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Effect of Vaginal Mesh Hysteropexy vs Vaginal Hysterectomy With Uterosacral Ligament Suspension on Treatment Failure in Women With Uterovaginal Prolapse
A Randomized Clinical Trial

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IMPORTANCE Vaginal hysterectomy with suture apical suspension is commonly performed for uterovaginal prolapse. Transvaginal mesh hysteropexy is an alternative option.

OBJECTIVE To compare the efficacy and adverse events of vaginal hysterectomy with suture apical suspension and transvaginal mesh hysteropexy.

DESIGN, SETTING, PARTICIPANTS At 9 clinical sites in the US Pelvic Floor Disorders Network, 183 postmenopausal women with symptomatic uterovaginal prolapse were enrolled in a randomized superiority clinical trial between April 2013 and February 2015. The study was designed for primary analysis when the last randomized participant reached 3 years of follow-up in February 2018.

INTERVENTIONS Ninety-three women were randomized to undergo vaginal mesh hysteropexy and 90 were randomized to undergo vaginal hysterectomy with uterosacral ligament suspension.

MAIN OUTCOMES AND MEASURES The primary treatment failure composite outcome (re-treatment of prolapse, prolapse beyond the hymen, or prolapse symptoms) was evaluated with survival models. Secondary outcomes included operative outcomes and adverse events, and were evaluated with longitudinal models or contingency tables as appropriate.

RESULTS A total of 183 participants (mean age, 66 years) were randomized, 175 were included in the trial, and 169 (97%) completed the 3-year follow-up. The primary outcome was not significantly different among women who underwent hysteropexy vs hysterectomy through 48 months (adjusted hazard ratio, 0.62 [95% CI, 0.38-1.02]; $P = .06$; 36-month adjusted failure incidence, 26% vs 38%). Mean (SD) operative time was lower in the hysteropexy group vs the hysterectomy group (111.5 [39.7] min vs 156.7 [43.9] min; difference, −45.2 [95% CI, −57.7 to −32.7]; $P = <.001$). Adverse events in the hysteropexy vs hysterectomy groups included mesh exposure (8% vs 0%), ureteral kinking managed intraoperatively (0% vs 7%), granulation tissue after 12 weeks (1% vs 11%), and suture exposure after 12 weeks (3% vs 21%).

CONCLUSIONS AND RELEVANCE Among women with symptomatic uterovaginal prolapse undergoing vaginal surgery, vaginal mesh hysteropexy compared with vaginal hysterectomy with uterosacral ligament suspension did not result in a significantly lower rate of the composite prolapse outcome after 3 years. However, imprecision in study results precludes a definitive conclusion, and further research is needed to assess whether vaginal mesh hysteropexy is more effective than vaginal hysterectomy with uterosacral ligament suspension.

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Surgery for uterovaginal prolapse is common. In an analysis of a US database from 2007 to 2011, an estimated 13% of women underwent pelvic organ prolapse surgery by the age of 80 years.[1] In a 2016 British Society of Urogynecology survey with a 42% response rate, 75% of 212 urogynecology surgeons considered vaginal hysterectomy the procedure of choice for women with uterovaginal prolapse.[2] Uterine-sparing suspension techniques, known as hysteropexy, are increasing in usage, but in a US inpatient hospital database from 2002 to 2012, hysteropexy accounted for 5% of uterovaginal prolapse procedures and hysterectomies were performed 8 times more often.[3] In a survey of 244 US women with an 89% response rate, 36% preferred uterine preservation, 20% preferred hysterectomy, and 44% were ambivalent assuming comparable outcomes at the time of uterovaginal prolapse repair.[4] The broad range of age, goals, and expectations of women who seek prolapse surgical correction and the elective nature of treatment are ideally weighed in a shared decision-making process grounded in sound scientific evidence.

A 2016 Cochrane review of trials comparing apical suspensions for management of uterovaginal prolapse found that no conclusion could be reached regarding superiority of uterine-preserving surgery using mesh reinforcement vs surgical procedures including vaginal hysterectomy.[5] Although transvaginal mesh procedures are controversial, few high-quality, long-term data compare apical transvaginal mesh with native tissue procedures and both the US Food and Drug Administration and the UK National Institute for Health and Care Excellence recommend further research on transvaginal mesh procedures.[6]

To address this evidence gap, the Study of Uterine Prolapse Procedures Randomized Trial (the SUPeR trial) was designed to compare effectiveness and adverse events of 2 transvaginal apical suspension strategies for uterovaginal prolapse: mesh-augmented hysteropexy and vaginal hysterectomy with suture apical suspension.

Key Points

Question Is there a difference in treatment failure for vaginal mesh hysteropexy vs vaginal hysterectomy with uterosacral ligament suspension in women with uterovaginal prolapse?

Findings In this randomized clinical trial that included 175 postmenopausal women with symptomatic uterovaginal prolapse undergoing surgical intervention, vaginal mesh hysteropexy compared with vaginal hysterectomy with uterosacral ligament suspension resulted in a hazard ratio for a composite measure of treatment failure of 0.62 after 3 years. This was not statistically significant, but the CI was wide and the *P* value was .06.

Meaning Although vaginal mesh hysteropexy did not result in a statistically significantly better outcome compared with vaginal hysterectomy with uterosacral ligament suspension, the wide CI for the treatment effect precludes a definitive conclusion, and further research is needed to assess whether vaginal mesh hysteropexy is more effective than vaginal hysterectomy with uterosacral ligament suspension.

Methods

Study Design and Procedures

This 9-center, randomized, superiority trial, with enrollment from April 2013 to February 2015 and follow-up until February 2018, compared anatomic and functional outcomes in women with uterovaginal prolapse after a vaginal mesh hysteropexy (hysteropexy) or a vaginal hysterectomy with uterosacral ligament vault suspension (hysterectomy). The study was conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development–sponsored Pelvic Floor Disorders Network. The trial design has been published in detail[7] and the protocol and statistical analysis plan can be found in Supplement 1. The senior statistician (D.W.) remained masked through June 13, 2018, before which all substantive revisions to the statistical analysis plan were made. The protocol was approved by an independent data and safety monitoring board assembled by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and institutional review boards at each site. Participants provided written informed consent.

Study Population

Eligible participants included women aged at least 21 years requesting vaginal surgery for symptomatic uterovaginal prolapse beyond the hymen. Participants were amenorrheic for at least 1 year to allow masking, had completed childbearing, and had uterine descent into the lower half of the vagina. Women with prior uterine suspensions, prior synthetic grafts for prolapse repair, or uterine abnormalities were excluded (**Figure 1**). Detailed inclusion and exclusion criteria are provided in Supplement 1. For study generalizability and inclusivity, all races/ethnicities were included; participants self-classified their race/ethnicity with options defined by the investigator.

