95% confidence interval between hysteropexy and hysterectomy is 0.63 (0.39, 1.03) with the covariate-adjusted estimates for 36 month failure rates and 95% confidence intervals at 0.26 (0.15, 0.35) in the hysteropexy group and 0.38 (0.25, 0.48) in the hysterectomy group. The failure probability from the sensitivity non-parametric interval-censored Kaplan-Meier analysis is also shown. [35]

## eFigure 6. Smoothed Hazard Rates for the Composite Primary Outcome Comparing Hysteropexy to Hysterectomy




The Epanechnikov kernal-smoothed hazard rates shown are from the non-parametric interval-censored Kaplan-Meier analysis in Figure 2. Overall, the hazard rate in the hysterectomy group is higher than the hysteropexy group except in the period of approximately 18 to 30 months where the rates appear similar.

## eTable 1. Concomitant procedures

| Outcome, n (%) | Hysteropexy N=88[a] | Hysterectomy N=87[a] | Risk Difference (95% CI)[b] | p-value[b] |
|---|---|---|---|---|
| Concomitant retropubic midurethral sling | 29 (33%) | 31 (36%) | -3% (-17%, 11%) | 0.71 |
| Concomitant transobturator midurethral sling | 12 (14%) | 13 (15%) | -1% (-12%, 9%) | 0.80 |
| Concomitant anterior repair | 79 (90%) | 62 (71%) | 19% (7%, 30%) | 0.002 |
| Concomitant posterior repair/perineorrhaphy | 51 (58%) | 50 (57%) | 0% (-14%, 15%) | 0.95 |

[a] Sample size is 88 for Hysteropexy and 87 for Hysterectomy unless otherwise specified

[b] Risk differences, 95% confidence intervals, and p-values are based on Mantel-Haenszel estimates for the risk difference with Wald-type confidence intervals.

## eTable 2. Perioperative Outcomes

| Outcome | Hysteropexy N=88 | Hysterectomy N=87 | Risk/Mean Difference (95% CI)[a] | p-value[a] |
|---|---|---|---|---|
| Estimated blood loss in ml, N | 88 | 87 | | |
| Mean (SD) | 141.1 (104.0) | 147.5 (97.4) | -6.3 (-36.4, 23.7) | 0.68 |
| Blood transfusion rate, n/N (%) | 0/88 | 2/87 (2%) | -2% (-8%, 2%) | 0.25 |
| Urethral catheter still in at discharge, n/N (%) | 29/88 (33%) | 29/87 (33%) | -0% (-14%, 14%) | 0.96 |
| Voiding spontaneously at discharge, n/N (%) | 52/88 (59%) | 48/87 (55%) | 4% (-11%, 19%) | 0.60 |
| Days in hospital, N | 88 | 87 | | |
| Mean (SD) | 1.1 (0.7) | 1.3 (1.4) | -0.2 (-0.5, 0.2) | 0.30 |
| Return to operating room, n/N (%) | 0/88 | 1/87 (1%) | -1% (-6%, 3%) | 0.50 |
| Intensive care unit admission, n/N (%) | 1/88 (1%) | 2/87 (2%) | -1% (-7%, 4%) | 0.62 |
| Modified dindo complications [b] (in hospital), N | 88 | 87 | | 0.57 |
| Grade IVa, n (%) | 1 (1%) | 2 (2%) | | |
| Grade IIIb, n (%) | 1 (1%) | 1 (1%) | | |
| Grade IIIo, n (%) | 3 (3%) | 5 (6%) | | |
| Grade IIb, n (%) | 0 | 2 (2%) | | |
| Grade IIa, n (%) | 0 | 1 (1%) | | |
| Grade I, n (%) | 13 (15%) | 9 (10%) | | |
| None, n (%) | 70 (80%) | 67 (77%) | | |
| Hemostatic agent use, n/N (%) | 2/88 (2%) | 5/87 (6%) | -3% (-11%, 3%) | 0.28 |

[a] Mean differences, 95% confidence intervals, and p-values are unadjusted and based on t-tests for normally distributed continuous outcomes. P-values for ordinal categorical measures are from Cochran-Mantel-Haenszel chi-square tests using standardized midranks. Risk differences, 95% confidence intervals, and p-values are unadjusted and based on Mantel-Haenszel estimates for the risk difference with Wald-type confidence intervals for nominal categorical measures with expected cell counts > 5, otherwise the exact risk difference and 95% confidence limits are obtained by exact methods based on the score statistic based on Chan and Zhang [40] and the p-values are from Fisher's exact tests.

