

GYNECOLOGY

A posterior anal sling for fecal incontinence: results of a 152-patient prospective multicenter study

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BACKGROUND: The transobturator posterior anal sling (TOPAS) system is a posterior anal sling that is a minimally invasive, self-fixating polypropylene mesh intended to treat fecal incontinence (FI) in women who have failed conservative therapy.

OBJECTIVE: We are reporting 1-year outcome in a prospective, multicenter study under investigational device exemption, evaluating this new treatment modality.

STUDY DESIGN: A total of 152 women were implanted with the TOPAS system at 14 centers in the United States. FI was assessed preoperatively and at the 12-month follow up with a 14-day bowel diary, Cleveland Clinic Incontinence Scores, and FI Quality of Life questionnaires. Treatment success was defined as reduction in number of FI episodes of $\geq 50\%$ compared to baseline. Missing bowel diary data were considered treatment failures. The Wilcoxon signed rank test was used to compare changes observed at 12 months vs baseline.

RESULTS: Mean age was 59.6 years old (SD 9.7). The mean duration of FI was 110 mo (range 8-712) months. Mean length of the implant procedure was 33.4 (SD 11.6) minutes. Mean EBL was 12.9 (SD 10.5) mL. Average follow-up was 24.9 months. At 12 months, 69.1% of patients met the criteria for treatment success, and 19% of subjects reported complete

continence. FI episodes/wk decreased from a median of 9.0 (range 2-40) at baseline to 2.5 (range 0-40) ($P < .001$). FI days decreased from a median of 5.0 (range 1.5-7) at baseline to 2.0 (range 0-7) ($P < .001$) over a 7-day period. FI associated with urgency decreased from a median at baseline of 2.0 (range 0-26) to 0 (range 0-14.5) ($P < .001$). The mean Cleveland Clinic Incontinence Scores decreased from 13.9 at baseline to 9.6 at 12 months ($P < .001$). FI Quality of Life scores for all 4 domains improved significantly from baseline to 12 months ($P < .001$). A total of 66 subjects experienced 104 procedure- and/or device-related adverse events (AEs). Most AEs were short in duration and 97% were managed without therapy or with nonsurgical interventions. No treatment-related deaths, erosions, extrusions, or device revisions were reported. The most common AE categories were pelvic pain ($n = 47$) and infection ($n = 26$). Those subjects experiencing pelvic pain had a mean pain score (0-10 scale, 0 = no pain) during the 12-month follow-up of 1.2 (SD 2.4).

CONCLUSION: The TOPAS system provides significant improvements in FI symptoms and quality of life with an acceptable AE profile and may therefore be a viable minimally invasive treatment option for FI in women.

Introduction

Fecal incontinence (FI) (also called “accidental bowel leakage”) is defined as the involuntary loss of solid or liquid stool that causes social or hygienic problems.¹ According to systematic reviews, it is estimated that FI affects between 0.4-18% of the general population.² FI increases with age, from 2% in younger patients to close to 20% in older populations.^{3,4} Estimates from large population studies indicate approximately 5-10% of all adult women in the United States have FI with at least monthly incontinent episodes.⁴⁻⁷ FI has socially devastating effects on patients including shame, embarrassment,

depression, poor self-image, and social isolation.⁸⁻¹⁰

The initial first-line therapy for FI is conservative management with dietary modification, pharmacologic intervention, and/or pelvic floor muscle training. Patients who fail conservative management may be offered a sphincter repair for a disrupted external anal sphincter, injection of bulking agents,¹¹ sacral nerve stimulation,^{12,13} or possibly placement of an artificial bowel sphincter¹⁴ or percutaneous tibial nerve stimulation.¹⁵ Unfortunately, none of these techniques have become a panacea for the treatment of FI patients. Therefore, new treatment modalities for FI are needed.

The TOPAS treatment for FI system is a new surgical device for women with FI first described by Rosenblatt et al.¹⁶ The procedure is minimally invasive and uses a needle-based delivery system to place through a transobturator approach a self-fixating, polypropylene mesh tape posterior to the anal canal (Figure 1).

Although the exact mechanism of action is unknown at the present time, it most likely facilitates the normal closing mechanism by enhancing focal structural support. The aim of the present study was to assess the efficacy and safety of the TOPAS system in treating FI under the rigors of a Food and Drug Administration (FDA)-approved investigational protocol.