Randomization

Participants consented to remaining masked to treatment assignment for the study duration unless a medical indication for unmasking was identified. Participants were randomized 1:1 in the operating room with an automated web-based system using permuted blocks with block sizes of 2 or 4 stratified by site.[8] Concomitant native tissue vaginal prolapse repairs, such as anterior or posterior repairs, perineal reconstruction, and full-length mesh midurethral slings for stress urinary incontinence, were permitted.

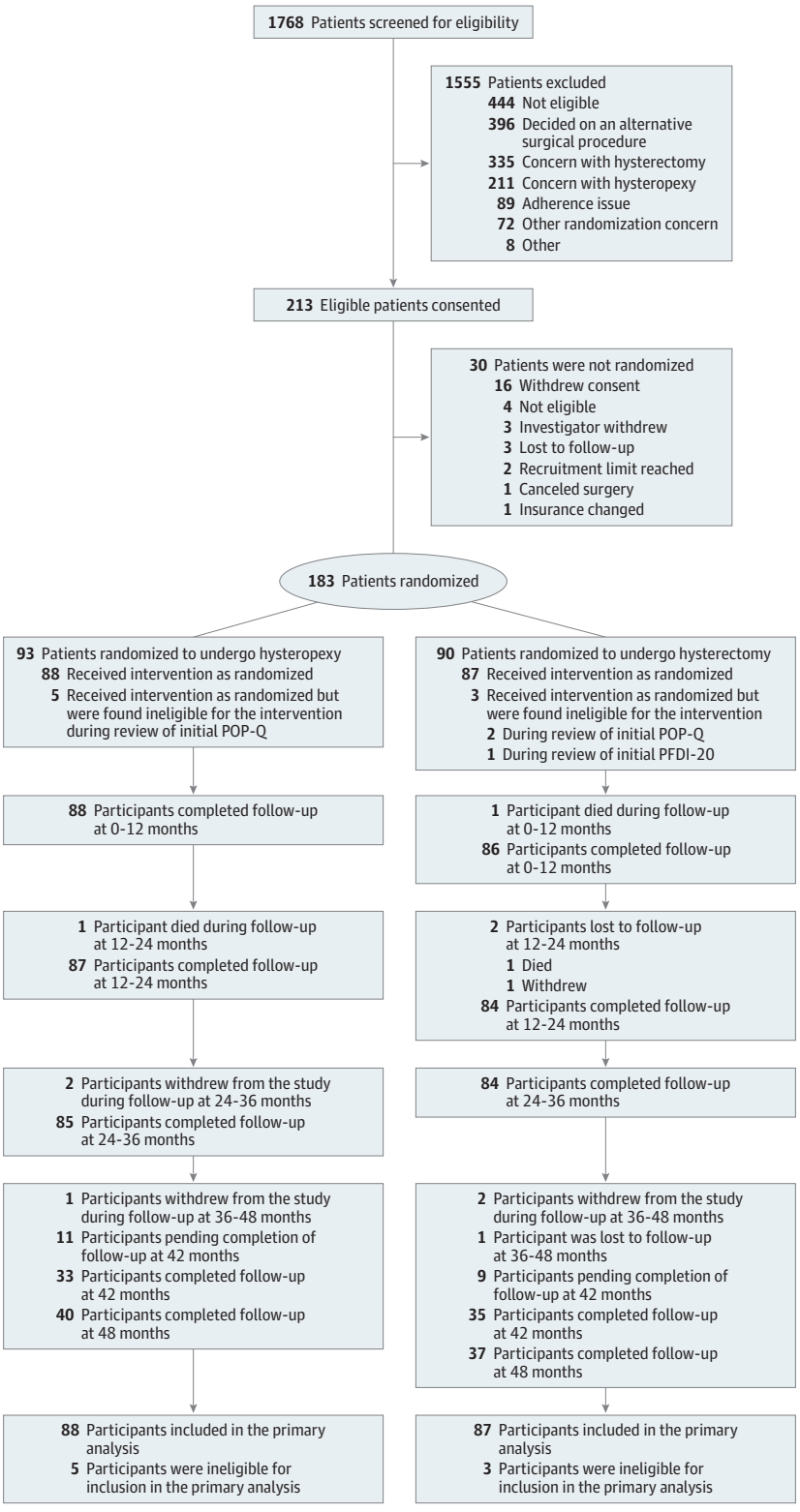
Interventions

Surgeon certification required performance of at least 5 recent procedures of each intervention; surgery standardization can be found in the protocol in Supplement 1. Briefly, hysteropexy was standardized with the Uphold LITE transvaginal mesh support system (Boston Scientific) and the uterosacral ligament suspension required 1 permanent and 1 delayed absorbable suture on each side (eFigures 1 and 2 in Supplement 2).

Outcomes

Operative and perioperative outcomes were captured on prespecified case report forms and included planned and performed concomitant procedures, operative time, estimated blood loss, number and types of sutures used, a Pelvic Organ

Figure 1. Participants in a Study of the Effect of Vaginal Mesh Hysteropexy vs Vaginal Hysterectomy on Treatment Failure in Women With Uterovaginal Prolapse



Perforated colonic diverticulum was the cause of death for the participant lost to follow-up in the hysterectomy group at 0-12 months, lung cancer was the cause of death for the participant in the hysteropexy group during follow-up at 12-24 months, and leukemia was the cause of death for the participant in the hysterectomy group during follow-up at 12-24 months. POP-Q indicates Pelvic Organ Prolapse Quantification; PFDI, Pelvic Floor Distress Inventory.

Prolapse Quantification (POP-Q)[9] examination at the end of the procedure, and an adverse event report form that included anesthesia complications and a comprehensive medical, surgical, and organ injury survey. A hospital stay case report form

included blood transfusions, intensive care unit admissions, postoperative tests, length of catheterization, and a second adverse event survey.

Study visits were conducted at 6-month intervals with all participants, including those who experienced treatment failure and/or re-treatment. Study personnel masked to treatment assignment administered the patient questionnaires and the comprehensive 5-page adverse event survey. The pelvic examination for prolapse assessment, suture, and mesh exposure was performed by a clinician other than the surgeon. At each visit, participants were queried about their knowledge of their treatment allocation.

The primary outcome was a composite measure of treatment failure that included any of the following: (1) re-treatment for prolapse (pessary fitting or surgery); (2) anatomic outcomes, defined as any POP-Q[9] measure beyond the hymen; and (3) symptomatic outcomes, defined as a positive response (and any degree of bother other than "not at all") to the Pelvic Floor Distress Inventory[10] question "Do you usually have a bulge or something falling out that you can see or feel in your vaginal area?"

