Original Research

Transvaginal Mesh Compared With Native Tissue Repair for Pelvic Organ Prolapse

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OBJECTIVE: To compare the safety and effectiveness of transvaginal mesh repair and native tissue repair, in response to a U.S. Food and Drug Administration (FDA) 522 study order to assess co-primary endpoints of superiority and noninferiority.

METHODS: This was a prospective, nonrandomized, parallel cohort, multi-center trial comparing transvaginal mesh with native tissue repair for the treatment of pelvic organ prolapse. The primary endpoints were composite treatment success at 36 months comprised of anatomical success (defined as pelvic organ prolapse quantification [POP-Q] point Ba≤0 and/or C≤0), subjective success (vaginal bulging per the PFDI-20 [Pelvic Floor Distress Inventory]), and retreatment measures, as well as rates of serious device-related or serious procedure-related adverse events. Secondary endpoints included a composite outcome similar to the primary composite outcome but with anatomical success defined as POP-Q point Ba<0 and/or C<0, quality-of-life measures, mesh exposure and mesh- and procedure-related complications. Propensity score stratification was applied.

RESULTS: Primary endpoint composite success at 36 months was 89.3% (201/225) for transvaginal mesh and 80.2% (389/485) for native tissue repair, demonstrating noninferiority at the preset margin of 12% (propensity score–adjusted treatment difference 6.5%, 90% CI −0.2% to 13.2%). Using the primary composite endpoint, transvaginal mesh was not superior to native tissue repair (*P*=.056). Using the secondary composite endpoint, superiority of transvaginal mesh over native tissue repair was noted (*P*=.009), with a propensity score–adjusted difference of 10.6% (90% CI 3.3–17.9%) in favor of

See related editorial on page 973.

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transvaginal mesh. Subjective success for both the primary and secondary endpoint was 92.4% for transvaginal mesh, 92.8% for native tissue repair, a propensity score–adjusted difference of −4.3% (CI −12.3% to 3.8%). For the primary safety endpoint, 3.1% (7/225) of patients in the transvaginal mesh (TVM) group and 2.7% (13/485) of patients in the native tissue repair (NTR) group developed serious adverse events, demonstrating that transvaginal mesh was noninferior to native tissue repair (−0.4%, 90% CI −2.7% to 1.9%). Overall device-related and/or procedure-related adverse event rates were 35.1% (79/225) in the TVM group and 46.4% (225/485) in the NTR group (−15.7%, 95% CI −24.0% to −7.5%).

CONCLUSION: Transvaginal mesh repair for the treatment of anterior and/or apical vaginal prolapse was not superior to native tissue repair at 36 months. Subjective success, an important consideration from the patient-experience perspective, was high and not statistically different between groups. Transvaginal mesh repair was as safe as native tissue repair with respect to serious device-related and/or serious procedure-related adverse events.

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Pelvic organ prolapse (POP) affects 3–6% of women based on symptoms and up to 50% of women based on vaginal examination.[1] Pelvic organ prolapse negatively affects quality of life (QOL) and mental health.[2] Symptoms include bothersome vaginal bulge sensation, difficulty voiding, obstructed defecation, urinary incontinence, fecal incontinence, and sexual dysfunction. The most common site of POP is the anterior vaginal wall.[1]

Many women will fail conservative management (eg, pelvic floor muscle training, pessaries) or desire more definitive treatment; the lifetime likelihood of undergoing surgery for POP in women ranges between 6% and 18%.[1] Unfortunately, recurrence rates are reported to be close to 40% after native tissue repair, with the anterior compartment being the most common site of recurrence (approximately 13%).[3,4] Some studies of mesh augmented repairs have been shown to have better subjective and objective outcomes than native tissue repair in the anterior compartment[5–9]; however, other studies have found higher complications with transvaginal mesh, such as mesh exposure and dyspareunia.[7] Many of the meshes used in these trials were larger and denser than the newer generation of transvaginal mesh. Randomized controlled trials have reported low mesh exposure rates with even lower reoperation rates of 6% or lower.[5,10]

After a 2011 panel to investigate concerns over potential complications associated with transvaginal mesh, the U.S. Food and Drug Administration (FDA) issued 522 postmarket surveillance study orders for companies that market transvaginal mesh devices for treatment of POP.[11] This study was designed in accordance with recommendations from the 2011 FDA panel. The objective was to compare the long-term safety and effectiveness of transvaginal mesh to native tissue repair over 36 months in women surgically treated for anterior and/or apical POP.

METHODS

In this postmarket prospective, nonrandomized, parallel cohort, multi-center trial (27 sites), patients received transvaginal mesh (Uphold LITE) or native tissue repair for surgical treatment of symptomatic POP. Patients in the native tissue repair (NTR) group were identified from a pool of shared controls from the Uphold LITE 522 study and the American Urogynecologic Society (AUGS) Pelvic Floor Disorders Registry (Appendix 1, available online at http://links.lww.com/AOG/C707). Study centers were chosen by the sponsor and enrolled patients in one arm of the study. Written institutional review board approval was obtained before study commencement and after each protocol amendment from the local institutional review board at academic centers and the Western institutional review board for independent research centers. Written informed consent was obtained from all patients before any study-related activity.