Materials and Methods

This was a prospective, multicenter, single-arm study to assess the efficacy and safety of the TOPAS system for the treatment of FI in women. A maximum of 225 patients were allowed to be enrolled (ie, defined as signing the study informed consent form) and a total of 152 patients were initially planned for TOPAS system implantation at 8 colorectal surgical and 7 urogynecology study centers in the United States. Each center could implant a maximum of 28 patients. Participating surgeons underwent training on cadavers and were

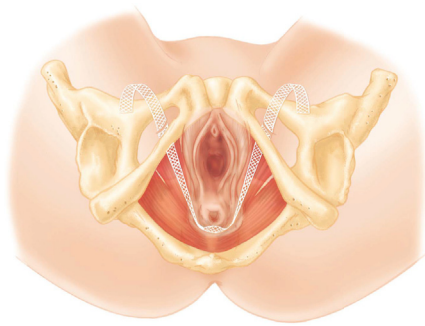
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FIGURE 1
Implanted transobturator
posterior anal sling



Mellgren et al. Posterior anal sling for treatment of FI. *Am J Obstet Gynecol* 2016.

proctored by more experienced colleagues during the first 2 implantations. An independent data and safety monitoring board reviewed trial progress and safety. The study protocol was approved by the FDA and the institutional review boards at all participating institutions. The trial was registered with Clinicaltrials.gov (NCT01090739).

All patients had FI symptoms for at least 6 months and had failed at least 2 modalities of conservative therapies (dietary modification, pharmacologic intervention, or pelvic floor muscle training). Inclusion criteria included: female patients, ≥ 18 years of age, negative colon cancer screening if ≥ 50 years old, and ≥ 4 FI episodes in a 14-day period (Table 1). Exclusion criteria included: pregnancy or planning a future pregnancy, stage III and IV pelvic prolapse, recent pelvic surgery, inflammatory bowel disease, diarrhea, external rectal prolapse, previous rectal resection, active pelvic infection, or sacral nerve stimulator (Table 1). To characterize the population, all patients had within a year of implantation a baseline anal manometry and endoanal ultrasound performed per institutional protocol. Results were not used as inclusion or exclusion criteria.

Surgical procedure and follow-up

All patients received perioperative prophylactic antibiotics. The study device consisted of a single piece of knitted,

type I polypropylene, monofilament mesh that was placed using a trans-obturator approach. The mesh was placed via a tunnel created between 2 small buttock incisions and then passed lateral to the rectum and vagina, around the ischiopubic bone, and out through the obturator foramen on each side using a curved insertion needle. Tensioning of the mesh was completed by pulling both the mesh and sheath assembly arms upward together until gentle tension was palpable in the mid anal canal. The insertion sheaths were then removed and the mesh was automatically self-fixated to the tissues.

Study follow-up visits for implanted patients were scheduled at 14-28 days (safety assessment only), and at 3, 6, and 12 months.

Primary efficacy objective

The primary efficacy objective was to demonstrate that implantation with the TOPAS system resulted in treatment success in $>50\%$ of the study patients. Treatment success was defined as at least a 50% reduction in the number of FI episodes from baseline to 12 months postoperatively as measured with a 14-day bowel diary (Responder₅₀).

A bowel diary was completed pre-treatment and at each visit. It recorded the number of FI episodes during a consecutive 14-day period and included information about urgency, consistency, and amount. Patients with missing 12-month bowel diaries were considered treatment failures for the primary efficacy endpoint analysis. The total sum of episodes was calculated as the first 14 consecutive days of data from the diary. If <10 days were available, that data point was considered missing.

Secondary efficacy objectives and safety

Secondary efficacy objectives included the reduction in incontinent days and urge FI episodes as measured from the bowel diary, reduction in FI symptom severity as measured by the Cleveland Clinic Incontinence Score (CCIS),¹⁷ the improvement in quality of life as measured by the FI Quality of Life

(FIQOL) questionnaire,¹⁸ the effect on pelvic pain as measured by a 0- to 10-point numeric pain score, and to record and summarize all adverse events (AEs).