Secondary outcomes included group differences in operative and perioperative outcomes; individual anatomic measures of the POP-Q examination; and presence, severity, and effect of prolapse, urinary, bowel, and pain symptoms as measured by the Pelvic Floor Distress Inventory,[11] Patient Global Impression of Improvement,[10] Incontinence Severity Index,[12] Pelvic Floor Impact Questionnaire,[11] Functional Activity Scale,[13] and surgical pain and body part pain scales.[14] Sexual function was assessed with the Pelvic Organ Prolapse/Incontinence Sexual Function Questionnaire, IUGA-Revised (PISQ-IR)[15] and body image was assessed using the body image scale.[16,17]

Sample Size Calculation

The study was designed as a superiority trial. The hysterectomy group was assumed to have a failure risk of 20% at 24 months, based on 15% anatomic failure and an additional 5% symptom failure.[18] A 2012 hysteropexy study reported a 2% 12-month anatomic failure risk,[19] which corresponds to a 2-year risk of 4%, assuming a constant hazard. Adding a similar estimated symptom failure suggested that the hysteropexy group would have a 2-year failure risk in the range of 7% to 10%. The corresponding between-group difference in failure risk of 10% to 13% was considered clinically meaningful. The planned 180 participants were originally estimated to provide power of 0.89 to detect a risk difference of 10% (10% failure for the hysteropexy group vs 20% failure for the hysterectomy group) at 2 years, corresponding to a hazard ratio of 0.47 assuming an exponential failure distribution. However, after all participants completed at least 4 years of follow-up, an error was found in the original sample size calculation, and the planned 180 participants actually provided a power of 0.86 to detect a risk difference of 12% (8% failure for the hysteropexy group vs 20% failure for the hysterectomy group) at 2 years (eTable 5 in Supplement 2).

Statistical Analysis

Primary and secondary efficacy analyses were performed on all randomized, eligible patients; safety analyses and secondary sensitivity analyses were performed on all randomized participants. All analyses were based on a statistical analysis plan prepared by a masked statistician with all analytic decisions based on masked data reviews. The analysis was planned to occur when the last participant reached 3 years of follow-up. The significance level for the primary analysis was set at $\alpha = .047$ to account for an interim analysis conducted at $\alpha = .009$ after the last participant reached 2 years of follow-up. Because all analyses other than the primary analysis are considered exploratory or supportive, CIs and *P* values are descriptive with no adjustments for multiple comparisons. Analyses were performed using SAS software, version 9.4 or higher (SAS Institute).

Primary superiority analyses used a proportional hazard survival model to account for interval-censored data and an aggregate time-varying hazard. The piecewise exponential baseline hazard specified 4 constant-hazard periods (0-12 months, 12-24 months, 24-36 months, and >36 months), was determined by masked review of the aggregate survival distribution, and controlled for site consistent with study randomization and prior prolapse surgery per clinical standards. Sensitivity analyses were conducted without covariate adjustment, using nonparametric maximum likelihood estimation,[20] and on the full randomized population with the same proportional hazard model. Individuals who withdrew or were lost to follow-up were treated as randomly censored.

To account for missed visits and early discontinuations, linear and generalized linear mixed models were used to evaluate changes from baseline to 12, 24, and 36 months for secondary continuous and binary outcomes measured longitudinally, with site included in the models as a covariate and visit time treated as a categorical measure. Differences between treatment groups for time-specific measures of composite failure and aggregate binary measures of efficacy and adverse events were assessed with Mantel-Haenszel tests stratified by site, standard χ^2 tests, or Fisher exact tests, while differences in other continuous measures were evaluated with *t* tests.

Results

Study Population, Group Assignments, and Treatment

Between April 2013 and February 2015, 183 women were randomized (93 in the hysteropexy group and 90 in the hysterectomy group) at 9 sites by 34 female pelvic medicine and reconstructive surgery subspecialists. The primary analysis was performed when the last randomized participant reached 3 years of follow-up in February 2018. Eight participants deemed ineligible on masked data review were excluded from the primary analysis. Of the 175 randomized participants eligible for inclusion in the primary analysis, 6 discontinued participation at or prior to 36 months and 153 attended their 36-month visit (Figure 1). Missed 6-month interval follow-up visits through 36 months ranged from 1.2% to 9.5%. Missing data were treated as missing at random. Baseline demographic and clinical characteristics were similar between the groups (**Table 1**).

Concomitant retropubic midurethral slings were performed on 29 of 88 women (33%) in the hysteropexy group and

Table 1. Participant Baseline Characteristics in a Study of the Effect of Vaginal Mesh Hysteropexy vs Vaginal Hysterectomy on Treatment Failure in Women With Uterovaginal Prolapse

Characteristic	Treatment Group, No. (%)[a]	
	Hysteropexy (n = 88)	Hysterectomy (n = 87)
Age, mean (SD), y	65.5 (7.3)	66.2 (7.4)
Race		
White	73 (83)	77 (89)
Black	8 (9)	3 (3)
American Indian/ Alaskan Native	0	4 (5)
Asian	2 (2)	1 (1)
More than 1	0	1 (1)
Other	5 (6)	1 (1)
Hispanic or Latina, No./total (%)	9/85 (11)	7/85 (8)
Marital status		
Married/living with partner	56 (64)	58 (67)
Single	9 (10)	7 (8)
Divorced/separated	16 (18)	13 (15)
Widowed	7 (8)	9 (10)
Education	(n = 86)	(n = 85)
Less than high school	6 (7)	5 (6)
High school/GED	31 (36)	26 (31)
Associate college degree	22 (26)	19 (22)
4-y college degree	16 (19)	20 (24)
Graduate degree	11 (13)	15 (18)
Health insurance		
Medicaid/Medicare	48 (55)	51 (59)
Private	36 (41)	33 (38)
Other	4 (5)	3 (3)
Medical history		
Gravidity, median (IQR)	3 (2-5)	3 (2-4)
Parity, median (IQR)	3 (2-3)	2 (2-3)
BMI, mean (SD)	28.9 (4.0)	28.2 (4.4)
Postmenopausal	86 (98)	85 (98)
History of smoking	22 (25)	21 (24)
Current smoker	3 (3)	1 (1)
Prior stress urinary incontinence surgery	4 (5)	4 (5)
Prior pelvic organ prolapse surgery	5 (6)	4 (5)
Other prior pelvic surgery	42 (48)	43 (49)
Duration of pelvic organ prolapse symptoms, median (IQR), mo	26 (11-56)	33 (12-58)
POP-Q measurement, mean (SD), cm[b]		
Ba	3.3 (2.0)	3.0 (2.2)
Bp	0.4 (3.0)	0.7 (3.0)
C	0.4 (3.5)	0.7 (3.6)
TVL	9.1 (1.1)	9.1 (1.1)
POP-Q stage[c]		
2	15 (17)	19 (22)
3	63 (72)	59 (68)
4	10 (11)	9 (10)
Postvoid residual, mL	(n = 88)	(n = 86)
Median (IQR)	40 (10-80)	30 (7-80)
Patient-reported outcome scores, mean (SD)		
Pelvic Floor Distress Inventory[d]	112.9 (56.9)	109.5 (50.0)
Pelvic Organ Prolapse Distress Inventory[d]	49.1 (23.6)	47.8 (21.0)
Urogenital Distress Inventory[d]	42.5 (26.0)	38.3 (26.5)
Colorectal Anal Distress Inventory[d]	21.3 (21.1)	23.3 (18.3)
Pelvic Floor Impact Questionnaire[e]	57.5 (59.6)	56.8 (58.5)
Pelvic Organ Prolapse Impact Questionnaire[e]	18.7 (24.8)	20.9 (22.0)
Urinary Impact Questionnaire[e]	27.6 (27.2)	22.8 (27.8)
Colorectal Anal Impact Questionnaire[e]	11.2 (20.4)	13.2 (20.8)
Incontinence Severity Index[f]	4.6 (4.2)	3.5 (3.5)
Functional Activity Scale[g]	88.8 (15.1)	87.7 (16.5)
Surgical pain scale[h]	1.8 (2.4)	1.9 (2.3)
Body part pain scale[i]	0.9 (1.1)	0.8 (1.1)
Body image scale[j]	6.4 (6.4)	5.3 (6.0)
PISQ-IR score of sexually active women[k]	(n = 30)	(n = 40)
Mean (SD)	3.0 (0.5)	2.9 (0.4)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GED, general educational development; IQR, interquartile range; ISI, Incontinence Severity Index; PISQ-IR, Pelvic Organ Prolapse/Incontinence Sexual Function Questionnaire, IUGA-Revised; POP-Q, Pelvic Organ Prolapse Quantification; TVL, total vaginal length.