Eligible women were aged 18 years or older, had POP with the leading edge at or beyond the hymen (ie, pelvic organ prolapse quantification [POP-Q][12] scores of Ba≥0 for prolapse of the anterior compartment alone, C≥0 for prolapse of the apical compartment alone, or C≥−1/2 total vaginal length and Ba≥0 for multicompartment prolapse including the anterior and apical compartments), reported a bothersome bulge they could see or feel per the PFDI-20 (Pelvic Floor Distress Inventory)[13] (question 3, response of 2 or higher [ie, "somewhat", "moderately", or "quite a bit"]), provided written informed consent, and were able to comply with follow-up. Patients were excluded if they were pregnant or intended to become pregnant; had an active or chronic systemic infection; had a history of pelvic organ cancer; were undergoing or had previously undergone

radiation, laser therapy, or chemotherapy in the pelvic area; had taken systemic steroids within the past month or immunosuppressive or immunomodulatory treatment within the past 3 months; had a systemic connective tissue disease; had a known neurologic or medical condition affecting bladder function; were seeking obliterative vaginal surgery as treatment for POP; had previous prolapse repair with mesh in the target compartment; were planning to undergo a concomitant prolapse repair with mesh in the nontarget compartment; were unable to conform to the modified dorsal lithotomy position; had chronic systemic pain that included the pelvic area or chronic focal pain involving the pelvis; had uncontrolled diabetes mellitus; were participating in or planned to participate in another device or drug study during this study; or had known hypersensitivity to polypropylene mesh.

Unblinded physician-assessed and patient-reported data were collected at time points including a baseline visit before surgery, during the procedure, at discharge, and at follow-up visits at 6, 12, 18, 24, and 36 months. See Appendix 2, available online at http://links.lww.com/AOG/C707, for measures collected at each time point. All procedures were performed with either transvaginal mesh or native tissue repair, per study arm assignment. Concomitant procedures were allowed at physician discretion. Race was included as part of standard demographic data collection to account for any potential differences by race in baseline symptoms. All patients who completed the 36-month visit were considered to have completed the study.

The primary endpoint was improvement in POP severity at 36 months compared with baseline, that is, superiority of transvaginal mesh over native tissue repair at 36 months. Effectiveness was assessed by a composite of objective and subjective measures as described in Table 1. A co-primary endpoint of the study was to achieve noninferiority of transvaginal mesh to native tissue repair for safety by comparing rates of serious device-related and/or serious procedure-related complications (serious adverse events) at 36 months. A *serious adverse event* was defined per Code of Federal Regulations Title 21 §803.3 as an injury or illness that was life-threatening, that resulted in permanent impairment of a body function or permanent damage to a body structure, or that required medical or surgical intervention to preclude impairment of a body function or permanent damage to a body structure, or death.

The primary effectiveness endpoints of superiority and noninferiority were determined by the FDA. Notably, the FDA required that the primary objective outcome measure include points that were the same as objective inclusion criteria (prolapse at the introitus with POP-Q point Ba≤0 and/or C≤0). Because of this, the investigators added a secondary composite outcome measure that required improvement in objective measure (prolapse above the introitus POP-Q point Ba<0 and/or C<0). The subjective success and retreatment components of the composite outcomes were the same for the primary and secondary endpoints. Secondary endpoints included: 1) the composite outcome measure as described in Table 1; 2) incidence of mesh exposure; 3) incidence of de novo dyspareunia; 4) improvement in subject-specific outcomes at 36 months compared with baseline (pelvic floor symptoms per the PFDI-20, QOL per the PFIQ-7 [Pelvic Floor Impact Questionnaire], change in sexual functioning per the PISQ-12 [Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire],[14] and pain per the TOMUS [Trial of Mid-Urethral Slings] questionnaire[15]); 5) improvement per the PGI-I (Patient Global Impression of Improvement) for Prolapse[16]; 6) absence of re-

Table 1. Composite Definitions of Successful Treatment at 36 Months

Measure	Primary Endpoint	Secondary Endpoint
Anatomic success		
Anterior	POP-Q point Ba≤0; "at or above the hymen"	POP-Q point Ba<0; "above the hymen"
Apical	POP-Q point C<−1/2 TVL for multicompartment prolapse or POP-Q point C≤0 for single compartment apical prolapse; "at or above the hymen"	POP-Q point C<−1/2 TVL for multicompartment prolapse or POP-Q point C<0 for single compartment apical prolapse; "above the hymen"
Subjective success	Denies symptoms of vaginal bulging: PFDI-20 question 3 is less than 2	Denies symptoms of vaginal bulging: PFDI-20 question 3 is less than 2
Retreatment	No additional surgical treatment for POP in the segment(s) of the vagina treated at the index surgery or no pessary use since index surgery	No additional surgical treatment for POP in the segment(s) of the vagina treated at the index surgery or no pessary use since index surgery

POP-Q, pelvic organ prolapse quantification; TVL, total vaginal length; PFDI-20, Pelvic Floor Distress Inventory.

intervention or re-surgery for recurrence or persistence of POP or mesh exposure; and 7) device- or procedure-related pelvic pain, infection, vaginal shortening, atypical vaginal discharge, neuromuscular problems, vaginal scarring, de novo vaginal bleeding, fistula formation, or de novo voiding dysfunction.