All AEs for the TOPAS system were recorded. AEs were either volunteered spontaneously by the subject or discovered as a result of questioning or physical exam by the study center. All AEs reported by the study centers were reviewed and adjudicated by an AE adjudication committee.

Statistical analysis

Using a Responder₅₀ rate for sacral neuro modulation treatment reported by Tjandra et al¹⁹ at 61.7%, a fixed-sample-size design with a sample size of $N = 152$ would achieve 84.9% power to reject the null hypothesis. However, to account for the unknown Responder₅₀ rate, this study was designed to allow an interim reassessment of sample size by employing the 2-stage adaptive design of Bauer and Köhne.²⁰ Stage I consisted of the first 80 patients implanted. The primary objective was considered met if the P value for the stage I was $< .0087$. When the stage I cohort reached 1-year follow-up, an interim analysis was performed. Subjects missing 12-month follow-up data for any reason were included as treatment failures. The primary objective of the study was met at the end of the stage I, with a P value of .0048 (1-sided exact binomial test). Based on the interim analysis, the DSMB recommended that no sample size adjustment to stage II was needed. The results of the interim analysis were not shared with the clinical team and study investigators.

This report presents the “nominal” data for the study results based on all implanted subjects, similar to a conventional study design, where the final sample size is assumed as fixed in advance. Changes from baseline were analyzed with the Wilcoxon signed rank test or repeated measures mixed models. With the exception of the primary endpoint (which used a 1-sided binomial test as described above), all other tests of significance were 2-sided, with P value $< .05$ considered

statistically significant. Univariate logistic regression models was performed to examine the effect of the baseline covariates on treatment success.

Statistical analyses were performed with software (SAS, Version 9.2; SAS Institute Inc, Cary, NC).

Results

A total of 207 patients were enrolled, of which 152 patients were implanted with the TOPAS system in 14 of the 15 study centers (Figure 2). Patient characteristics are found in Table 2. The most common medical history items were hysterectomy/oophorectomy (49%), prolapse and/or urinary incontinence repair (46%), gastroesophageal reflux disease (41%), hypertension (38%), depressive disorder (36%), systemic pain condition (36%), hyperlipidemia (34%), and pelvic area pain (33%). All subjects who were ≥ 50 years old had a negative cancer screening examination of the colon within the past 3 years prior to informed consent.

The majority of implanted patients (93%) had resting tone present at digital rectal examination. Anorectal manometry recorded the mean maximum resting pressure at 31 ± 22 mm Hg and the mean maximum squeeze pressures at 60 ± 43 mm Hg. On endoanal ultrasound, 52% had an external sphincter defect (mean size 96 ± 45 degrees) and 28% had an internal sphincter defect (mean size 110 ± 54 degrees). A univariate logistic regression model was performed to examine the effect of the following baseline covariates on treatment success at 12 months: medical specialty (colorectal/urogynecologist), age, body mass index, baseline FI episodes, vaginal deliveries, FI etiology, internal and external sphincter defects, anal manometry variables, smoking, and medical history. None of the baseline covariates were significantly associated with treatment success. Therefore, no particular patient characteristics were identified from the overall study population that would suggest a subpopulation benefiting more or less from TOPAS system treatment.

At baseline, 40% of implanted patients were taking a medication to treat

TABLE 1
Inclusion and exclusion criteria

Inclusion criteria

- Adult (age ≥ 18 y) female.
- FI symptoms for minimum of 6 mo.
- ≥ 4 FI episodes in 14-d period.
- Failed 2 modalities of conservative therapies, eg, dietary modification, pharmacologic intervention, or pelvic floor muscle training.
- Age < 50 y or if age ≥ 50 y, has had negative cancer screening examination of colon according to screening guidelines (colonoscopy or barium enema + flexible sigmoidoscopy) within past 3 y prior to informed consent date. (Note: if not done, investigating physician must provide written justification for not having this exam and must be following American Cancer Society guidelines.)