[a] Sample size is 88 for the hysteropexy group and 87 for the hysterectomy group unless otherwise specified.

[b] The TVL from the posterior fornix to the hymen when POP-Q point C is reduced to its full normal position. POP-Q point C represents either the most distal edge of the cervix or the leading edge of the vaginal cuff (hysterectomy scar); point Bp, the most distal position of any part of the upper posterior vaginal wall and has a range of −3.0 cm to TVL; point Ba, the most distal position of any part of the upper anterior vaginal wall and has a range of −3.0 cm to TVL. Patients without pelvic organ prolapse have negative values. See eFigure 3 in Supplement 2 for additional information.

[c] POP-Q stage 2 indicates that the vagina is prolapsed between 1 cm above and 1 cm below the hymen; stage 3, the vagina is prolapsed more than 1 cm beyond the hymen but is not everted within 2 cm of its length; stage 4, the vagina is everted to within 2 cm of its length.

[d] The Pelvic Floor Distress Inventory score ranges from 0 (least distress) to 300 (most distress) and is a sum of the 3 subscale scores (Pelvic Organ Prolapse Distress Inventory, Urogenital Distress Inventory, and Colorectal Anal Distress Inventory), each ranging from 0 (least distress) to 100 (most distress).

[e] The Pelvic Floor Impact Questionnaire score ranges from 0 (least impact) to 300 (most adverse impact) and is a sum of 3 subscale scores (Pelvic Organ Prolapse Impact Questionnaire, Urinary Impact Questionnaire, and Colorectal Anal Impact Questionnaire), each ranging from 0 (least impact) to 100 (most adverse impact). A midrange score for these subscales implies bother from prolapse, urinary incontinence, or fecal incontinence.

[f] The ISI score ranges from 0 (no incontinence) to 12 (severe incontinence) and is a product of the frequency and volume of urine loss; a person losing small splashes of urine a few times per week would score a 6.

[g] The Functional Activity Scale score ranges from 0 to 100, with higher values indicating better functional activity. Patients who underwent surgical hernia repair with independent daily living and no comorbidities have a mean value of 80.[13]

[h] The surgical pain scale score for pain within the past 24 hours during normal activities ranges from 0 (no pain) to 10 (most intense pain).

[i] The body part pain scale score for mean pain in 7 different body areas within the last 24 hours ranges from 0 (no pain) to 10 (most intense pain).

[j] The body image scale score ranges from 0 (no symptoms/distress) to 24 (severe symptoms/distress). A mean score of 8 is typical in patients with cancer.[16]

[k] PISQ-IR mean score ranges from 1 (worse sexual experience) to 5 (better sexual experience). Midrange scores are common in women with pelvic floor disorders.[21]

31 of 87 (36%) in the hysterectomy group (difference, −0.03; [95% CI, −0.17 to 0.11]) (eTable 1 in Supplement 2). Concomitant transobturator midurethral slings were performed on 12 of 88 women (14%) in the hysteropexy group and 13 of 87 (15%) in the hysterectomy group (difference, −0.01; [95% CI, −0.12 to 0.09]) (eTable 1 in Supplement 2). Anterior repair was more commonly performed on women in the hysteropexy group (79 of 88 [90%]) than in the hysterectomy group (62 of 87 [71%]) (difference, 0.19 [95% CI, 0.07-0.30]; $P = .002$). Mean (SD) operative time was lower in the hysteropexy group compared with the hysterectomy group (111.5 [39.7] min vs 156.7 [43.9] min; difference, −45.2 [95% CI, −57.7 to −32.7]; $P < .001$) (**Table 2**).

Primary Outcome

No statistically significant difference in failure risk was demonstrated for the composite primary outcome between groups; the adjusted hazard ratio of failure for hysteropexy vs hysterectomy was 0.62 ([95% CI, 0.38-1.02]; $P = .06$) (**Figure 2**). At 36 months, the model-estimated failure was 26% (95% CI, 15%-35%) for the hysteropexy group and 38% (95% CI, 25%-49%) for the hysterectomy group (Figure 2). Sensitivity analyses with nonparametric approaches, without covariate adjustment, and based on the full population yielded similar results (eFigures 4 and 5 in Supplement 2). The proportional hazards assumption was violated when tested with a treatment × time interaction ($P < .001$). Graphical assessment (eFigure 6 in Supplement 2) indicated that the smoothed failure hazard rate in the hysterectomy group was higher than in the hysteropexy group, except from approximately 18 to 30 months, during which the rates were similar. Therefore, the hazard ratio should be interpreted as an average relative risk across time rather than a relative risk applicable at all times.

Cumulative failures, noncumulative failure status, and failure categories at 12, 24, and 36 months are shown in **Table 3**. Failure rates based on status at attended visits for both groups are lower than that obtained from the survival (cumulative) models that assumed permanent failure. For example, the 36-month discrete time point failure rate for hysteropexy was 21% compared with 26% estimated from the covariate-adjusted survival model (33% observed); the failure rate for the hysterectomy group was 27% compared with 38% estimated from the adjusted survival model (42% observed). The majority of failures were either anatomic or anatomic and symptomatic, with few symptom-only failures.