The power calculation was based on a superiority assumption with a binary primary outcome. Based on the composite endpoint of anatomic and symptomatic success at 36 months, success was assumed to be 70.0% for native tissue repair and 85.0% for transvaginal mesh.[17–21] With a two-sided type I error of 0.05 and type II error of 0.1 (power 90%), 316 patients (158 per arm) were needed to detect a 15% difference between groups. In addition to a superiority assumption, statistical testing was performed for noninferiority using a −12% margin.[22] To assess for safety, the overall serious adverse event rate was anticipated to be approximately 14%.[22] With a type I error of 0.05 and type II error of 0.20 (power 80%), 298 patients (149 per arm) were needed to detect noninferiority with a 10% margin. Using the above calculations and assuming a 20% loss to follow-up, a total of 414 patients (207 per arm) was anticipated as necessary to achieve the 330 patients (165 per arm) needed for analysis.

Owing to the observational study design, a propensity score stratification method was used to assess the balance between treatment arms on relevant baseline characteristics. The propensity score analysis was performed by independent statisticians blinded to all clinical outcome data. This analysis included all patients enrolled in the intention-to-treat (ITT) cohort from both study arms. The propensity score was estimated through logistic regression of the treatment arm on the baseline characteristics in Table 2. The patients were then divided into five propensity score strata corresponding to the quintiles of the propensity score.

After stratification, the balance of treatment arms on relevant baseline characteristics was assessed.[23,24] A statistical test was performed to evaluate the null hypothesis of equality of the treatment arms, adjusting for propensity score stratum. The Mantel-Haenszel

Table 2. Baseline Characteristics and Assessment of Balance Between Treatment Arms

	Treatment Arm		*P*	
Variable	TVM	NTR	Before Stratification*	After Stratification†
Age (y)	66.6±10.8 (225) (32.5, 67.6, 88.2)	62.4±10.6 (485) (27.1, 64.1, 91.0)	<.001	.83
Race, White	93.3 (210/225)	84.9 (409/482)	.001	.68
BMI (kg/m^2)	28.4±6.1 (225) (15.1, 27.5, 57.8)	28.1±5.4 (485) (17.2, 27.1, 56.5)	.46	.81
Smoking, current	8.0 (18/224)	7.8 (38/485)	.93	.91
Diabetes	14.2 (32/225)	13.0 (63/485)	.65	.92
Menopausal	92.9 (209/225)	83.3 (404/485)	<.001	.84
Prolapse repair, prior	17.3 (39/225)	10.3 (50/485)	.009	.75
Hysterectomy, prior	65.3 (147/225)	30.1 (146/485)	<.001	.33
Estrogen use at baseline	35.6 (80/225)	32.4 (157/485)	.40	.98
POP-Q				
Apical: C	−1.5±3.7 (225) (−9.0, −3.0, 10.0)	−0.8±3.8 (485) (−9.0, −1.0, 12.0)	.028	.90
Anterior: Ba	2.5±1.4 (225) (−1.5, 2.0, 7.5)	1.9±2.0 (485) (−3.0, 1.5, 12.0)	<.001	.67
Posterior: Bp	−0.7±1.7 (225) (−3.0, −1.0, 7.0)	−0.4±2.1 (485) (−3.0, −1.0, 12.0)	.08	.91
Concomitant SUI repair	56.4 (127/225)	48.0 (233/485)	.037	.93
Surgeon volume greater than the median	45.8 (103/225)	52.0 (252/485)	.13	.90

TVM, transvaginal mesh; NTR, native tissue repair; BMI, body mass index; POP-Q, pelvic organ prolapse quantification; SUI, stress urinary incontinence.

Data are mean±SD (sample size [n]) (minimum, median, maximum) or % (n/N) unless otherwise specified.

* Chi-squared test (categorical variables) or one-way analysis of variance F-test (continuous variables).