Exclusion criteria

- Unable or unwilling to sign informed consent form or comply with study requirements.
- Currently enrolled in or plans to enroll in any concurrent drug and/or device study that may confound results of this study as determined by AMS.
- Allergic to polypropylene.
- Pregnant or planning future pregnancy.
- < 12 mo (365 d) Postpartum.
- Pelvic prolapse ≥ 1 cm beyond hymen (stage III and IV).
- Had stress urinary incontinence or anterior repair within 3 mo (90 d) prior to TOPAS sling system implantation.
- Had hysterectomy, sphincteroplasty, or posterior surgery within 6 mo (180 d) prior to TOPAS sling system implantation.
- Had rectal surgery (eg, rectopexy) within 12 mo (365 d) of TOPAS sling system implantation.
- Planning pelvic surgery within 12 mo (365 d) postimplant.
- Current grade III or IV hemorrhoids.
- Neurological or psychological condition as cause of FI, eg, MS, dementia, brain tumor.
- Diagnosed inflammatory bowel disease (eg, ulcerative colitis or Crohn's disease).
- Chronic, watery diarrhea, unmanageable by drugs or diet, as primary cause of FI.
- Severe chronic constipation, including obstructive defecatory disorder.
- External full-thickness rectal prolapse.
- A history of laxative abuse within past 5 y.
- Previous rectal resection.
- Active pelvic infection, perianal or rectovaginal fistula.
- Congenital anorectal malformations or chronic fourth-degree lacerations and cloacae.
- History of therapeutic radiation for cancers of pelvis.
- Currently implanted with sacral nerve stimulator.
- Contraindicated for surgery or having any condition that would compromise wound healing.

AMS, American Medical Systems; FI, fecal incontinence; MS, multiple sclerosis.

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the symptoms of FI and the most common were stool bulking agents (14%) or opioid-receptor agents (19%). The use of medications to treat the symptoms of FI (ie, number of medications taken) did not change significantly from baseline to 12 months for either treatment responders or nonresponders (36.8%).

The TOPAS system procedure was completed in 33 ± 12 (range 11-71) minutes and 98% of the cases were completed in < 60 minutes. Blood loss was minimal (mean of 13 ± 10 mL) and patients were able to return home at mean 11 ± 11 (range 2-57) hours after

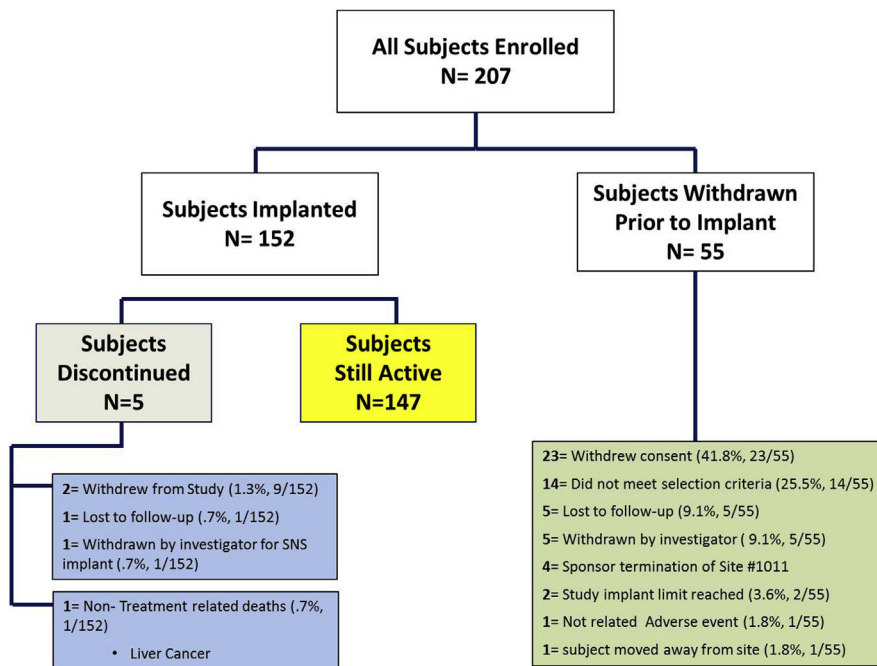
the procedure. The majority (79%) of the implant procedures were completed under general anesthesia.

Follow-up was performed at the prespecified follow-up time intervals and 5 subjects (3%) had exited the study at 12 months.

Primary efficacy objective

Treatment success (Responder₅₀) was observed in 66% of the patients at 3 months, 65.1% at 6 months, and 69% at 12 months (Figure 3). There was no statistically significant difference in the 12-month Responder₅₀ rates between study centers ($P = .154$) or between

FIGURE 2
Subject enrollment summary through 12 months of follow-up



Mellgren et al. Posterior anal sling for treatment of FI. *Am J Obstet Gynecol* 2016.

colorectal surgical and urogynecology centers ($P = .216$).