Secondary Outcomes

Secondary outcomes at 36 months are shown in Table 2. Mean (SD) postoperative anterior wall support (measured via POP-Q point Ba) was better in the hysteropexy vs hysterectomy group at 36 months (−1.2 [1.4] cm vs −0.7 [1.5] cm; difference, −0.5 [95% CI, −0.9 to 0.0]; $P = .05$) and mean (SD) total vaginal length was longer in the hysteropexy vs hysterectomy group (8.5 [1.1] cm vs 7.7 [1.2] cm; difference, 0.7 [95% CI, 0.4-1.1]; $P < .001$). Ninety percent of participants in the hysteropexy group and 89% in the hysterectomy group reported "much better" or "very much better" improvement on the Patient Global Impression of Improvement at 36 months (risk difference, 0.00 [95% CI, −0.09 to 0.10]; $P = .93$) and no between-group differences were demonstrated in patient-reported surgical pain, pelvic pain, or body image.

Seventy of 175 women (40%) were sexually active before surgery (eTable 3 in Supplement 2). Sexual function among the sexually active women, measured by the PISQ-IR total score, improved by an adjusted mean of 0.3 points (95% CI, 0.1-0.5) after surgery for both groups (adjusted mean difference, 0.00 [95% CI, −0.2 to 0.3]; $P = .84$) (Table 2). Dyspareunia prevalence rates among sexually active women decreased from 10 of 26 women (38%) to 5 of 26 (19%) in the hysteropexy group and 17 of 37 (46%) to 5 of 31 (16%) in the hysterectomy group (eTable 3 in Supplement 2). Any postoperative dyspareunia identified by specific complications or adverse events and the systematic collection of open-ended adverse events throughout the course of the trial occurred in 9 of 93 participants (10%) in the hysteropexy group and 2 of 90 (2%) in the hysterectomy group (risk difference, 0.07 [95% CI, 0.01-0.14]; $P = .03$). De novo dyspareunia as measured by the PISQ-IR was only recorded in 3 women in the hysterectomy group and 2 in the hysteropexy group (Table 2).

At 36 months, 131 of 173 women (75%) reported that they remained masked to their treatment, with no difference in masking between groups (risk difference, 0.05 [95% CI, −0.08 to 0.18]; $P = .46$) (Table 2). Of participants who stated that they knew their treatment group, 26 of 30 (87%) were correct, with no evidence of a between-group difference (risk difference, −0.17 [95% CI, −0.47 to 0.10]; $P = .29$). The most common sources of unmasking were insurance paperwork, imaging studies, and conversations with physicians not involved in the study.

Adverse Events

Ureteral "kinking" (7%) and midurethral sling mesh exposures (5%) were only observed in the hysterectomy group (Table 2). The hysteropexy group had an 8% mesh exposure rate. Based on observations starting 12 weeks after the surgical procedure, granulation tissue and permanent suture exposure were less common in the hysteropexy group than the hysterectomy group (granulation tissue: 1% vs 11%; permanent suture exposure: 3% vs 21%). No mesh exposures, granulation tissue, or suture exposures required reoperation. No patients in the hysteropexy group developed any significant uterine pathology during the 3 years of follow-up. The most common other adverse events for all 183 participants during the 3 to 4 years of follow-up were urinary tract infections, stress urinary incontinence, urgency incontinence, and constipation, with no evidence of between-group differences (eTable 4 in Supplement 2).

Discussion

Among women with symptomatic uterovaginal prolapse undergoing vaginal surgery, vaginal mesh hysteropexy compared with vaginal hysterectomy with uterosacral ligament suspension did not result in a significantly lower rate of the composite prolapse outcome after 3 years. However, because

Table 2. Secondary Outcomes in a Study of the Effect of Vaginal Mesh Hysteropexy vs Vaginal Hysterectomy on Treatment Failure in Women With Uterovaginal Prolapse

Outcome	Hysteropexy (n = 88)	Hysterectomy (n = 87)	Risk/Mean Difference (95% CI)[a]	*P* Value[a]
Physical Examination at 36 Months				
Pelvic Organ Prolapse Quantification measurements, mean (SD)[b]	(n = 78)	(n = 74)		
Ba	−1.2 (1.4)	−0.7 (1.5)	−0.5 (−0.9 to 0.0)	.05
Bp	−1.7 (1.5)	−1.8 (1.3)	0.0 (−0.4 to 0.5)	.84
C	−5.7 (2.3)	−5.8 (1.9)	0.1 (−0.6 to 0.8)	.74
TVL	8.5 (1.1)	7.7 (1.2)	0.7 (0.4 to 1.1)	<.001
POP-Q point C <−0.5 × TVL, No./total (%)	69/78 (88)	68/74 (92)	−3 (−13 to 6)	.48
Perioperative Outcomes				
Operative time, min	(n = 88)	(n = 87)		
Mean (SD)	111.5 (39.7)	156.7 (43.9)	−45.2 (−57.7 to −32.7)	<.001
Catheterization days	(n = 87)	(n = 85)		
Median (IQR)	1 (1-3)	1 (1-3)		.54
Ureteral kink recognized intraoperatively, No./total (%)	0/88	6/87 (7)	−7 (−15 to −2)	.01
Postoperative Complications				
Hysteropexy mesh exposure[c]				
No./total (%)	7/88 (8)			
Binomial, 95% CI, %[d]	3.3 to 15.7			
Midurethral sling mesh exposure, No./total (%)[c]	0/41	2/44 (5)	−5 (−15 to 5)	.49
After 12 wk, No./total (%)[c]				
Excessive granulation tissue	1/88 (1)	10/87 (11)	−10 (−17 to −3)	.005
Suture exposure	3/88 (3)	18/87 (21)	−17 (−27 to −8)	<.001
Patient-Reported Outcomes at 36 mo[e]				
PGII [much better or very much better], No./total (%)[f]	70/78 (90)	67/75 (89)	0 (−9 to 10)	.93
Pelvic Floor Distress Inventory[g]	(n = 78)	(n = 75)		
Adjusted mean (95% CI)	−79.8 (−91.7 to −67.8)	−80.1 (−92.3 to −67.8)	0.3 (−16.3 to 16.9)	.97
POPDI[g]	(n = 78)	(n = 75)		
Adjusted mean (95% CI)	−40.1 (−45.2 to −35.0)	−40.2 (−45.5 to −35.0)	0.1 (−7.0 to 7.2)	.98
Urogenital Distress Inventory[g]	(n = 78)	(n = 75)		
Adjusted mean (95% CI)	−28.3 (−34.2 to −22.4)	−28.2 (−34.3 to −22.2)	−0.0 (−8.2 to 8.2)	>.99
CRADI[g]	(n = 78)	(n = 75)		
Adjusted mean (95% CI)	−11.4 (−15.6 to −7.2)	−11.6 (−15.9 to −7.2)	0.2 (−5.7 to 6.1)	.95
PFIQ[g]	(n = 78)	(n = 75)		
Adjusted mean (95% CI)	−43.4 (−54.6 to −32.2)	−50.4 (−61.9 to −38.8)	7.0 (−8.6 to 22.5)	.38
POPIQ[g]	(n = 78)	(n = 45)		
No.	78	74		
Adjusted mean (95% CI)	−16.0 (−21.0 to −11.1)	−19.9 (−25.0 to −14.8)	3.9 (−3.0 to 10.7)	.27
Urinary Impact Questionnaire[g]	(n = 78)	(n = 75)		
Adjusted mean (95% CI)	−21.3 (−26.3 to −16.2)	−20.6 (−25.8 to −15.4)	−0.6 (−7.7 to 6.4)	.86
CRAIQ[g]	(n = 78)	(n = 74)		
Adjusted mean (95% CI)	−6.1 (−10.3 to −1.9)	−9.8 (−14.1 to −5.5)	3.7 (−2.1 to 9.6)	.21
Incontinence Survey Index[g]	(n = 78)	(n = 75)		
Adjusted mean (95% CI)	−1.9 (−2.7 to −1.1)	−1.6 (−2.5 to −0.8)	−0.3 (−1.4 to 0.8)	.60
New or worsening stress urinary incontinence, No./total (%)[c]	18/88 (20)	12/87 (14)	7 (−4 to 18)	.24
New or worsening urgency urinary incontinence, No./total (%)[c]	21/88 (24)	14/87 (16)	8 (−4 to 20)	.20
New or worsening fecal incontinence, No./total (%), %[c]	13/88 (15)	6/87 (7)	8 (−1 to 17)	.09
Functional Activity Scale[g]	(n = 78)	(n = 75)		
Adjusted mean (95% CI)[g]	5.6 (2.8 to 8.5)	4.8 (1.9 to 7.7)	0.8 (−3.1 to 4.8)	.68