[b] Grade I: Any deviation from the normal intraoperative or postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications
Grade IIa: Oral administration of drugs other than such allowed for grade I, excluding antibiotics
Grade IIabx: Oral administration of drugs other than such allowed for grade I, including antibiotics
Grade IIb: IV administration of drugs other than such allowed for grade I, including antibiotics; blood transfusions and total parenteral nutrition are also included
Grade III: Requiring surgical, endoscopic or radiological intervention
Grade IIIo: Additional surgical measures required during SUPeR procedure
Grade IIIa: Intervention not under general anesthesia
Grade IIIb: Intervention under general anesthesia
Grade IV: Life-threatening complication (including CNS complications--brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks) requiring intermediate care or ICU management
Grade IVa: Single organ dysfunction (including dialysis)
Grade IVb: Multiorgan dysfunction
Grade V: Death of a patient

## eTable 3. Sexual function and dyspareunia results from PISQ-IR[a]

| Outcome[b] | Hysteropexy N=88 | Hysterectomy N=87 | Risk Difference (95% Confidence Interval)[c] | p-value[c] |
|---|---|---|---|---|
| Baseline, n/N (%) | | | | |
| Sexually active | 30/88 (34%) | 40/87 (46%) | -12% (-26%, 3%) | 0.11 |
| Sexually active, have dyspareunia [a] | 10/26 (38%) | 17/37 (46%) | -7% (-32%, 17%) | 0.55 |
| Not sexually active, have dyspareunia [a] | 19/58 (33%) | 15/45 (33%) | -1% (-19%, 18%) | 0.95 |
| 36 months, n/N (%) | | | | |
| Sexually active | 29/74 (39%) | 34/73 (47%) | -7% (-23%, 9%) | 0.37 |
| Sexually active, have dyspareunia [a] | 5/26 (19%) | 5/31 (16%) | 3% (-17%, 23%) | 0.76 |
| Not sexually active, have dyspareunia [a] | 10/42 (24%) | 4/35 (11%) | 12% (-4%, 29%) | 0.16 |

[a] The Pelvic Organ Prolapse Incontinence Sexual Questionnaire-IUGA Revised (PISQ-IR). Sexually active, have dyspareunia (PISQ-IR, usually or always have) is defined among women who were sexually active as experiencing pain during sexual intercourse at time point of interest. Not sexually active, have dyspareunia (PISQ-IR, strongly agree or somewhat agree) is defined among women who were not sexually active as not engaging in sexual intercourse due to fear of pain during sexual intercourse at time point of interest.

[b] Some participants responded to the sexually active item on the PISQ-IR, but did not respond to the corresponding dyspareunia item on the PISQ-IR.

[c] Risk differences, 95% confidence intervals, and p-values are unadjusted and based on Mantel-Haenszel estimates for the risk difference with Wald-type confidence intervals for nominal categorical measures.

