Urinary Incontinence Treatment Network (UITN)

E-TOMUS:

Extended Trial Of Mid-Urethral Slings

February 25, 2009

TABLE OF CONTENTS

APPENDICES

A. BACKGROUND

Epidemiological studies demonstrate that many women who undergo SUI surgery still experience bothersome urinary incontinence later in life. Although the etiology for bothersome incontinence after SUI surgery may be due to incontinence subtypes other than SUI, these women continue to experience a decline in their quality of life from incontinence symptoms[1]. The long-term outcomes of SUI procedures have not been studied sufficiently. Surgeons currently use relatively short-term outcome data for long-term counseling. This is an important component of pre-operative counseling for most patients, especially those with long life expectancies following their surgery.

In addition, long-term data regarding complications such as mesh erosion into the vagina and urethra is lacking. Although there are several papers reporting long-term outcomes of mid-urethral sling procedures at 3 or 5-years, the follow-up in these studies often consists only of questionnaires and/or urodynamic studies without any report of physical exam findings[2-7]. Some patients present with vaginal bleeding, discharge, pain, or dyspareunia leading to the diagnosis of mesh erosion; however, mesh sling erosions can be asymptomatic and have been identified up to 5-years post-operatively[8, 9]. Ward and Hilton followed women who underwent retropubic tension free vaginal tapes (TVT) for 5-years. They reported 3 vaginal mesh erosions in their series, 2 of which were not diagnosed until 5-years after the initial surgery. They also reported mesh erosion into the bladder, which was not identified until 5-years after surgery. The authors acknowledged these data likely underestimate the number of women with mesh erosions after TVT as less than 50% of the patients had a physical exam at 5 years[8]. Given this paucity of long-term follow-up and potential for asymptomatic mesh erosions, we need rigorous, complete, and accurate long-term follow-up to know the true rate and natural history of mesh complications after midurethral sling procedures.

Longer term follow up will also provide valuable data on the effect of SUI surgery on other pelvic disorders. Existing case series suggest that SUI procedures may worsen or cause pelvic organ prolapse[10]. The rate of subsequent re-operation for pelvic disorders is an important component of pre-operative counseling.

Participants enrolled in TOMUS provide a valuable cohort of women in which to evaluate the long-term treatment sequela and natural history of the retropubic and transobturator midurethral sling procedures. The current published literature lacks high quality data on the long-term success and complications of mid-urethral sling procedures. This prospective cohort study will address some of the limitations in the existing literature by providing a minimum of 7-years of follow-up (5-years after 24 month TOMUS outcomes are collected) of a large, well-characterized cohort of women from various ethnic and socioeconomic backgrounds who underwent midurethral sling surgery for SUI.

B. STUDY AIMS

E-TOMUS is an observational study of women who have completed participation in the Trial Of Mid-Urethral Slings (TOMUS), a randomized trial comparing retropubic and transobturator midurethral sling procedures in women undergoing surgery for stress urinary incontinence (SUI). The TOMUS study follows participants for 2-years after surgery. Since 2-years is too short to evaluate long-term sequelae of the procedures, the goal of E-TOMUS is to follow participants for 5 additional years to compare the long-term continence rates, complication rates and overall pelvic floor outcomes of the two procedures.

B1. Primary Aim

To describe continence rates over 7-years following the index surgery and to compare the long-term outcomes of the retropubic and transobturator midurethral sling procedures for the treatment of SUI in the TOMUS cohort.

B2. Secondary Aims

1. To compare the rates of long-term re-intervention for urinary incontinence, including the types of treatments.

2. To report long-term complications after midurethral sling procedures, including mesh erosion and to determine if differences in complications exist between the surgical cohorts.

3. To compare the rates and types of pelvic floor symptoms, sexual function, satisfaction, and impact on quality of life following the midurethral sling procedures.

4. To compare the natural history of urge incontinence (symptoms and treatment) in women with either persistent or de-novo urge incontinence with women without urge incontinence, both within and between surgical cohorts.

5. To identify clinical and urodynamic parameters associated with long-term continence and incontinence, including re-treatment within and between surgical cohorts.

6. To determine changes in pelvic organ prolapse and rates of treatment for prolapse within and between surgical cohorts.