(continued)

Table 2. Secondary Outcomes in a Study of the Effect of Vaginal Mesh Hysteropexy vs Vaginal Hysterectomy on Treatment Failure in Women With Uterovaginal Prolapse (continued)

Outcome	Hysteropexy (n = 88)	Hysterectomy (n = 87)	Risk/Mean Difference (95% CI)[a]	*P* Value[a]
SPS-rest[g]	(n = 78)	(n = 75)		
Adjusted mean (95% CI)	−0.5 (−1.0 to −0.1)	−0.6 (−1.1 to −0.2)	0.1 (−0.5 to 0.7)	.77
SPS-normal[g]	(n = 78)	(n = 75)		
Adjusted mean (95% CI)	−0.7 (−1.2 to −0.2)	−0.7 (−1.2 to −0.2)	−0.0 (−0.7 to 0.6)	.97
SPS-exercise[g]	(n = 31)	(n = 29)		
Adjusted mean (95% CI)	−1.2 (−2.0 to −0.5)	−0.9 (−1.7 to −0.1)	−0.4 (−1.5 to 0.7)	.50
SPS-worst[g]	(n = 75)	(n = 74)		
Adjusted mean (95% CI)	−0.8 (−1.4 to −0.3)	−0.5 (−1.1 to 0.0)	−0.3 (−1.1 to 0.5)	.47
Body part pain scale score[g]	(n = 78)	(n = 75)		
Adjusted mean (95% CI)	−0.5 (−0.7 to −0.3)	−0.3 (−0.5 to −0.1)	−0.2 (−0.5 to 0.1)	.19
Pelvic pain, No./total (%)[h]	6/88 (7)	9/87 (10)	−4 (−12 to 5)	.40
All treated participants	6/93 (6)	9/90 (10)	−4 (−12 to 4)	.38
Daily	3/88 (3)	4/87 (5)	−1 (−8 to 6)	.72
Body image scale score[g]	(n = 77)	(n = 75)		
Adjusted mean (95% CI)	−4.9 (−6.1 to −3.7)	−3.8 (−5.0 to −2.6)	−1.1 (−2.7 to 0.6)	.20
Sexual Function and Dyspareunia at 36 Months				
PISQ-IR change from baseline of sexually active[g]	(n = 23)	(n = 27)		
Adjusted mean (95% CI)	0.3 (0.1 to 0.5)	0.3 (0.1 to 0.5)	0.0 (−0.2 to 0.3)	.84
Dyspareunia, No./total (%)[i]				
All treated participants	9/93 (10)	2/90 (2)	7 (1 to 14)	.03
Sexually active with de novo dyspareunia (PISQ-IR)	0/19	1/25 (4)	−4 (−21 to 14)	>.99
Not sexually active with de novo dyspareunia (PISQ-IR)	2/38 (5)	2/27 (7)	−2 (−20 to 12)	>.99
Evaluation of Masking at 36 Months, No./Total (%)				
Remained masked at 36 mo	68/88 (77)	63/87 (72)	5 (−8 to 18)	.46
Correctly stated what procedure they underwent[j]	10/13 (77)	16/17 (94)	−17 (−47 to 10)	.29

Abbreviations: CRADI, Colorectal Anal Distress Inventory; CRAIQ, Colorectal Anal Impact Questionnaire; PFIQ, Pelvic Floor Impact Questionnaire; PGII, Patient Global Impression of Improvement; PISQ-IR, Pelvic Organ Prolapse/Incontinence Sexual Questionnaire, IUGA Revised; POPDI, Pelvic Organ Prolapse Distress Inventory; POPIQ, Pelvic Organ Prolapse Impact Questionnaire; POP-Q, Pelvic Organ Prolapse Quantification; SPS, surgical pain scale.

[a] Unless otherwise specified, mean differences, 95% CIs, and *P* values are unadjusted and based on *t* tests for normally distributed continuous outcomes, and *P* values for nonnormal continuous outcomes (summarized with medians) are from Wilcoxon Rank Sum tests. Unless otherwise specified, risk differences, 95% CIs, and *P* values are unadjusted and based on Mantel-Haenszel estimates for the risk difference with Wald-type CIs for nominal categorical measures with expected cell counts >5, otherwise the exact risk difference and 95% CI limits are obtained by exact methods based on the score statistic based on Chan and Zhang[22] and the *P* values are from Fisher exact tests.

[b] For definitions of the Pelvic Organ Prolapse Quantification measurements, refer to footnote b in Table 1.

[c] Mesh exposure, excessive granulation tissue, suture exposure, new or worsening stress urinary incontinence, urgency urinary incontinence, and fecal incontinence are identified based on specific complications/adverse events collected at follow-up visits at 6 months through 5 years and the systematic collection of open-ended adverse events throughout the trial.

[d] Binomial 95% CIs for proportions are based on the exact Clopper-Pearson method.