† Mantel-Haenszel test (categorical variables) or two-way analysis of variance F-test (continuous variables) adjusting for stratum.

test was used for each categorical characteristic. For each continuous relevant baseline characteristic, the null hypothesis was assessed based on a two-way analysis of variance. The balance of treatment arms on relevant baseline characteristics was further assessed by evaluating the null hypothesis of homogeneity across the propensity score strata.[25]

Analysis was performed using both the ITT and per-protocol cohorts. Patients were considered ITT once surgery was initiated (ie, incision in vagina). All patients in the ITT cohort who received the assigned device and had no major protocol deviations were part of the per-protocol analysis. Propensity score stratification was applied to the primary and secondary endpoint analysis. Multiple imputation was used to address missing data for the primary and secondary effectiveness endpoints. Available case analysis was also presented. Noninferiority was demonstrated through a CI approach, and an inequality test was performed for the superiority hypothesis. Analyses were conducted using SAS 9.4.

RESULTS

Enrollment began on October 10, 2013, and was completed for both treatment arms on December 31, 2016. Three hundred thirty-seven patients were screened, and 289 patients were enrolled in the study (225 in the transvaginal mesh [TVM] group and 64 in the NTR group). There were an additional 421 patients from the AUGS Pelvic Floor Disorders Registry (Appendix 1, http://links.lww.com/AOG/C707), for a total of 485 patients in the NTR group. A total of 710 patients screened for eligibility: 225 underwent transvaginal mesh placement and were included in the ITT analysis, and 171 completed all follow-up visits at 36 months (54 [24%] lost to follow-

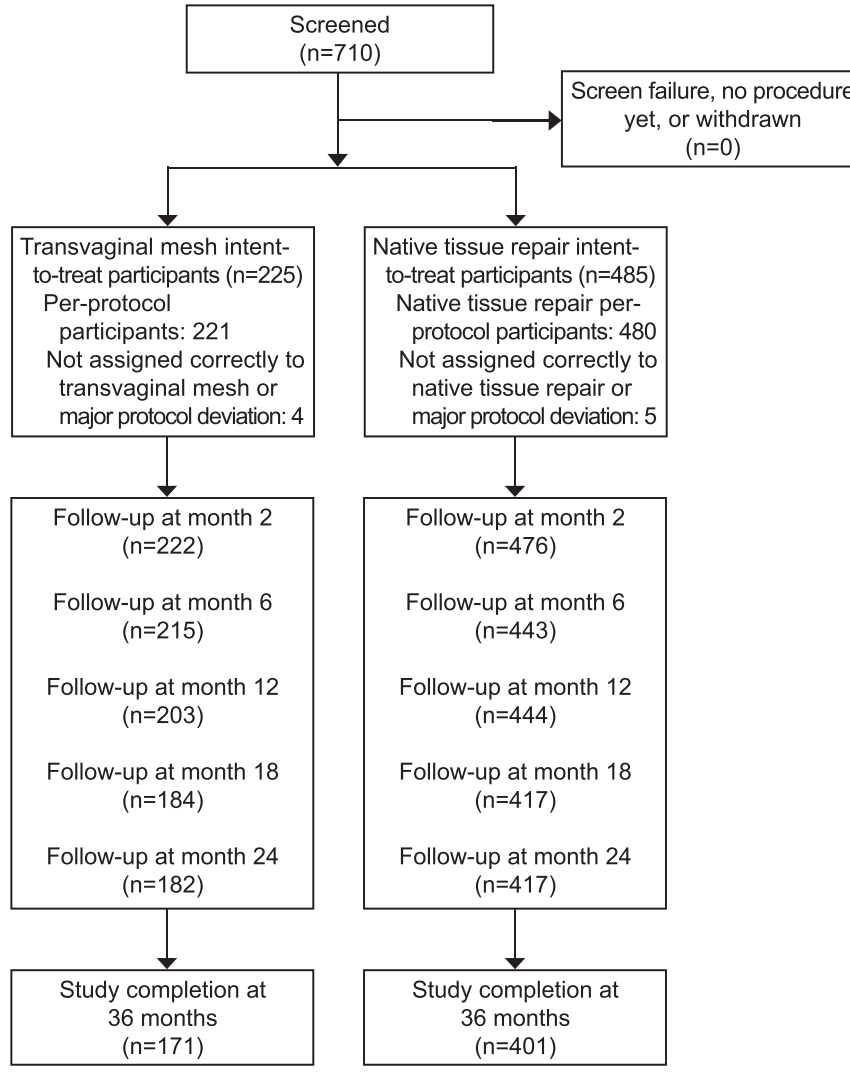

Fig. 1. Study enrollment and follow-up flow chart.

Kahn. Transvaginal Mesh vs Native Tissue Repair. Obstet Gynecol 2022.

up); 485 (comparison group) underwent native tissue repair and were included in the ITT analysis, with 401 (83%) completing 36-month follow-up (84 [17%] lost to follow-up). See Figure 1.

The baseline characteristics and balance assessment are displayed in Table 2. Without propensity score adjustment, patients in the TVM arm were older with a higher prevalence of prior prolapse repair, hysterectomy, or stress urinary incontinence repair. Patients differed between arms in degree of prolapse per POP-Q measurement. Surgeon experience was not significantly different between groups. The propensity score was higher in the TVM arm on average; however, the arms overlapped in propensity score distributions.