C. STUDY SCHEMA

The design of E-TOMUS extends the follow-up of women enrolled in TOMUS to 7 years after the index surgery. There will be no interventions as part of this protocol. Women will be invited to participate in E-TOMUS at completion of their 24-month TOMUS outcome visit. Participation in E-TOMUS will last for up to 5-years after the originally projected 24-month TOMUS primary endpoint. Due to the potential for delayed mesh-related complications and the need to assess pelvic support, an in-person visit is required to complete an examination. Visits will be conducted annually starting at month 36 following the index surgery.

D. DEFINITION OF TREATMENT SUCCESS

For purposes of this extended follow-up, continence or treatment success will be defined as:

- No self-reported stress-type UI symptoms (Medical, Epidemiologic and Social Aspects of Aging questionnaire (MESA)[11]: response of “rarely” or “never” for each stress-type symptom); and
- No re-treatment for SUI (including anti-incontinence surgery, treatment with a device, periurethral bulking agents, medication, behavioral treatment, etc.).

Treatment failure is therefore defined by the occurrence of one or both of the following:

- Self-reported stress-type UI symptoms (response of "sometimes" or "often" on the MESA questionnaire); or,
- Any retreatment for SUI (e.g. surgical, pharmacological, device or behavioral) at any point after the initial surgery for urine leakage.

E. STUDY POPULATION

The study population will consist of TOMUS patients who have not undergone any surgical retreatment for SUI and who consent to extended follow-up.

E1. Inclusion Criteria

1. Signed consent form.

E2. Exclusion Criteria

1. Surgical retreatment for SUI.

F. MEASURES

F1. Primary Outcome Measures

a. MESA

Self-reported stress-type UI symptoms will be collected using selected items regarding stress and urge-type UI symptoms taken from the questionnaire for the Medical, Epidemiologic, and Social Aspects of Aging Project (MESA)[1]. The items query the patient's description of how urine loss occurred. Questions referring to loss of urine at times of exertion such as laughing, sneezing, lifting, or bending over define SUI. Questions referring to urine loss preceded by an urge to void, or uncontrollable voiding with little or no warning define urge incontinence. Symptoms associated with urine loss of both urge and stress-types define "mixed" incontinence.

b. Retreatment for SUI

Additional treatment includes additional anti-incontinence surgery, collagen injections or periurethral bulking injections, and medications or behavioral treatments (i.e. behavioral treatment for SUI is defined as a formal structured treatment program, which therefore excludes informal discussion, suggestions and/or handouts) specific to SUI as follows:

Surgery:

- Burch colposuspension
- Sling procedure
- Needle suspension (Raz, Pereyra, Stamey, Gittes, etc.)
- Suburethral plication
- Collagen injections or periurethral bulking agents
  (NB: Surgery for prolapse is not defined as failure of SUI procedure.)

  (NB: Surgical "take down" of a sling is not defined as failure of SUI procedure; rather, "take down" is considered a complication, as is the broader category of voiding dysfunctions requiring treatment.)

Pharmacologic treatment:

- Alpha-agonists
- Duloxetine
  (NB: Estrogen treatment is not defined as failure of SUI procedure.)

Other treatments:

- Pelvic muscle rehabilitation (with or without biofeedback) for the indication of treatment of SUI
  (NB: PMR for treatment of urge incontinence is not defined as failure of SUI procedure.)
- Devices such as vaginal cones, pessary, urethral plugs or patches for SUI
  (NB: Pessary for prolapse is not defined as failure of SUI procedure.)

F2. Secondary Outcome Measures

a. Complications

Long-term complications of primary interest include:

Mesh Complication: Vaginal, urethral, bladder; erosion (defined as after primary healing, into an organ or surrounding tissue); exposure (defined as mesh visualized through a prior incision area with or without an inflammatory reaction).

Recurrent UTI: Presumed UTI with treatment, ≥3 in 1 year AFTER 6 week visit.

Fistula:

-Vesicovaginal: connection between bladder and vagina resulting in passage of urine per vaginum

-Urethrovaginal: connection between urethra and vagina resulting in passage of urine per vaginum

NOTE: Foreign body reaction in space of Retzius resulting in vaginal discharge or bleeding or granulation tissue in vagina is NOT a fistula.

Granulation Tissue: Granulation at the TOMUS surgical site. (If there is granulation at a concomitant surgery site, that should be reported as an "other" [code 99] adverse event.)