## eTable 4. Adverse Events by System Organ Class and Preferred Term[a] - All Treated Participants

| System Organ Class[b] | Preferred Term | Hysteropexy (N=93) Evt[c] | Hysteropexy (N=93) n[c] (%) | Hysterectomy (N=90) Evt[c] | Hysterectomy (N=90) n[c] (%) | Total (N=183) Evt[c] | Total (N=183) n[c] (%) |
|---|---|---|---|---|---|---|---|
| Any | Any | 256 | 73 ( 78%) | 240 | 75 ( 83%) | 496 | 148 ( 81%) |
| Infections and infestations | Any | 73 | 38 ( 41%) | 80 | 39 ( 43%) | 153 | 77 ( 42%) |
| | Bacterial vaginosis | 4 | 4 ( 4%) | 1 | 1 ( 1%) | 5 | 5 ( 3%) |
| | Cellulitis | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Clostridium difficile colitis | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Fungal infection | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Groin abscess | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Pyelonephritis | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Urinary tract infection | 59 | 34 ( 37%) | 69 | 39 ( 43%) | 128 | 73 ( 40%) |
| | Urosepsis | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Vaginal infection | 3 | 3 ( 3%) | 5 | 5 ( 6%) | 8 | 8 ( 4%) |
| | Vulvovaginal candidiasis | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Vulvovaginal mycotic infection | 1 | 1 ( 1%) | 2 | 2 ( 2%) | 3 | 3 ( 2%) |
| | Wound infection | 1 | 1 ( 1%) | 1 | 1 ( 1%) | 2 | 2 ( 1%) |
| Renal and urinary disorders | Any | 62 | 37 ( 40%) | 39 | 27 ( 30%) | 101 | 64 ( 35%) |
| | Bladder spasm | 0 | 0 ( 0%) | 2 | 2 ( 2%) | 2 | 2 ( 1%) |
| | Dysuria | 3 | 2 ( 2%) | 0 | 0 ( 0%) | 3 | 2 ( 1%) |
| | Haematuria | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Hydronephrosis | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Nocturia | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Stress urinary incontinence | 22 | 19 ( 20%) | 13 | 12 ( 13%) | 35 | 31 ( 17%) |
| | Urethral caruncle | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Urethral cyst | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Urethral pain | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Urge incontinence | 21 | 19 ( 20%) | 13 | 13 ( 14%) | 34 | 32 ( 17%) |
| | Urinary incontinence | 1 | 1 ( 1%) | 2 | 2 ( 2%) | 3 | 3 ( 2%) |
| | Urinary retention | 10 | 6 ( 6%) | 8 | 7 ( 8%) | 18 | 13 ( 7%) |
| Reproductive system and breast disorders | Any | 40 | 27 ( 29%) | 28 | 18 ( 20%) | 68 | 45 ( 25%) |

| System Organ Class[b] | Preferred Term | Hysteropexy (N=93) Evt[c] | Hysteropexy (N=93) n[c] (%) | Hysterectomy (N=90) Evt[c] | Hysterectomy (N=90) n[c] (%) | Total (N=183) Evt[c] | Total (N=183) n[c] (%) |
|---|---|---|---|---|---|---|---|
| | Atrophic vulvovaginitis | 8 | 7 ( 8%) | 1 | 1 ( 1%) | 9 | 8 ( 4%) |
| | Bartholin's cyst | 1 | 1 ( 1%) | 1 | 1 ( 1%) | 2 | 2 ( 1%) |
| | Cervical polyp | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Dyspareunia | 9 | 8 ( 9%) | 2 | 2 ( 2%) | 11 | 10 ( 5%) |
| | Fallopian tube prolapse | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Pelvic pain | 3 | 3 ( 3%) | 8 | 7 ( 8%) | 11 | 10 ( 5%) |
| | Perineal pain | 1 | 1 ( 1%) | 1 | 1 ( 1%) | 2 | 2 ( 1%) |
| | Postmenopausal bleeding secondary to atrophy | 5 | 4 ( 4%) | 1 | 1 ( 1%) | 6 | 5 ( 3%) |
| | Postmenopausal haemorrhage | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Rectocele | 0 | 0 ( 0%) | 2 | 2 ( 2%) | 2 | 2 ( 1%) |
| | Uterine haemorrhage | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Vaginal bleeding | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Vaginal erosion | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Vaginal haematoma | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Vaginal scarring | 4 | 4 ( 4%) | 0 | 0 ( 0%) | 4 | 4 ( 2%) |
| | Vaginotomy | 1 | 1 ( 1%) | 1 | 1 ( 1%) | 2 | 2 ( 1%) |
| | Vulvovaginal adhesion | 1 | 1 ( 1%) | 2 | 2 ( 2%) | 3 | 3 ( 2%) |
| | Vulvovaginal discomfort | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Vulvovaginal pain | 0 | 0 ( 0%) | 4 | 4 ( 4%) | 4 | 4 ( 2%) |
| | Vulvovaginal pruritus | 3 | 3 ( 3%) | 1 | 1 ( 1%) | 4 | 4 ( 2%) |
| Gastrointestinal disorders | Abdominal distension | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Abdominal pain | 3 | 3 ( 3%) | 2 | 2 ( 2%) | 5 | 5 ( 3%) |
| | Any | 31 | 23 ( 25%) | 34 | 24 ( 27%) | 65 | 47 ( 26%) |
| | Colitis | 2 | 1 ( 1%) | 2 | 2 ( 2%) | 4 | 3 ( 2%) |
| | Colitis ischaemic | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Constipation | 6 | 5 ( 5%) | 15 | 13 ( 14%) | 21 | 18 ( 10%) |
| | Diarrhoea | 2 | 2 ( 2%) | 0 | 0 ( 0%) | 2 | 2 ( 1%) |
| | Diverticular perforation | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Enteritis | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Faecal incontinence | 11 | 10 ( 11%) | 5 | 4 ( 4%) | 16 | 14 ( 8%) |