Secondary efficacy objectives

The median number of FI episodes decreased from 9 (range 2-40) episodes per week at baseline to 2.5 (range 0-47) episodes per week at 3 months, 2.5 (range 0-33) episodes per week at 6 months, and 2.5 (range 0-40) episodes per week at 12 months ($P < .001$) (Figure 3). At 12 months, 19% of all implanted patients achieved complete continence and an additional 23% reported >75% reduction of FI episodes (Figure 4). Urge FI episodes improved from 4 (range 0-26) episodes per week at baseline to 0 (range 0-8) episodes per week at 3 months, 0 (range 0-9) episodes per week at 6 months, and 0 (range 0-14) episodes per week at 12 months ($P < .001$).

The median number of incontinent days per week decreased from 5.0 (range 1.5-7) days at baseline to 2.0 (range 0-7) days per week at 12 months ($P < .001$). The CCIS contains 5 items on the frequency of solid, liquid, and gas

incontinence; pad usage; and lifestyle alteration (all scored from 0-4). The total score on this scale ranges from 0 (complete continence) to 20 (complete incontinence). The median CCIS decreased from 14 (range 5-20) at baseline to 10 (range 0-20) at 3 months, 10 (range 0-18) at 6 months, and 10 (range 0-17) at 12 months ($P < .001$). The FIQOL questionnaire consists of 29 questions that comprise 4 domains: Coping, Lifestyle, Embarrassment, and Depression. The FIQOL questionnaire is scored separately for each domain ranging from 1-4 with a higher score indicating a higher quality of life. FI-related quality of life improved and all 4 domains in FIQOL improved at 3, 6, and 12 months ($P < .001$) (Figure 5).

Safety

There were 104 AEs (in 66 patients) that were deemed to be treatment related (Table 3); 98 of these were nonserious and 6 were serious AEs. There were no erosions, extrusions or organ perforations. Two patients experienced immediate postoperative constipation that

resolved quickly (mean duration 7.0 days). There was no indication that this brief defecation disorder was related to sling tension.

There were 47 pain-related AEs in 41 patients. Of these, buttock pain/discomfort was most common (14 events in 12 patients) followed by pelvic pain/discomfort (11 events in 11 patients) and groin pain/discomfort (9 events in 8 patients). For the patients with pelvic area pain AEs, the mean numeric pelvic pain score (0-10 scale) collected during the 3-, 6-, and 12-month follow-up visits was 1.2 ± 2.4 .

Seventeen of the pain AE events did not necessitate any treatment; 29 were treated medically and 1 surgically. Pain was usually mild and no pain AE event was a serious AE per FDA definitions. All but 10 of these events were resolved at the 12-month follow-up. The patient who underwent surgical intervention was undergoing physical therapy for sciatica since 2010 with physical therapy. The sciatica symptoms deteriorated 113 days after the TOPAS system implant and required spinal surgical treatment, which resolved the symptoms.

There were 6 serious AEs that included 2 patients with worsening prolapse that needed surgical repair (resolved), 1 patient with chronic obstructive pulmonary disease (resolved), 1 patient with posttraumatic stress disorder (started prior to study inclusion; not resolved), 1 patient with deep venous thrombosis (resolved), and 1 methicillin-resistant *Staphylococcus aureus* (MRSA) infection. The MRSA infection was not in the surgical site in a patient with known MRSA. One patient died from liver cancer (not treatment related). Two patients were classified as having an abscess near the incision sites. Both were given oral antibiotics: one drained spontaneously and the other resolved without drainage. Neither required surgical or inpatient management and both resolved without sequelae.