Voiding Dysfunction: Defined as a complication if one of the following criteria are met:

- Uses a catheter to facilitate bladder emptying at or beyond the 6 week visit OR
- Has undergone medical therapy to facilitate bladder emptying at or beyond the 6 week visit OR
- Has undergone surgical therapy to facilitate bladder emptying at anytime after TOMUS surgery.

De Novo Urge Incontinence: At or beyond the 6-week visit, in the absence of a positive urine dipstick, a baseline pure SUI patient now answers.

1. Any MESA urge question "sometimes" or "often," AND/OR,
2. Has initiated treatment with anticholinergic medication for urge incontinence.

Persistent Urge Incontinence (will be tracked, but not reported as a complication.) At or beyond the 6 week visit a baseline mixed patient answers,

1. Any MESA urge question "sometimes" or "often," AND/OR,
2. Has initiated treatment with anticholinergic medication for urge incontinence

NOTE:

- Baseline status definitions for urge incontinence are as follows:
  - Pure SUI
    1. All MESA urge questions are answered “never” or “rarely,” AND,
    2. Patient is not being treated with anticholinergic medication for urge incontinence.
  - Mixed SUI
    1. Any MESA urge question is answered "sometimes" or "always," AND/OR,
    2. Patient is being treated with anticholinergic medication for urge incontinence.

b. Quality of Life and Patient Bother

Health-related QOL is a multidimensional concept which encompasses well-being that is related to health and is distinguished from measures of health and functional status. Two condition-specific measures will be used in this trial so as to be sensitive enough to detect change, i.e. the International Consultation on Incontinence Questionnaire (ICIQ)[13] and the Incontinence Impact Questionnaire (IIQ) developed by Shumaker et al[12]. The former measure assesses the impact of UI on everyday life whereas the latter measure assesses the impact of UI on various activities, roles, and emotional states. Patient bother will be measured by the subscales of the Urogenital Distress Inventory (UDI) measuring stress UI symptoms, urge symptoms and voiding symptoms[12]. Adequate validity, reliability and sensitivity to change have been reported by the authors.

c. Sexual Function

Sexual function will be assessed using the short form of the Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12)[12], a validated, 12-item, condition-specific measure. A Spanish version of the PISQ-12 has been validated and will be used in this study.

d. Patient Satisfaction with Treatment Outcome

A 9-item self-administered questionnaire developed for the SISTEr trial will be used to assess this outcome. These items measure patient satisfaction with surgery related to activities previously restricted by urinary incontinence symptoms and to emotions associated with urinary incontinence, as well as providing a measure of patients’ global sense of satisfaction with the outcome.

An additional measure of satisfaction is the Patient Global Impression of Improvement (PGI-I) questions which assess patients’ overall appraisal of their response to treatment[13]. Patient responses to PGI-I correlate to condition specific quality of life measures.

F3. Physical Exam

The following data will be collected from the physical examination.

a. Pelvic Organ Prolapse

The pelvic organ prolapse evaluation will be performed according to the guidelines established by the International Continence Society[1614] The procedure will be standardized as demonstrated in a videotape produced by Duke University Medical Center (“Pelvic Organ Prolapse Quantification Examination”) and described in the Physical Examination Procedures Manual. Data will also be collected about surgery for prolapse repair.

b. Urine Dipstick

A clean catch urine dipstick will be collected at each visit; however, given the challenges of long-term follow-up, outcomes will be collected regardless of dipstick results. Positive dipsticks will be sent for urine culture and positive results will be captured.

c. Post-void Residual Urine Volume

Post void residuals will be obtained according to clinical care (ultrasound or straight catheterization).

F.4 Independent Variables

There are three groups of independent variables:

- Sociodemographic characteristics race; marital status; education; occupation;
- Risk factors for UI: age; parity; weight of largest baby; menopause status and use of HRT; BMI; previous anti-incontinence and gynecologic surgery; current medications..

F5. Intervening Variables

Intervening variables that might affect the outcomes of interest consist of the following three categories:

- Pelvic comorbidity: pelvic organ prolapse (POP-Q);
- Pre-operative urodynamic values;
- Comorbidities: measured with the Charlson Comorbidity Index.
- Depression, measured by the PHQ-9[15] the depression module of the PRIME-MD diagnostic instrument for common mental disorders.