[e] The PGII score ranges from 1 (very much better) to 7 (very much worse) and has been dichotomized as better (≤2) or worse (>2). Refer to Table 1 footnotes for ranges and clinical interpretation of the other patient-reported measures.

[f] Adjusted risk differences, 95% CIs, and *P* values comparing the proportions of binary outcomes of the groups was planned to be obtained from generalized linear models with identity link adjusted for site, intervention, visit, and interaction between intervention and visit, while modeling the within-participant correlations across visits as autoregressive order 1. This specified adjusted model did not converge for the binary PGII response ("much better" or "very much better" improvement), and unadjusted risk difference at 36 months was obtained.

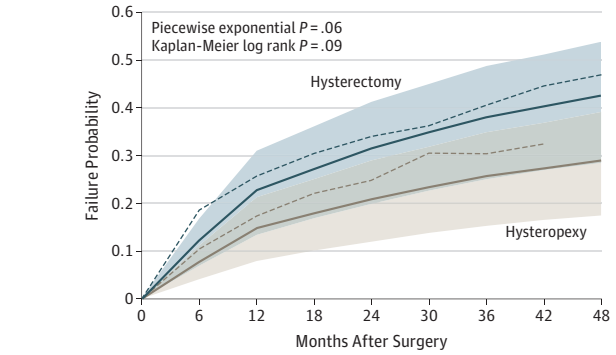
[g] Adjusted means, mean difference, 95% CIs, and *P* values comparing the change from baseline of continuous outcomes of the intervention groups are obtained from general linear models adjusted for site, intervention, visit, and interaction between intervention and visit, while modeling the within-participant correlations across visits with an auto-regressive order 1. The n shown is for month 36; however, models were fitted using all participants with at least 1 postbaseline visit.

[h] Pelvic pain and daily pelvic pain occurring at least 12 weeks after surgical intervention are identified based on both specific complications/adverse events collected at follow-up visits at 6 months through 5 years and the systematic collection of open-ended adverse events throughout the trial.

[i] Dyspareunia is identified based on specific complications/adverse events collected at 6-month through 5-year follow-up visits and the systematic collection of open-ended adverse events throughout the course of the trial. Sexually active with de novo dyspareunia (response of "usually" or "always have" in response to the PISQ-IR question, "Do you have pain during sexual intercourse?") is defined as women who were sexually active at baseline and at 3 years experiencing pain during sexual intercourse only at 3 years. Not sexually active with de novo dyspareunia (PISQ-IR response of "strongly agree" or "somewhat agree") is defined as women who were not sexually active at baseline due to reasons other than fear of pain during sexual intercourse and became sexually inactive at 3 years due to fear of pain during sexual intercourse.

[j] Of the 24 women in the hysterectomy group and 20 in the hysteropexy group who reported they had become unmasked, 7 in each group did not provide a guess as to what procedure they underwent.

Figure 2. Failure Probability for the Composite Primary Outcome Comparing Hysteropexy With Hysterectomy in Women With Uterovaginal Prolapse



No. at risk

Hysterectomy	87	69	59	53	14
Hysteropexy	88	77	66	54	24

Failure probability from survival analysis excluding the 8 ineligible participants was conducted using an interval-censored proportional hazard model with an assumed baseline piecewise exponential hazard with 4 constant hazard periods: (0-12 months, 12-24 months, 24-36 months, and >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 (7 in the hysteropexy group and 3 in the hysterectomy group), 50 participants were censored between 36 and 48 months (27 in the hysteropexy group and 23 in the hysterectomy group), and 50 were censored at or beyond 48 months (27 in the hysteropexy group and 23 in the hysterectomy group). The median (IQR) follow-up time was 36.0 (18.0-48.0) months for the hysteropexy group and 36.0 (9.0-48.0) for the hysterectomy group. The hazard rate in the hysteropexy group (incidence density per person-year) in year 1 was 0.16; year 2, 0.07; year 3, 0.06; and beyond 3 years, 0.05. In the hysterectomy group, the hazard rate in year 1 was 0.26; year 2, 0.12; year 3, 0.10; and beyond 3 years, 0.08. The failure probability from the sensitivity nonparametric interval-censored Kaplan-Meier analysis is represented by the dotted lines.[23] The solid lines represent the piecewise exponential model and the 95% CI for the piecewise exponential model is shown by the blue shaded area for the hysterectomy group and the tan shaded area for the hysteropexy group.

the point estimate favored hysteropexy with a CI that was wide and only slightly crossed the null value, the remaining uncertainty is too great to either establish benefit or to rule out the originally hypothesized magnitude of treatment effect. While small differences in anterior prolapse measures and increased vaginal length favored the mesh hysteropexy group, these did not result in differences in patient-reported outcome measures. Higher anterior repair rates in the hysteropexy group may account for the small improvements observed in anterior prolapse support. The mesh exposure rate of 8% was higher than previously reported for this hysteropexy technique,[19,25] but congruent with rates reported after vaginal surgery augmented with mesh.[26,27] No exposures required surgical intervention.

Both groups reported improvements in sexual function, and dyspareunia and pain and de novo dyspareunia rates were low. All other complications with long-term sequelae were not different between groups.

While commonly performed at the time of a surgical procedure for prolapse, hysterectomy is performed to allow exposure to supporting ligaments, while possibly increasing morbidity, such as infection and bleeding.[28] The mean operative time in the hysterectomy group was 45 minutes longer than in the hysteropexy group, implying increased risk and cost of this approach to prolapse repair for unknown benefit. The findings are consistent with a 2018 systematic review of hysteropexy vs hysterectomy for prolapse repair in which hysteropexy was favored in the short term for decreased blood loss, shorter operative times, and similar anatomic outcomes.[29] None of the trials compared mesh hysteropexy with hysterectomy with uterosacral ligament suspension, and randomized trials involving suture hysteropexy and vaginal hysterectomy have at most 12 months of follow-up.[29-32]

The current trial provides new information for failure rate ascertainment. The finding that failure rates were higher with a cumulative survival approach than at discrete time points suggests that participants migrate across categorical definitions of success and failure and questions the appropriateness of the assumption that with prolapse surgery, "once a failure, always a failure." The dynamic aspect of prolapse is supported by previous anatomic studies and should be considered in future studies.[33] Failure rates for mesh hysteropexy in the current study were generally higher than anticipated and higher than those reported in previous cohort studies with shorter follow-up and less rigor in evaluation and failure definition.[19,25,34] Failure rates in this study are consistent with the literature on native tissue vaginal prolapse repair.[18] The differences between the anticipated failure rates and the failure rates in this study are attributable to the minimal literature on hysteropexy outcomes when this study was designed, the cumulative survival approach, the longer duration of follow-up, and the rigor of the outcome evaluation.