Table 3 shows the initial procedure characteristics for the full ITT population. Patients in the TVM group had shorter procedure lengths, lower estimated blood loss, and shorter lengths of stay than those in the NTR group. Procedures varied between groups, and percentages reflect concomitant procedures. Hysterectomies were more common in the NTR population.

For the ITT population with the multiple imputation method of missing data handling (Table 4), the TVM group had an 89.3% composite success rate at 36 months compared with 80.2% composite success for native tissue repair. Because the lower bound of the propensity score–adjusted CI of −0.2% was greater than the predefined −12% margin, noninferiority of transvaginal mesh compared with native tissue repair for effectiveness was established and a test for superiority was performed. The TVM group was not superior to the NTR group for the primary composite effectiveness endpoint (P=.056) at 36 months when anatomical success was defined as in Table 1. The use of transvaginal mesh for the treatment of anterior and/or apical vaginal prolapse was at least as effective as native tissue repair, and the outcome of noninferiority was consistent regardless of the method for handling missing data or whether data from the ITT or per-protocol cohorts were analyzed.

In the ITT population at 36 months (Table 5), composite treatment success rates of 88.8% in the TVM group and 80.6% in the NTR group were observed, consistent with the per-protocol analysis. The objective anatomic success rate was 98.2% for transvaginal mesh and 88.9% for native tissue repair. Subjective success and no retreatment rates both were similar between the TVM and NTR groups (propensity score–adjusted differences of −4.3% [95% CI −12.3% to 3.8%] for subjective success and 1.7% [95% CI −1.7% to 5.1%] for no retreatment.

The numerically higher composite success rate for the TVM group was driven by the anterior compartment anatomic success component. Similar results were noted within each component of the primary effectiveness endpoint at the 36-month follow-up period and were not statistically different. Both treatment methods achieved a high rate of objective and subjective success and maintained durable prolapse repair evidenced by low retreatment rates at 36 months.

In the ITT cohort, 3.1% of the TVM group and 2.7% of the NTR group developed serious adverse events within 36 months postindex procedure (Table 6). The use of transvaginal mesh for the treatment of anterior and/or apical vaginal prolapse was as safe as native tissue repair with respect to the serious adverse event rate at 36 months. Appendix 3, available online at http://links.lww.com/AOG/C707, summarizes serious adverse events by type.

Table 3. Initial Procedure Characteristics for Patients in the Intention-to-Treat Cohort

	TVM	NTR
Length of stay (d)	1.2 (0.1, 3.1)	1.2 (0.1, 6.2)
Length of procedure (min)	70 (22, 269)	116 (0, 343)
Estimated blood loss (mL)	75 (0, 3,100)	100 (0, 900)
During index procedure: hysterectomy	4.0 (9/225)	61.0 (296/485)
Vaginal vault prolapse repair	62.2 (140/225)	88.9 (431/485)
Hysteropexy	24.4 (55/225)	4.1 (20/485)
Cystocele repair	98.7 (222/225)	89.1 (432/485)
Enterocele repair	24.0 (54/225)	40.4 (196/485)
Rectocele repair	54.2 (122/225)	66.2 (321/485)
Concomitant antiincontinence procedure	56.4 (127/225)	48.0 (233/485)
Concurrent fecal incontinence procedure	0.4 (1/225)	4.1 (20/485)

TVM, transvaginal mesh; NTR, native tissue repair.
Data are median (minimum, maximum) or % (n/N).

Table 4. Composite Anatomic and Symptomatic Success at 36 Months, Using Primary Effectiveness Endpoint Success Definition*

Missing Data Handling Method and Analysis Population	TVM	NTR	Unadjusted Treatment Difference (TVM−NTR) (%)	Propensity Score–Adjusted Treatment Difference (TVM−NTR)	
				Estimate (%) (90% CI)	*P* of Superiority Test†
Multiple imputation					
ITT‡	89.3 (201/225)	80.2 (389/485)	8.9 (3.7–14.2)	6.5 (−0.2 to 13.2)	.056
Per protocol	90.1 (199/221)	80.1 (384/480)	10.1 (5.5–14.6)	6.2 (−1.1 to 13.4)	.081
Available case analysis					
ITT	88.8 (150/169)	80.6 (319/396)	8.2 (3.0–13.4)	4.3 (−3.3 to 12.0)	.176
Per protocol	89.2 (148/166)	80.9 (318/393)	8.2 (3.1–13.4)	3.2 (−5.0 to 11.5)	.258

TVM, transvaginal mesh; NTR, native tissue repair; ITT, intention-to-treat.
Data are % (n/N) or estimate (90% CI) unless otherwise specified
* Anatomic success in anterior compartment defined as POP-Q point Ba≤0; point C≤0 for apical compartment.
† Inequality test with 5% two-sided type I error.
‡ If the lower bound of the propensity score–adjusted CI is greater than −12%, noninferiority of TVM to NTR is demonstrated.