F6. Schedule of Measurements

Data will be collected at annual in-person visits starting 36 months after index surgery. All measures will be collected at each visit (see Appendix A).

G. DATA COLLECTION AND DATA MANAGEMENT

All data collection will be performed by certified Interviewers/Data Collectors and/or Principal Investigators. Certification of study personnel will be maintained and updated as outlined in the TOMUS QA Plan. Also, all data management rules as outlined in TOMUS will apply. To that end, the visit window for all contacts in years 3-7 will be the same as that for follow-up at 24 months, i.e. ± 1 month (31 days).

H. STATISTICAL CONSIDERATIONS:

H1. Projected Sample Size

The sample size for E-TOMUS was estimated on the basis of experience with the E-SISTEr extended follow-up study. In that study, 74% of women who participated in SISTEr consented for E-SISTEr. Of the 26% not enrolled, about half (46%) were unreachable and the remaining (54%) declined. For E-TOMUS, we expect to be able to reach all the women who have not received (surgical?) re-treatment for stress incontinence, 80% of the original sample, and we anticipate that approximately 85% of those will enroll. This will result in an initial enrollment in E-TOMUS of 400 women.

Estimates of retention and completion of study visits are also informed by the E-SISTEr experience. With follow-up currently ranging from 18 to 42 months, approximately 94% are still participating, although a smaller percentage completes each visit. Completion rates for the in-person visits are approximately 72%, while the participation rates for the telephone follow-up interviews are about 80%. Therefore, in E-TOMUS we expect that 90% (n=360) of the enrollees will complete one or more of the follow-up visits and that about 70% (n=280) will complete each visit.

This projected sample size is adequate for comparing the treatment groups by the statistical methods described below. The time-to-event methods and mixed effect repeated measures analysis allow us to include data from women who have incomplete follow-up. These methods maximize the sample sizes available for analysis. The width of the confidence intervals is proportional to the inverse of the sample size. That is, as the sample size increases, the width of the confidence intervals decreases. Thus we will make optimum use of the available data.

In addition, this sample is large enough for detecting as statistically significant large differences between the groups. For example, for comparing success rates at a single time point, a sample of 280 women (140 in each treatment group) will provide 80% power to detect, at the 5% significance level, a difference in success rates of 12 percentage points or more, if the success rate in the lower group is 80% and a difference in success rates of 16 percentage points or more if the rate is 50%. Pooling the data across visits and using time-to-event methods will increase the power. With 360 women, the log-rank survival analysis has greater than 80% power to detect differences in success rates between treatment groups of 11 percentage points or more, if the success rate in the lower group is 80% and a difference of 15 points or more if the success rate is 50%.

H2. Analysis Plan

The research aims of this extended follow-up are different from those of the TOMUS study, which was designed as an equivalence trial and sought to define a range of equivalence for which the two surgical arms could be declared equivalent. In that study, confidence intervals on the estimated difference between treatment groups will be compared to the equivalence limits established for that study. In the extended follow-up study, we will continue to estimate the differences, and 95% confidence intervals, in the continence rates and other pelvic floor outcomes between the surgical procedures.

H3. Analysis of the Primary Aim

To compare the two surgical arms with regard to the E-TOMUS primary outcome (defined above), we will compute the percent of women in each treatment arm who meet the definition of success at yearly intervals post treatment. P_1 is defined as the success rate in the retropubic midurethral sling arm and P_2 is defined as the success rate in the transobturator midurethral sling arm. Time-to-failure analyses (Kaplan-Meier plots and log-rank tests) will be used to estimate the difference between the two treatment arms in the estimated annual success rates and the 95% confidence intervals.

H4. Analysis of the Secondary Aims

Cross classification and the Chi-square test or Fisher's exact test will be used for unadjusted comparison of dichotomous outcomes (re-treatment rates, pelvic floor symptoms, de novo urge incontinence, etc.). Treatment comparisons will be adjusted for covariates with the multiple logistic regression model for dichotomous endpoints and proportional hazards models for time-to-failure analyses.

Analysis of continuous outcomes (quality of life, satisfaction, etc.) will be based on change from baseline and will use mixed model repeated measures analysis of variance. In addition to comparing treatment groups with respect to satisfaction with surgery, the analysis of this outcome will include an evaluation of expectations of surgery as a predictor of satisfaction.