Comment

The present study demonstrates that the TOPAS system provides symptomatic relief in a majority of patients with FI

and that this improvement is sustained for at least 12 months in a rigorous FDA-regulated study. The primary efficacy objective for this study was met, since 69.1% of the patients achieved at least a 50% reduction in FI episodes at 12 months using a stringent analysis in which patients with missing 12-month bowel diaries were considered treatment failures. This is comparable with other device treatment options such as transanal bulking agents and sacral nerve stimulation, which reported Responder₅₀ rates of 52% and 73%, respectively, at 12 months, using similar stringent analysis methods.^{13,21}

In addition, the reduction in FI episodes was accompanied by improvements in the secondary efficacy parameters, including a reduction in incontinent days and urge episodes, and improvements in quality of life. Reduction in fecal urgency may be especially important, since it has been found to be the most bothersome symptom for patients with FI.²² FI impairs patients' quality of life and patients frequently limit their lifestyle when they have FI symptoms.²³ It is therefore important that the improvement in FI symptoms also translated into an improvement in quality of life, which was assessed with the validated FIQOL instrument.

The TOPAS system was implanted successfully in all patients taken to the operating room. No intraoperative AEs were reported and the procedure was completed in <1 hour in 98% of the patients. This single and safe intervention, usually as an outpatient surgery, can offer an advantage when compared to some other therapies for FI. Unlike some other novel FI treatments, success after TOPAS system placement does not rely on patient compliance with any long-term maintenance or follow-up plan. In other words, patients who experience relief of symptoms and uncomplicated healing after this relatively minor procedure could simply be instructed to seek another appointment down the road if symptoms were to recur. The mechanism of function of the TOPAS system is still undefined. The authors believe the effect may be related

TABLE 2
Demographics and baseline fecal incontinence characteristics of all implanted patients (N = 152)

Variable	Value
Age, y	59.6 ± 9.7
Height, in	64.4 ± 2.5
Weight, lb	163.6 ± 32.3
BMI, kg/m ²	27.8 ± 5.4
Ethnicity	
White/Caucasian	137 (90.1%)
Black/African American	10 (6.6%)
American Indian/First Nations/Alaska Native	0 (0.0%)
Asian	1 (0.7%)
Hispanic/Latina	3 (2.0%)
Native Hawaiian/other Pacific Islander	0 (0.0%)
Other	1 (0.7%)
Obstetric history	
Gravidity	3.0 ± 1.8
Parity	2.6 ± 1.4
No. of vaginal deliveries	2.4 ± 1.5
No. of cesarean deliveries	0.1 ± 0.5
Menopausal status	
Premenopausal	20 (13.2%)
Perimenopausal	6 (3.9%)
Postmenopausal	126 (82.9%)
Duration of FI, mo	110.0 ± 113.5
Etiology of FI ^a	
Anorectal trauma	6 (3.9%)
Obstetric trauma	87 (57.2%)
Idiopathic/unknown	62 (40.8%)
Other	4 (2.6%)

Data are mean ± SD for continuous variables and N (%) for categorical variables.

BMI, body mass index; FI, fecal incontinence.

^a Multiple etiologies could be entered for single subject.

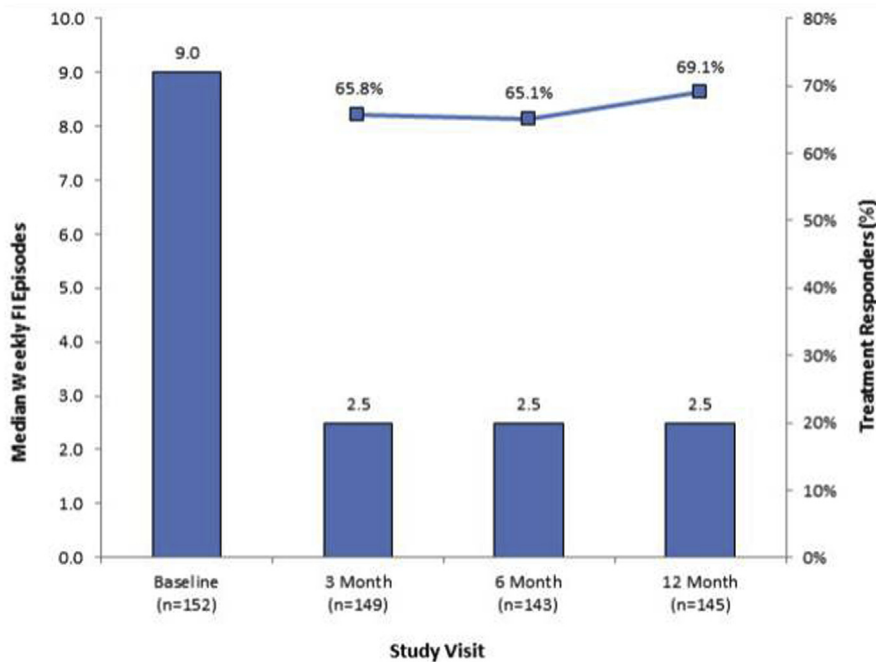
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to support of the pelvic floor, similar to the effect of the midurethral sling for urinary incontinence.