Kaplan-Meier curves for serious complication–free survival in the ITT population exhibited considerable overlap and demonstrated no difference in the serious adverse event rates between groups over time (Appendix 4, available online at http://links.lww.com/AOG/C707). The curves also demonstrated that the majority of serious adverse events occurred within the first 6 months postindex procedure.

Using the secondary composite criteria, transvaginal mesh was superior to native tissue repair at 36 months, with an 83.6% composite success rate for transvaginal mesh compared with 72.7% for native tissue repair (Table 7). Noninferiority was established, and the propensity score–adjusted treatment difference of 10.6% was in favor of the TVM arm when anatomical success was defined as Ba<0 (anterior compartment) or C<0 (apical compartment). In the ITT population at 36 months for observed cases, composite treatment success rates of 83.4% in the TVM group and 73.0% in the NTR group were observed (Table 8). The anatomical success rate was 89.3% in the TVM group and 80.3% in the NTR group. Subjective success and no retreatment rates were the same as for the primary endpoint, 92.4% for transvaginal mesh, 92.8% for native tissue repair for subjective success, and 97.3% for transvaginal mesh, 95.5% for native tissue repair for no retreatment.

Within 36 months, the overall device-related or procedure-related adverse event rates were similar between the TVM and NTR arms: 35.1% in the TVM

Table 5. Composite Anatomic and Symptomatic Treatment Success in Patients in the Intention-to-Treat Cohort at 36 Months, Using Primary Effectiveness Endpoint Success Definition*

Success Measure	TVM	NTR	Group Difference (95% CI)	
			No Propensity Score Adjustment	With Propensity Score Adjustment
36-mo composite success	88.8 (150/169)	80.6 (319/396)	8.2 (2.0–14.4)	4.3 (−4.8 to 13.5)
Objective success	98.2 (166/169)	88.9 (351/395)	9.4 (5.7–13.1)	10.1 (6.8–13.4)
Anterior compartment	98.8 (167/169)	88.1 (310/352)	10.7 (7.0–14.5)	10.8 (7.4–14.2)
Apical compartment	98.8 (167/169)	96.5 (359/372)	2.3 (−0.2 to 4.8)	2.9 (0.8–5.0)
Posterior compartment†	95.3 (161/169)	98.0 (388/396)	−2.7 (−6.2 to 0.8)	−1.3 (−4.2 to 1.6)
Subjective success	92.4 (157/170)	92.8 (371/400)	−0.4 (−5.1 to 4.3)	−4.3 (−12.3 to 3.8)
No retreatment for POP	97.3 (219/225)	95.5 (463/485)	1.9 (−0.9 to 4.7)	1.7 (−1.7 to 5.1)

TVM, transvaginal mesh; NTR, native tissue repair; POP, pelvic organ prolapse.
Data are % (n/N) for the observed case analysis, unless otherwise specified.
* Anatomic success in anterior compartment defined as POP-Q point Ba≤0; point C≤0 for apical compartment.
† Posterior compartment is not a component of the primary efficacy endpoint with success defined as POP-Q point Bp≤0.

Table 6. Serious Device-Related and/or Procedure-Related Complications at 36 Months

Analysis Population	TVM*	NTR*	Unadjusted Treatment Difference (TVM−NTR) (%)	Propensity Score–Adjusted Treatment Difference (TVM−NTR) (%)
ITT†	3.1 (7/225)	2.7 (13/485)	0.4 (−1.8 to 2.7)	−0.4 (−2.7 to 1.9)
Per protocol	3.2 (7/221)	2.5 (12/480)	0.7 (−1.6 to 2.9)	−0.2 (−2.4 to 2.1)
As treated	3.1 (7/225)	2.7 (13/485)	0.4 (−1.8 to 2.7)	−0.4 (−2.7 to 1.9)

TVM, transvaginal mesh; NTR, native tissue repair; ITT, intention-to-treat.
Data are % (n/N) or estimate (90% CI) unless otherwise specified
* Denominator is number of patients in the cohort.
† If the upper bound of the propensity score–adjusted CI is less than 10%, noninferiority of TVM to NTR is demonstrated.

group and 46.4% in the NTR group (Table 9). Most of device-related and procedure-related adverse events occurred within the first 6 months after surgery. Appendix 5, available online at http://links.lww.com/AOG/C707, displays outcomes on de novo dyspareunia, pelvic pain, de novo voiding dysfunction, and other adverse events. No significant differences between groups were noted on any of these outcomes.

A total of 13 mesh exposures were observed in 11 patients over the course of the study (4.9% exposure rate). Two of the 11 patients each reported two separate mesh exposure events. Only one of these exposure events was classified as a serious adverse event, and it resolved without sequelae after outpatient surgical intervention. More detail on mesh exposure events is presented in Appendix 6, available online at http://links.lww.com/AOG/C707.