| System Organ Class[b] | Preferred Term | Hysteropexy (N=93) Evt[c] | Hysteropexy (N=93) n[c] (%) | Hysterectomy (N=90) Evt[c] | Hysterectomy (N=90) n[c] (%) | Total (N=183) Evt[c] | Total (N=183) n[c] (%) |
|---|---|---|---|---|---|---|---|
| | Gastric ulcer | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Gastrooesophageal reflux disease | 1 | 1 ( 1%) | 1 | 1 ( 1%) | 2 | 2 ( 1%) |
| | Haemorrhoids | 1 | 1 ( 1%) | 1 | 1 ( 1%) | 2 | 2 ( 1%) |
| | Ileus | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Levator syndrome | 2 | 2 ( 2%) | 0 | 0 ( 0%) | 2 | 2 ( 1%) |
| | Nausea | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Peritoneal perforation | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Rectal haemorrhage | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Small intestinal obstruction | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Vomiting | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| Injury, poisoning and procedural complications | Any | 19 | 12 ( 13%) | 33 | 30 ( 33%) | 52 | 42 ( 23%) |
| | Bladder injury | 2 | 2 ( 2%) | 1 | 1 ( 1%) | 3 | 3 ( 2%) |
| | Femoral nerve injury | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Hysteropexy mesh exposure | 12 | 7 ( 8%) | 0 | 0 ( 0%) | 12 | 7 ( 4%) |
| | Midurethral sling mesh exposure | 0 | 0 ( 0%) | 3 | 2 ( 2%) | 3 | 2 ( 1%) |
| | Post procedural haemorrhage | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Postoperative thrombosis | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Procedural complication | 2 | 2 ( 2%) | 0 | 0 ( 0%) | 2 | 2 ( 1%) |
| | Retained fragment of surgical packing | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Suture exposure after 12 wks. | 3 | 3 ( 3%) | 17 | 17 ( 19%) | 20 | 20 ( 11%) |
| | Ureteric kink | 0 | 0 ( 0%) | 7 | 7 ( 8%) | 7 | 7 ( 4%) |
| | Vaginal laceration | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| Musculoskeletal and connective tissue disorders | Any | 15 | 8 ( 9%) | 7 | 6 ( 7%) | 22 | 14 ( 8%) |
| | Arthralgia | 2 | 2 ( 2%) | 0 | 0 ( 0%) | 2 | 2 ( 1%) |
| | Back pain | 3 | 3 ( 3%) | 1 | 1 ( 1%) | 4 | 4 ( 2%) |

| System Organ Class[b] | Preferred Term | Hysteropexy (N=93) Evt[c] | Hysteropexy (N=93) n[c] (%) | Hysterectomy (N=90) Evt[c] | Hysterectomy (N=90) n[c] (%) | Total (N=183) Evt[c] | Total (N=183) n[c] (%) |
|---|---|---|---|---|---|---|---|
| | Flank pain | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Groin pain | 3 | 2 ( 2%) | 0 | 0 ( 0%) | 3 | 2 ( 1%) |
| | Joint stiffness | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Joint swelling | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Musculoskeletal chest pain | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Musculoskeletal pain | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Neck pain | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Osteoarthritis | 4 | 3 ( 3%) | 0 | 0 ( 0%) | 4 | 3 ( 2%) |
| | Pain in extremity | 0 | 0 ( 0%) | 2 | 2 ( 2%) | 2 | 2 ( 1%) |
| | Tendonitis | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| Skin and subcutaneous tissue disorders | Any | 2 | 2 ( 2%) | 11 | 10 ( 11%) | 13 | 12 ( 7%) |
| | Excessive granulation tissue after 12 wks. | 1 | 1 ( 1%) | 10 | 10 ( 11%) | 11 | 11 ( 6%) |
| | Rash | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Urticaria | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| Vascular disorders | Any | 3 | 2 ( 2%) | 2 | 2 ( 2%) | 5 | 4 ( 2%) |
| | Deep vein thrombosis | 3 | 2 ( 2%) | 0 | 0 ( 0%) | 3 | 2 ( 1%) |
| | Haematoma | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Phlebitis | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| General disorders and administration site conditions | Any | 3 | 3 ( 3%) | 1 | 1 ( 1%) | 4 | 4 ( 2%) |
| | Device malfunction | 2 | 2 ( 2%) | 0 | 0 ( 0%) | 2 | 2 ( 1%) |
| | Feeling hot | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Local swelling | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| Nervous system disorders | Any | 2 | 2 ( 2%) | 2 | 1 ( 1%) | 4 | 3 ( 2%) |
| | Sciatica | 2 | 2 ( 2%) | 2 | 1 ( 1%) | 4 | 3 ( 2%) |
| Respiratory, thoracic and mediastinal disorders | Any | 3 | 3 ( 3%) | 1 | 1 ( 1%) | 4 | 4 ( 2%) |
| | Pulmonary embolism | 2 | 2 ( 2%) | 0 | 0 ( 0%) | 2 | 2 ( 1%) |
| | Pulmonary oedema | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Respiratory failure | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |

| System Organ Class[b] | Preferred Term | Hysteropexy (N=93) Evt[c] | Hysteropexy (N=93) n[c] (%) | Hysterectomy (N=90) Evt[c] | Hysterectomy (N=90) n[c] (%) | Total (N=183) Evt[c] | Total (N=183) n[c] (%) |
|---|---|---|---|---|---|---|---|
| Cardiac disorders | Any | 1 | 1 ( 1%) | 1 | 1 ( 1%) | 2 | 2 ( 1%) |
| | Arrhythmia | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Atrial fibrillation | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| Investigations | Any | 1 | 1 ( 1%) | 1 | 1 ( 1%) | 2 | 2 ( 1%) |
| | Blood culture positive | 0 | 0 ( 0%) | 1 | 1 ( 1%) | 1 | 1 ( 1%) |
| | Urine analysis abnormal | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| Surgical and medical procedures | Any | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |
| | Ureteral stent insertion | 1 | 1 ( 1%) | 0 | 0 ( 0%) | 1 | 1 ( 1%) |

[a] System Organ Class and Preferred Term are coded using Medical Dictionary for Regulatory Activities (MedDRA).

[b] Systematic collection of open-ended adverse events throughout the course of the trial are presented in descending order of frequency for System Organ Class grouping.

[c] For each adverse event, the total number of events is presented (Evt) as well as the distinct number of participants experiencing each adverse event (n).

**eTable 5. Sample Size Calculations[a]**

| Total Sample Size | Power as a function of 2-year effect size—assuming 2-year failure of 20% in the hysterectomy group, and a range of 7% to 10% in the hysteropexy group, with a 2-year enrollment period and 36-month follow-up after the last enrollment | | | |
|---|---|---|---|---|
| | ∆= 0.10<br>10% vs 20%<br>HR=0.472 | Δ=0.11<br>9% vs 20%<br>HR=0.423 | Δ=0.12<br>8% vs 20%<br>HR=0.374 | Δ=0.13<br>7% vs 20%<br>HR=0.325 |
| 160 | 63% | 73% | 81% | 88% |
| 180 | 69% | 78% | 86% | 92% |
| 200 | 73% | 82% | 89% | 94% |
| 220 | 77% | 86% | 92% | 96% |
| 240 | 81% | 89% | 94% | 97% |
| 260 | 84% | 91% | 96% | 98% |
| 280 | 86% | 93% | 97% | 99% |
| 300 | 89% | 94% | 98% | 99% |

[a] The power calculations are a revision of the calculations provided in the protocol based on the same parameters while correcting a calculation error that was identified after completion of the primary analysis. The calculation is based on a Log-Rank test assuming an exponential survival distribution, a 5% per year exponential loss-to-follow-up rate, and alpha = 0.047 at the final analysis after an O'Brien-Fleming adjustment for one interim analysis conducted at p=0.009.