The number of AEs reported is comparable to those reported for other FDA-approved protocols for FI. In this context, it is important to remember that the study was conducted under a strict FDA-approved protocol that mandates that all treatment-emergent health problems need to be reported as

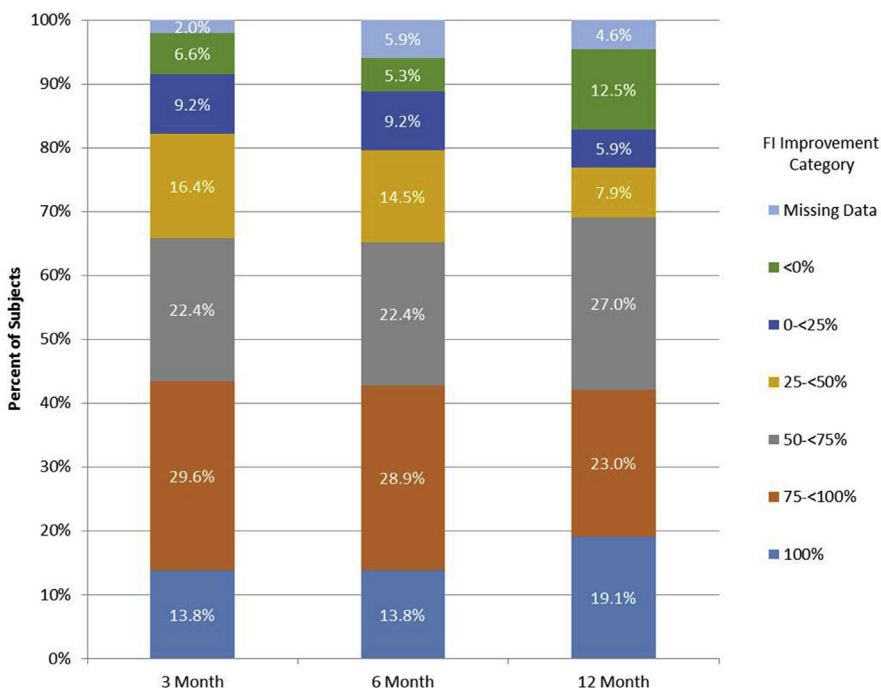
AEs. The majority of treatment-related AEs occurred within the first 3 months. The most common reported AE was mild pain that required no treatment (36%) or nonsurgical treatment (62%). It is noteworthy that a majority of patients with pain still experienced the same reduction in FI episodes and improvement in severity and quality-of-life parameters as did patients without pain.

FIGURE 3
Median number of FI episodes and Responder₅₀ rates



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FIGURE 4
Primary efficacy improvement categories



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The potential risk for exposure or extrusion of the mesh material itself is a unique risk of “mesh surgery.” Although exposure is most often curable, it can require operative reintervention to resolve. During this study, there were no reported cases of either extrusion or exposure of the implant material. This may be attributed to the location of the mesh outside the anal sphincters, which may act as a buffer between the mesh and the rectum. One of the more common groups of AEs after undergoing a mid-urethral pubovaginal sling can be attributed to placing or setting the sling too tight. During the TOPAS trial, no patient was believed to develop new symptoms of defecatory dysfunction that could be attributed to the sling being too tight.