The QOL measures indicated an overall improvement in both treatment arms. The benefit was noted and durable for all metrics collected. No statistically significant differences were seen between transvaginal mesh and native tissue repair on QOL outcomes (PFIQ-7, PFDI-20, PISQ-12, and TOMUS). The TOMUS questionnaire indicated an improvement in both groups for pain.

DISCUSSION

Using the primary composite endpoint, this study found that for women with anterior and/or apical compartment POP, treatment with transvaginal mesh did not achieve superiority over native tissue repair. Using adjusted propensity score stratification, the failure rate for transvaginal mesh was estimated at 6.5% lower than for native tissue repair at 3 years (P=.056). However, this primary anatomic outcome was mandated by the FDA and was criticized by investigators, because it included anatomic outcome measures unchanged from inclusion criteria (POP-Q point Ba≤0 and/or C≤0). For this reason, the secondary outcome measure was added that required demonstration of overall net improvement of the objective outcome compared with baseline examinations (POP-

Table 7. Composite Anatomic and Symptomatic Success at 36 Months, Secondary Effectiveness Endpoint*

Missing Data Handling Method and Analysis Population	TVM	NTR	Unadjusted Treatment Difference (TVM−NTR) (%)	Propensity Score–Adjusted Treatment Difference (TVM−NTR)	
				Estimate (90% CI) (%)	P of Inequality Test†
Multiple imputation					
ITT‡	83.6 (188/225)	72.7 (353/485)	10.9 (4.9–17.0)	10.6 (3.3–17.9)	.009
Per protocol	83.7 (185/221)	72.0 (346/480)	11.7 (6.1–17.2)	10.0 (2.6–17.5)	.014
Available case analysis					
ITT	83.4 (141/169)	73.0 (289/396)	10.5 (4.5–16.4)	8.2 (0.0–16.3)	.049
Per protocol	83.7 (139/166)	73.3 (288/393)	10.5 (4.5–16.4)	7.1 (−1.5–15.8)	.088

TVM, transvaginal mesh; NTR, native tissue repair; ITT, intention-to-treat.
Data are % (n/N) or estimate (90% CI) unless otherwise specified
* Anatomic success in anterior compartment defined as pelvic organ prolapse quantification point Ba<0; point C<0 for apical compartment.
† Inequality test with 5% two-sided type I error.
‡ If the lower bound of the propensity score–adjusted CI is greater than −12%, noninferiority of TVM to NTR is demonstrated.

Table 8. Composite Anatomic and Symptomatic Surgical Success in Patients in the Intention-to-Treat Cohort at 36 Months, Using Secondary Effectiveness Endpoint Success Definition*

Variable	TVM	NTR	Group Difference (95% CI)	
			No Propensity Score Adjustment	With Propensity Score Adjustment
36-mo composite success	83.4 (141/169)	73.0 (289/396)	10.5 (3.3–17.6)	8.2 (−1.5 to 17.9)
Objective success	89.3 (151/169)	80.3 (317/395)	9.1 (3.0–15.2)	11.2 (5.3–17.1)
Anterior compartment	91.1 (154/169)	78.7 (277/352)	12.4 (6.4–18.5)	13.8 (7.9–19.7)
Apical compartment	95.9 (162/169)	95.4 (355/372)	0.4 (−3.3 to 4.1)	0.6 (−3.1 to 4.4)
Posterior compartment†	91.7 (155/169)	93.4 (370/396)	−1.7 (−6.5 to 3.1)	−0.3 (−5.0 to 4.4)
Subjective success	92.4 (157/170)	92.8 (371/400)	−0.4 (−5.1 to 4.3)	−4.3 (−12.3 to 3.8)
No retreatment for POP	97.3 (219/225)	95.5 (463/485)	1.9 (−0.9 to 4.7)	1.7 (−1.7 to 5.1)

TVM, transvaginal mesh; NTR, native tissue repair; POP, pelvic organ prolapse.
Data are % (n/N) for the observed case analysis, unless otherwise specified.
* Anatomic success in anterior compartment defined as POP-Q point Ba<0; point C<0 for apical compartment.
† Posterior compartment is not a component of the primary efficacy endpoint with success defined as POP-Q point Bp<0.

Q point Ba<0 and/or C<0). When this secondary composite endpoint was analyzed, the TVM group did achieve superiority over the NTR group with an estimated treatment difference of 10.6% (P=.009). Subjective success, which was high and similar in both groups, was the same for both the primary and secondary endpoints, with a propensity score–adjusted difference of −4.3% (CI −12.3% to 3.8%) owing to the subjective success definitions being the same for the two endpoints. Adverse event and reoperation rates were low and transvaginal mesh was not inferior to native tissue repair in either category. In the TVM group, a total of 13 vaginal mesh exposure events was observed in 11 patients, representing 4.9% of patients. Patients in both groups had significant and sustained improvement in QOL assessments at 36 months and there were no differences between groups in QOL, nor in interventions for recurrence or in complication rates.