In 2016, the US Food and Drug Administration (FDA) reclassified transvaginal mesh for prolapse repair to a class III device and required postmarket surveillance studies. In February 2019, an FDA advisory panel concluded that to support a favorable benefit/risk, surgical mesh for transvaginal prolapse repair should be superior to native tissue repair at 36 months.[35] In April 2019, the FDA announced that superiority had not been demonstrated in the studies available at that time, and that manufacturers would no longer be permitted to market transvaginal mesh kits for repair of anterior/apical compartment prolapse.[6] Patients in the current study are being followed up for 60 months and the results and conclusions at 36 months could change with extended follow-up.

Trial strengths include the randomized design, masked participants, validated anatomic and patient-reported outcomes, and standardized adverse outcome collection. Three years constitutes the longest duration of follow-up available for a randomized clinical trial comparing mesh hysteropexy with vaginal hysterectomy with uterosacral ligament prolapse repair. Seventy-five percent of women remained masked to their study procedure, and all patient-reported outcome evaluators were masked to surgical intervention. Because participants or their evaluators may have certain beliefs about the presence or absence of a uterus, and because vaginal mesh is controversial, masking decreased potential biases related to

Table 3. Categorization of Participants by Failure Categories at 12, 24, and 36 Months in a Study of the Effect of Vaginal Mesh Hysteropexy vs Vaginal Hysterectomy Among Women With Uterovaginal Prolapse

Failure Outcomes	No. (%)		Risk Difference, % (95% CI)[a]
	Hysteropexy (n = 88)[a]	Hysterectomy (n = 87)[a]	
Cumulative Failures (Time-to-Event)[b]			
12-mo visit	(n = 88)	(n = 86)	
Failure, No./total (%)[b]	15/86 (17)	22/85 (26)	−8 (−21 to 4)
Initial failure type			
Re-treatment	0	1 (1)	
Anatomic and symptom failure	5 (6)	2 (2)	
Anatomic failure only	9 (10)	17 (20)	
Symptom failure only	1 (1)	2 (2)	
24-mo visit[b]	(n = 87)	(n = 85)	
Failure, No./total (%)[b]	21/80 (26)	29/83 (35)	−9 (−24 to 5)
Initial failure type			
Retreatment	0	1 (1)	
Anatomic and symptom failure	7 (9)	3 (4)	
Anatomic failure only	12 (15)	21 (25)	
Symptom failure only	2 (3)	4 (5)	
36-mo visit[b]	(n = 86)	(n = 85)	
Failure, No./total (%)[b]	26/79 (33)	34/81 (42)	−9 (−24 to 6)
Initial failure type			
Re-treatment	0	1 (1)	
Anatomic and symptom failure	9 (11)	6 (7)	
Anatomic failure only	14 (18)	23 (28)	
Symptom failure only	3 (4)	4 (5)	
At-Visit Failures			
12-mo visit[c]	(n = 88)	(n = 86)	
Failure, No./total (%)[b]	12/86 (14)	19/84 (23)	−9 (−21 to 3)
At-visit failure type			
Re-treatment	2 (2)	2 (2)	
Anatomic and symptom failure	3 (3)	4 (5)	
Anatomic failure only	6 (7)	11 (13)	
Symptom failure only	1 (1)	2 (2)	
24-mo visit[c]	(n = 87)	(n = 84)	
Failure, No./total (%)[b]	15/79 (19)	17/80 (21)	−3 (−16 to 10)
At-visit failure type			
Re-treatment	5 (6)	6 (8)	
Anatomic and symptom failure	1 (1)	3 (4)	
Anatomic failure only	7 (9)	6 (8)	
Symptom failure only	2 (3)	2 (3)	
36-mo visit[c]	(n = 85)	(n = 84)	
Failure, No./total (%)[b]	16/78 (21)	21/78 (27)	−6 (−19 to 7)
At-visit failure type			
Re-treatment	5 (6)	9 (12)	
Anatomic and symptom failure	4 (5)	1 (1)	
Anatomic failure only	7 (9)	10 (13)	
Symptom failure only	0	1 (1)	

[a] All missing data were considered to be missing completely at random and were excluded from both the numerator and denominator in the calculation of estimates and CIs. Point estimates and 95% CIs for risk difference in surgical failures between the treatment groups are based on Mantel-Haenszel estimates for the common risk difference stratified by site with Wald-type CIs with the estimate of the variance of the risk difference based on Sato.[24]

[b] Under the permanent failure state assumption, the number of participants at each visit includes all participants who were still participating in the study or had a failure outcome prior to withdrawal. The denominator for the cumulative failure at each visit includes all participants who were still participating in the study and attended the visit or had any failure outcome prior their withdrawal/missed visit. The failure type corresponding to the first failure time is shown, where the 4 failure types are mutually exclusive, with re-treatment failure prioritized above the anatomic and/or symptomatic failure types.

[c] Under the transient failure state assumption, the number of participants at each visit includes all participants who were still participating in the study. The denominator for the transient failures at each visit includes all participants who were still participating in the study and attended the visit or who missed the visit but had a re-treatment failure prior to their missed visit. The failure type corresponding to the failure at each time point is shown, where the 4 failure types are mutually exclusive, with re-treatment failure prioritized above the anatomic and/or symptomatic failure types and assumed to be a permanent state at all subsequent visits irrespective of the participant's attendance at the visit as long as the participant was still participating in the study. Anatomic and symptom failure components are considered to be transient conditions, and with outcomes at each time point based specifically on measurements obtained at that time point.

hysterectomy or mesh and participants were potentially less likely to be influenced by anti-mesh advertisements.

Limitations

This study has several limitations. First, generalizability may be limited because many women had preconceived ideas regarding hysterectomy, mesh, or randomization to a procedure that they would be masked from knowing and declined to participate. Second, to allow masking, the study was restricted to postmenopausal women, and only 70 of 175 participants (40%) were sexually active before surgery, limiting the ability to evaluate postoperative sexual function and

dyspareunia. Pain and dyspareunia rates could be different in younger patients. Third, all surgeons were female pelvic medicine and reconstructive surgery subspecialists with extensive surgical experience and results may not be generalizable to surgical procedures performed by nonsubspecialists or those without similar training. Fourth, 25% of participants were unmasked, which could have produced some potential bias in patient-reported secondary outcomes. Fifth, because the proportional hazard assumption was violated, the hazard ratio must be interpreted as an average relative risk across time rather than a relative risk applicable at each time.

Conclusions

Among women with symptomatic uterovaginal prolapse undergoing vaginal surgery, vaginal mesh hysteropexy compared with vaginal hysterectomy with uterosacral ligament suspension did not result in a significantly lower rate of the composite prolapse outcome after 3 years. However, imprecision in the study results precludes a definitive conclusion, and further research is needed to assess whether vaginal mesh hysteropexy is more effective than vaginal hysterectomy with uterosacral ligament suspension.

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