The patients enrolled in the study fit the strict inclusion/exclusion criteria for the study. This may limit the generalizability of the results, since our patient population is a subset of patients with FI. In addition, the enrolled patients were motivated and they were followed up periodically, which is a norm for all research studies. At the same time, this can also affect patient compliance and behavior, with other aspects like bowel management, when compared to patients not in a research study. Other study limitations include no control arm, a predominantly Caucasian population, and no monitoring or control of dietary habits. At the time this study was initiated, sacral neuro modulation was not FDA approved in the United States for the treatment of FI. Therefore, there was no surgical comparison available. We therefore chose to use the patients as their own control. Dietary habits can have an impact on bowel control. However, this population had already failed 2 treatments for FI, the majority including dietary and fiber manipulations. Monitoring daily food intake is onerous and we chose not to burden our patients with this task. We acknowledge the regression and exacerbation that does occur with chronic conditions such as FI that may impact our results. The majority of the implanting surgeons had no experience with the TOPAS device prior to this

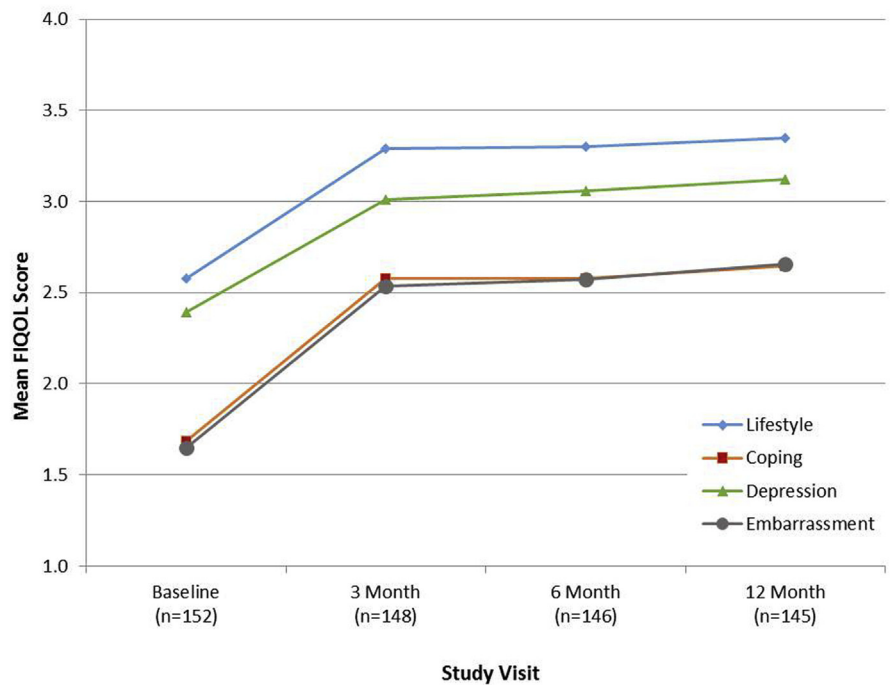
study. Each surgeon went through a specialized training protocol that included didactics, procedural videos, review of directions for use, and practice implantation in a fresh cadaver model. In addition, a minimum of 2 proctored cases were required for each investigator at a study center and additional proctoring was provided upon request. Assuming that all new TOPAS users go through a similar training process following FDA approval of the device, it is logical to assume that these data should therefore be reproducible.

In summary, the TOPAS system provides an improvement of FI symptoms and it is well tolerated by most patients. This study supports the reasonable assurance of the effectiveness and safety of the TOPAS system for the treatment of FI in women who have failed conservative therapies at follow-up for 12 months. Continued follow-up of patients in this study is needed to assess the long-term benefits and risks. ■

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FIGURE 5
Mean fecal incontinence quality of life scores (FIQOL)



Mellgren et al. Posterior anal sling for treatment of FI. Am J Obstet Gynecol 2016.

TABLE 3
Treatment-related adverse events

Adverse event category	No. of events	Patients, no. (%)
Pelvic pain	47	41 (27.0)
Infection	26	22 (14.5)
Incision site infection	9	9 (5.9)
Abscess	2	2 (1.3)
Other infection problem	15	14 (9.2)
Urinary problems	6	6 (3.9)
Worsening urinary incontinence	2	2 (1.3)
Other urinary problem	4	4 (2.6)
Pelvic organ prolapse	8	6 (3.9)
Pelvic organ prolapse (de novo)	4	3 (2.0)
Pelvic organ prolapse (worsening)	4	3 (2.0)
Bleeding	1	1 (0.7)
Defecatory dysfunction	2	2 (1.3)
Other	14	14 (9.2)
Total	104	66 (43.4)

Mellgren et al. Posterior anal sling for treatment of FI. Am J Obstet Gynecol 2016.

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