These results are similar to those reported at 36 months in a randomized trial by Nager et al[26] that compared transvaginal mesh hysteropexy to hysterectomy with native tissue repair (the SUPeR trial). Notably, both studies used the same small-volume/density mesh device. The overall success for both cohorts in this study was higher, possibly related to differences in study design, patient populations, or endpoint definitions. At 36-month follow-up, there was a 9.5% difference in composite success in favor of transvaginal mesh compared with a 12% difference reported in the SUPeR trial. In both trials, the 36-month point estimate and survival trends suggested transvaginal mesh's superiority, but wide CIs precluded the ability to establish superiority. However, in the recently reported 5-year data for the SUPeR trial, cumulative composite failure rates for the two groups clearly diverged, demonstrating transvaginal mesh's superiority.[27]

A post hoc sensitivity analysis of the primary composite effectiveness endpoint was conducted using the method described in the SUPeR study.[26] The failure probability was modeled using a proportional hazard survival model to account for interval censoring

Table 9. Device-Related and/or Procedure-Related Adverse Events in Patients in the Intention-to-Treat Cohort

	TVM	NTR	Group Difference (95% CI)	
			No Propensity Score Adjustment	With Propensity Score Adjustment
Overall adverse events				
Occurred within 6 mo	26.7 (60/225)	31.1 (151/485)	−4.5 (−11.6 to 2.6)	−8.7 (−16.5 to −1.0)
Occurred within 12 mo	30.7 (69/225)	36.5 (177/485)	−5.8 (−13.2 to 1.6)	−8.9 (−16.9 to −0.8)
Occurred within 18 mo	32.0 (72/225)	40.0 (194/485)	−8.0 (−15.5 to −0.5)	−11.5 (−19.6 to −3.4)
Occurred within 24 mo	32.4 (73/225)	42.5 (206/485)	−10.0 (−17.6 to −2.5)	−13.5 (−21.7 to −5.4)
Occurred within 36 mo	35.1 (79/225)	46.4 (225/485)	−11.3 (−18.9 to −3.6)	−15.7 (−24.0 to −7.5)

TVM, transvaginal mesh; NTR, native tissue repair.
Data are % (n/N) unless otherwise specified.

and controlled by stratification using the five propensity score strata. The piecewise exponential baseline hazard specified three constant hazard periods: 0–12 months, 12–24 months and 24–36 months. A statistically significant difference in treatment failure was demonstrated and the adjusted hazard ratio of failure for transvaginal mesh compared with native tissue repair was 0.561 (95% CI 0.366–0.860, P=.008).

The 2011 FDA review raised concerns regarding occurrence of pelvic pain and increased adverse events related to vaginal mesh use for prolapse.[11] In this study, serious adverse events did not differ between the TVM and NTR groups through 36-month follow-up. Additionally, this study found that at 36 months, the mesh exposure rate was 4.9%, lower than the 12% rate reported in a 2016 Cochrane Review.[9] This difference may be related to the lower overall surface area and lighter weight density of the mesh used in the current study as compared with older studies in the review. The term "mesh exposure" used in this article is consistent with AUGS-IUGA 2020 recommendations.[28]

In February 2019, an FDA advisory committee concluded that to support a favorable risk/benefit ratio, transvaginal mesh for prolapse repair should be superior to native tissue repair at 36 months, with comparable safety outcomes.[29,30] In April 2019, in the absence of complete and final data analysis, the FDA ordered manufacturers of transvaginal mesh for prolapse to stop selling and distributing their products.[31] The data presented here, together with those reported in the SUPeR trial, suggest that transvaginal mesh may be superior to native tissue repair, but a 3-year timeline to establish this may be too short.

Study strengths include its length, number of patients, prospective, multicenter approach, the use of composite outcome measures, the use of propensity score matching, and the analysis of both the ITT and per-protocol populations. Procedures in both groups were performed by surgeons experienced in native tissue repair or transvaginal mesh, depending on the group; thus, results likely represent best expected outcomes. Results may not be generalizable to transvaginal mesh or native tissue repair procedures performed by less experienced health care professionals.

Limitations include the lack of randomization and blinding. To account for potential confounders, propensity score stratification was used to balance treatment groups. As noted, ending the study at 36 months may have led to missing further separation in success rates between the TVM and NTR groups.

At 36-month follow-up, transvaginal mesh demonstrated noninferiority in the primary efficacy outcome and superiority of the secondary efficacy outcome over native tissue repair in patients with POP. The study also showed that transvaginal mesh is not inferior to native tissue repair in safety outcome measures. The outcomes reported here are comparable with those of the SUPeR trial at 36-months' follow-up and add to existing evidence that transvaginal mesh provides a safe, durable treatment for POP.

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Authors' Data Sharing Statement

Will individual participant data be available (including data dictionaries)? *No.*

What data in particular will be shared? *Not available.*

What other documents will be available? *Not available.*

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