I. INFORMED CONSENT PROCEDURES

Patients will be invited to participate in E-TOMUS after completing their 24 month TOMUS visit. No E-TOMUS activities will commence with first obtaining written informed consent.

J. REFERENCES

1. DIOKNO AC BK. Prevalence and outcomes of continence surgery in community dwelling women. J Urol 2003;170:507-511.
2. ANKARDAL M HB, LAUSTEN-THOMSEN N, CARNELID J, MILSOM I. Short- and long-term results of the tension-free vaginal tape procedure in the treatment of female urinary incontinence. Acta Obstet Gynecol Scand. 2006;85:986-992.
3. PORENA M CE, FREA B,. Tension-free vaginal tape versus transobturator tape as surgery for stress urinary incontinence: results of a multicentre randomised trial. Eur Urol. 2007;52:1481-1490.
4. HOLMGREN C NS, LANNER L, HELLBERG D. Long-term results with tension-free vaginal tape on mixed and stress urinary incontinence. Obstet Gynecol. 2005;106:38-43.
5. JELOVSEK JE BM, KARRAM MM, WALTERS MD, PARAISO MF. Randomised trial of laparoscopic Burch colposuspension versus tension-free vaginal tape: long-term follow-up. BJOG 2008;115:219-225.
6. CHENE G AJ, TARDIUE AS. Long-term results of tension-free vaginal tape (TVT) for the treatment of female urinary stress incontinence. Eur J Obstet Gynecol Reprod Biol. 2007;134:87-94.
7. WALTREGNY D GY, REUL O, HAMIDA W, BONNET P, DELEVAL J. TVT-O for the Treatment of Female Stress Urinary Incontinence: Results of a Prospective Study after a 3-year Minimum Follow-up. Eur Urol. 2008;53:401-410.
8. WARD KL HP. Tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence: 5-year follow up. BJOG 2008;115:226-233.
9. TSIVIAN A KO, MOGUTIN B. Tape related complications of the tension-free vaginal tape procedure. J Urol 2004;171:762-764.
10. WISKIND AK CS. The incidence of genital prolapse after the Burch colposuspension. Am J Obstet Gynecol 1992;167:399-404.
11. HERZOG AR, DIOKNO AC, BROWN MB, NORMOLLE DP, BROCK BM. Two-year incidence, remission, and change patterns of urinary incontinence in noninstitutionalized older adults. J Gerontol 1990;45:M67-74.
12. ROGERS RG CK, KAMMERER-DOAK D, KAHLSA S, QUALLS C. A short form of the Pelvic Organ Prolapse/Urinary Incotinence Sexual Questionnaire (PISQ-12). Intl Urogynecol J 2003;14:164-168.
13. YALCIN I, BUMP RC. Validation of two global impression questionnaires for incontinence. Am J Obstet Gynecol 2003;189:98-101.
14. BUMP RC MA, BO K, BRUBAKER LP, DELANEY JOL, SHULL BL, SMITH ARB. The standardization of terminology of pelvic organ prolapse and pelvic floor dysfunction. Am J Obstet Gynecol 1996;175:10-17.
15. Kroenke, K., R.L. Spitzer, and J.B. Williams, *The PHQ-9: validity of a brief depression severity measure.* J Gen Intern Med, 2001. **16**(9): p. 606-13.

Appendix A. Schedule of Measurements

	Year 3	Year 4	Year 5	Year 6	Year 7
Primary Outcomes					
MESA	✓	✓	✓	✓	✓
Re-treatment for SUI	✓	✓	✓	✓	✓
Secondary Outcomes					
Complications	✓	✓	✓	✓	✓
QOL	✓	✓	✓	✓	✓
Patient Bother	✓	✓	✓	✓	✓
Sexual Function	✓	✓	✓	✓	✓
Patient Satisfaction	✓	✓	✓	✓	✓
Urine Dipstick	✓	✓	✓	✓	✓
PVR	✓	✓	✓	✓	✓
POP-Q	✓	✓	✓	✓	✓
Intervening Variables					
Depression	✓	✓	✓	✓	✓
Comorbidities	✓	✓	✓	✓	✓