1. Has a poorly functioning urethral closure mechanism been shown to result in more leakage into the proximal urethra during Valsalva? Describe a study designed to evaluate this presumption.

To our knowledge, more urine leakage into the proximal urethra as a result of a poorly functioning urethral closure mechanism has not been directly demonstrated. However, there are numerous studies that demonstrate patients with intrinsic sphincter deficiency (ISD) have more severe incontinence and lower surgical success rates (1,2). If one considers intrinsic sphincter deficiency to be an urodynamic representation of a poorly functioning urethral closure mechanism, then this may represent evidence of more leakage into the urethra with Valsalva in those individuals. A study designed to directly evaluate the assumption that a poorly functioning urethral closure mechanism is associated with more urine leakage into the proximal urethra could involve video-urodynamic studies of individuals with and without ISD. If our assumption is true, individuals with ISD should have more frequent bladder neck funneling with Valsalva.

2. Has leakage of urine into the proximal urethra during Valsalva been shown to stimulate a reflex detrusor contraction?

The relationship between the stress and urge components of mixed urinary incontinence (MUI) is not well understood. Patients with MUI may have two independent defects: a primary detrusor dysfunction and a primary weak outlet. However, some investigators theorize that the etiologies of stress and

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urge incontinence are linked and that detrusor overactivity (DO) is a reflex response stimulated by leakage of urine into the proximal urethra during Valsalva. According to this “urethral event hypothesis”, an incompetent bladder outlet allows passage of urine during Valsalva, which in turn stimulates proximal urethral afferent nerves and provokes the micturition reflex and DO (3,4).

This hypothesis is supported by observations that patients with detrusor overactivity have significantly lower maximal urethral closure pressures on urethral pressure profilometry (5). In addition, patients with urodynamically proven detrusor overactivity have urethral sphincters, which are morphologically different (decreased smooth muscle thickness, diameter and circumference) than patients without detrusor overactivity (6). In an animal model, activation of urethral afferent nerve activity by urethral perfusion stimulated detrusor contraction and micturition (7). Webster et al. studied 73 patients with concomitant DO and stress incontinence (SUI). One third of these patients had a period of electromyographic silence immediately preceding an unstable detrusor contraction, leading the authors to conclude that the unstable contraction was induced by a urethral event and not a bladder abnormality (8).

Given data such as that above, some authors have previously advocated for bladder neck suspension in patients with DO and SUI to prevent this urethral-detrusor reflex (9). Fulford et al. performed video-urodynamic studies on 59 patients with SUI and urgency before and after pubovaginal sling surgery. In this study, postoperative resolution of urgency was significantly associated with a competent bladder neck on video-urodynamics (10). Finally, in one study of 73 women with MUI who underwent tension free vaginal tape procedures, low maximum urethral closure pressure was associated with persistent post-operative urge incontinence (11).

One argument against the “urethral event hypothesis” is that placement of a mid-urethral sling, which theoretically should not impact the bladder outlet, has similar cure rates for MUI as traditional bladder neck slings.

3. What urodynamic technique did the authors use to measure leak point pressure and maximum urethral closure pressure? What data exists pertaining to the bladder volume at which leak point pressure is measured?

Leak Point Pressure (LPP) and Maximum Urethral Closure Pressure (MUCP) were used to define our cohort of patients with intrinsic sphincter deficiency.

These urodynamic parameters are used to assess urethral function. We recognize that the data is still mixed regarding these parameters and many uncertainties remain related to definitions and standardization of measurement (i.e. catheter size, zeroing of the transducer, patient position, bladder volume, provoking maneuver, and timing).
In our study, ISD was defined as a positive abdominal leak point pressure of < 60 cm H2O and/or a maximum urethral closure pressure < 20 cm H2O on preoperative urodynamic testing. Abdominal leak point pressures were measured with a rectal catheter, during filling cystometry, and with the patient sitting upright. Valsalva and cough were both used to provoke leakage at a bladder volume of 200ml. Maximum urethral closure pressure was calculated by performing urethral pressure profilometry before filling cystometry, and by then subtracting the maximum intravesical pressure from the maximum urethral pressure.

Based on previous studies, it is clear that women with UI are more likely to leak during Valsalva with increasing vesical volume and that valsalva leak-point pressures decrease significantly with bladder filling. The volume at which leakage occurs correlates inversely with clinical severity, i.e. leakage at lower volumes correlates with higher clinical severity (12).