Inclusion and Exclusion Criteria

*Inclusion Criteria -*

1) Women aged 21 or older who have completed child -bearing

2) Prolapse beyond the hymen (defined as Ba, Bp, or C > 0 cm)

3) Uterine descent into at least the lower half of the vagina (defined as point C> -TVL/2))

4) Bothersome bulge symptoms as indicated on question 3 of the PFDI-20 form relating to 'sensation of bulging' or 'something falling out'

5) Desires vaginal surgical treatment for uterovaginal prolapse

6) Available for up to 60 month follow-up

7) Amenorrhea for the past 12 months from either menopause or endometrial ablation

8) Not pregnant, not at risk for pregnancy or agree to contraception if at risk for pregnancy (only applicable to the rare endometrial ablation patient)

9) Eligible for no cervical cancer screening for at least 3 years

*Exclusion Criteria –*

1) Previous synthetic material (placed vaginally or abdominally) to augment POP repair

2) Known previous uterosacral or sacrospinous uterine suspension

3) Known adverse reaction to synthetic mesh or biological grafts; these complications include but are not limited to erosion, fistula, or abscess

4) Chronic pelvic pain

5) Pelvic radiation

6) Cervical elongation- defined as an expectation that the C point would be Stage 2 or greater postoperatively if a hysteropexy was performed. (Note: cervical shortening or trachelectomy is

not an allowed intraoperative procedure within the hysteropexy treatment group).

7) Women at increased risk of cervical dysplasia requiring cervical cancer screening more often than every 3 years (e.g. HIV+ status, immunosuppression because of transplant related medications, Diethylstilbestrol (DES) exposure in utero, or previous treatment for cervical intraepithelial neoplasia (CIN)2, CIN3, or cancer)

8) Uterine abnormalities (symptomatic uterine fibroids, polyps, endometrial hyperplasia, endometrial cancer, or any uterine disease that precluded prolapse repair with uterine preservation in the opinion of the surgeon

9) Indication for ovarian removal (adnexal mass, BRCA 1/2 positivity, family history of ovarian cancer)

10) Current condition of amenorrhea caused by exogenous sex steroids or hypothalamic conditions.

Certification and Standardized Procedures for the 2 Surgeries in the SUPeR Study

*Vaginal Hysterectomy with Uterosacral Ligament Suspension*

Certification

Certification to perform the 'hysterectomy' procedure required experience of ≥20 vaginal hysterectomies and ≥20 uterosacral ligament suspension procedures with ≥5 each in the last 12 months and review of the DVD of the uterosacral ligament suspension procedure.

Standardization

(1) Uterosacral ligament suspension is performed through the vaginal incision after the vaginal hysterectomy.

(2) The placement of uterosacral ligament stitches is performed in such a way as to avoid neurovascular and ureteral compromise.

(3) One permanent and one delayed absorbable 0 or 2-0 monofilament suture (2 sutures per side; 4 sutures total) are placed in each ligament, extending to the ipsilateral anterior and posterior fibromuscular wall of the vaginal apex. The permanent sutures are placed near full thickness, excluding vaginal epithelium. The delayed absorbable sutures are placed full thickness through the vaginal walls. The type of suture material is recorded.

*(4) No plication of the uterosacral ligaments across the midline or culdoplasty is allowed.*

*Uphold Lite® Mesh Hysteropexy*

Certification

The hysteropexy was standardized with the Uphold LITE® transvaginal mesh support system (Boston Scientific). Certified 'hysteropexy' surgeons were required to have performed ≥20 sacrospinous

ligament dissections, with ≥10 anterior dissections to the ligament, ≥10 using the Capio® (Boston Scientific) auto suture device, and ≥5 Uphold LITE procedures and review of the DVD of the Uphold transvaginal mesh procedure uterosacral ligament suspension procedure.

Standardization

(1) Hydrodissection of the vaginal walls is performed with at least 30 mL of 0.25% bupivacaine with epinephrine or dilute vasopressin (20 units/50–100 mL)

(2) A 4-cm transverse vaginal incision is made in the anterior vaginal wall between the bladder neck and the cervix but at least 3 cm from the cervix so that the suture line will not overlap with the mesh.

(3) Blunt or sharp dissection is allowed to approach the sacrospinous ligament extraperitoneally.

(4) After confirmation of the location of the ischial spine, the tapered lead and mesh assembly is delivered into the sacrospinous ligament 1 to 2 fingerbreadths medial to the ischial spine.

(5) The most cephalic edge of the mesh is attached to the cervix with sutures.

(6) Mesh modifications (e.g., cutting) are strongly discouraged; any exceptions will be documented on operative case report forms.

(7) Tensioning is performed to suspend the apex without tense mesh arms.

(8) Vaginal closure is performed with 2-0 polyglactin suture.

(9) A vaginal pack and indwelling urethral catheter are placed and removed on postoperative day 1.