4. **What is the best practice for measuring urinary frequency? Compare and contrast the method used by the authors with other available methods.**

According to the IUGA/ICS 2010 Joint Report, daytime urinary frequency is defined as the complaint that micturition occurs more frequently during waking hours than previously deemed normal by that individual. In our study, we used a patient subjective report: the frequency item (#15) of the urinary subscale of Pelvic Floor Distress Inventory Short Form (PFDI-20) to assess symptom bother related to urinary frequency. The PFDI-20 is a validated, condition-specific patient reported outcomes measure that has been shown to be reliable, reproducible and responsive to change related to improvement with therapy. Other validated questionnaires for the assessment of symptom bother related to urinary frequency do exist, including the Bristol Female Lower Urinary Tract Symptoms (BFLUTS) questionnaire, the Kings Health Questionnaire (KHQ), and the Medical, Epidemiological, and Social aspects of Aging (MESA) Questionnaire. The above questionnaires, while validated, are nevertheless subjective measures of urinary symptom severity and are thus potentially affected by recall and reporting bias. On the other hand, these questionnaires are easy to administer and complete, at little cost to the investigator, and with minimal time commitment from the patient.

Another method for assessing urinary frequency would be a frequency-volume chart (FVC). A FVC, which is completed by the patient, requires at a minimum, recording of voided volumes and times of micturition for a 24-hour period. This method provides a more objective assessment of urinary symptoms and information about the degree of frequency, as well as the mean volume of urine at each void. Completing a FVC is generally well accepted by patients but its validity is contingent on the proper recording of data.
There is no consensus for best practice for measurement of urinary frequency and studies comparing the above methods are very limited. McCormack et al compared urinary frequency as determined by patient questionnaire (non-validated) to results obtained by FVCs in 88 patients and found overall poor agreement (13). Best practice may be to use both means of subjective and objective assessment of urinary frequency.

5. **What determined the type of mid-urethral sling used in each patient? Do the authors have an established protocol? If not, why not?**

As this was a retrospective cohort study involving midurethral sling surgeries performed by one of six fellowship trained Urogynecologists, sling choice was entirely at the discretion of the individual surgeon. There was no established protocol regarding sling choice for the patients in this study. However, the majority of women in this study had a retropubic sling placed (80%) and the proportion of retropubic vs. transobturator slings did not differ between the two groups.

6. **When is use of the Fisher exact test appropriate? What other test is often used when the number of study subjects varies? Why?**

Fisher’s exact test is used to compare categorical variables when sample sizes (cell frequencies) are low (< 5) or when the data are distributed unequally among the cells of a table. This is because the Chi-squared test, which is typically used to compare categorical data, provides only an approximation of the significance value that is less accurate when sample sizes are small.

7. **How did the proportions of detrusor overactivity on preoperative urodynamic testing compare between the ISD-MUI and non-ISD-MUI groups? Why is this important?**

A higher proportion of women with ISD-MUI had detrusor overactivity on preoperative urodynamic testing than women with non-ISD-MUI (60% vs. 30%, P= 0.02). This is important because the purpose of our study was to determine if ISD is independently associated with the persistence of frequency and urge incontinence after mid-urethral sling surgery in women with MUI. If a secondary variable (pre-operative DO) is directly associated with the exposure (ISD) and outcome (persistent post-surgical frequency and UUI) of interest it can act as a potential confounder. Although clinically, preoperative detrusor overactivity on urodynamic testing has not been shown to be associated with more severe UUI or sling failure, we did control for this potential confounder using multivariable logistic regression.

8. **The authors state the rate of de novo urge incontinence and/or frequency after surgery was 19% in “67 women with complaints of SUI only at baseline” [Results section paragraph 3]. How is this possible given the authors defined the study
population as those with “affirmative response to the urge incontinence item (no. 16) on the PFDI?"

Although our primary population of interest was women with MUI, the database utilized for the analysis also included women without MUI who underwent mid-urethral sling placement through our division in a 2-year time frame. All patients in the database underwent pre-operative multi-channel urodynamic testing confirming SUI. For analysis of our primary outcome, we included only the subset of women with preoperative MUI, defined as an affirmative response to the urge incontinence item (#16) on the PFDI-20. For a secondary analysis, we assessed the rate of de novo urge incontinence and/or frequency in the 67 women who had a negative response to this item.

9. **How many patients had data available from the 12-month postoperative visit?**

Of the 137 women with MUI, 79 (58%) had completed the PFDI at their 12-month visit. For the remainder of women, data from the 6-month PFDI was used.

10. **The authors state the objective cure rate of stress symptoms in both groups was 90 and 99% [Discussion paragraph 6]. How was objective cure assessed and defined in the study?**

Objective cure of stress incontinence was defined as a negative post-void cough stress test at the 12-month post-operative visit (6-month data was used if 12-month data was unavailable). The results of the cough stress test were recorded as positive if urine loss occurred with a cough or as negative if no urine loss was seen.

**References:**

