Treatment of mixed urinary incontinence

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KEY WORDS

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ABSTRACT

Introduction. Mixed urinary incontinence (MUI) is a prevalent condition and imposes a significant impact on a woman's quality of life. Treatment is often challenging, as a single modality may be inadequate for alleviating both the urge and stress component.

Materials and methods. A MEDLINE search was conducted regarding English-language literature pertaining to the pathophysiology, diagnosis of, and treatment for MUI. Non-English language articles were considered if they could be translated into English using GOOGLE translator.

Results. The identification of an ideal single treatment has also been made more challenging by the poor characterization of the pathophysiology of MUI. Behavioral and lifestyle modification, as well as pelvic floor muscle therapy, should be considered first-line options for all women with MUI. Treatment of the urge component with anti-muscarinics is effective; however the stress component is likely to persist after therapy. Anti-incontinence surgery may have a positive impact on both the stress and urge components of MUI, with emerging evidence suggesting that transobturator MUS may be associated with lower rates of *de novo* and persistent urge component compared to other procedures. The presence of concomitant, preoperative detrusor overactivity has not been consistently associated with postoperative outcomes.

Conclusions. The optimum treatment of MUI may often require multiple treatment modalities. While surgery may have a positive impact on both the urge and stress component, its implementation should be approached with caution and patients should be carefully selected. Detailed informed consent in women with MUI cannot be overstated.

INTRODUCTION

The International Continence Society defines mixed urinary incontinence (MUI) as the complaint of involuntary leakage of urine associated with urgency and also with exertion, effort, sneezing, or coughing [1]. It is estimated that over 30% of all incontinent women suffer from both stress urinary incontinence (SUI) and urgency urinary incontinence (UUI), with the urge component typically causing a significantly greater negative impact on health-related quality of life (HRQL) [2-5]. While the negative impact of MUI is substantial, the optimal treatment of this entity remains elusive owing to the difficulty in properly defining its etiology and pathophysiology. Women with MUI are theoretically eligible for treatment with all of the modalities used for treating SUI and UUI independently. Combinations of behavioral modification, pelvic floor physiotherapy, and pharmacotherapy can be used for treating mixed symptoms; however, women with both stress and urge symptoms may remain a difficult group to treat optimally. While surgical procedures for SUI have historically been restricted to those women whose urge component has already responded to other treatments, evidence is emerging that surgical therapy for MUI may be effective in addressing both stress and urge components [6]. On the other hand, anti-incontinence procedures may also worsen existing UUI or induce *de novo* storage urinary symptoms. The objectives of this review are to define the relationship between MUI and detrusor overactivity (DO) and evaluate the available literature regarding the efficacy of conservative (non-pharmaceutical, non-surgical), pharmaceutical, and surgical therapy in women with MUI.

Defining mixed urinary incontinence

One of the key challenges in treating MUI lies in properly defining this entity. The ICS definition entails a subjective complaint of both SUI and UUI; however, this definition may not be inclusive of other common definitions, as urodynamic MUI may be defined as the coexistence of SUI and DO [1, 7]. Scarpero found that both, DO with incontinence and DO without incontinence are included in definitions of MUI found in the literature and, at present, a proposed term that may differentiate the two (i.e. "mixed urodynamic incontinence") is not defined by the ICS [8, 9].

Additional considerations contribute to the difficulty in establishing a single definition of MUI. First, the stress component of MUI may be objective and "overt", or it can be classified as "occult", when SUI is elicited only after reduction of pelvic organ prolapse. Second, SUI may be absent from a subjective symptom history but elicited during urodynamic evaluation, suggesting that, on occasion, SUI may be potentially misperceived as an urge event. Third, in addition to DO, UUI may be associated with urethral relaxation or an uninhibited premature micturition reflex [10]. Finally, the urge component in MUI may be superimposed on SUI as a behavioral response. Chou et al. postulated that the UUI component of MUI may be different than that of pure UUI, as a significantly higher proportion of their patients with pure UUI exhibited DO [11]. The authors felt that UUI may be over diagnosed in patients with SUI who misinterpreted their fear of leaking from SUI for UUI. Clearly, the absence of a universal definition of MUI makes study comparison difficult.

Diagnosis of MUI

The diagnosis of MUI should ideally rely on a symptom evaluation and urodynamic assessment owing to the inconsistent relationship between urodynamic- and symptom-based diagnoses [1, 7]. Most studies of MUI have reported outcomes in a specific subset of women with urodynamic SUI and DO without urinary incontinence. Despite DO and UUI occurring concurrently in up to 50% of SUI cases, several authors have noted a lack of correlation between urodynamically-demonstrated DO and subjective urinary

urgency, frequency, and UUI [12]. Foster et al. documented DO in 25% of women with stage III or IV pelvic organ prolapse; however, the authors noted no difference in the proportion of baseline UUI, urgency, or frequency in comparing women with and without DO [13]. Duckett and Basu likewise observed that the symptoms of urgency, frequency, and UUI were poorly associated with the diagnosis of DO [14]. The conclusions of both studies are consistent with previous reports that describe the sensitivity of UUI to predict DO on urodynamics to be as low as 8% [15]. Hence, the inconsistency between UUI and DO further complicates the definition of the urge component in women with MUI. These findings also suggest that diagnostic modalities other than laboratory urodynamics may be useful in the evaluation of women with MUI. Radley et al. have suggested that these women undergo ambulatory urodynamics, citing a higher detection rate of DO with this technique [16]. Certainly, the routine implementation of ambulatory urodynamics may carry a concern of DO over diagnosis; however, changes in technique, such as the use of a patient-completed symptom diary and placement of one transducer in the bladder, may decrease the over diagnosis of DO by almost two thirds [7].

Potential relationships between the urge and stress components of MUI

Further difficulty may be encountered when attempting to establish a connection between the urge and stress components of MUI. Several theories have been proposed regarding the etiology of UUI in the context of SUI. Some have focused on a common etiology with a focus on the proximal urethra and bladder neck. Jung et al. demonstrated that urethral perfusion of saline across the bladder neck in anesthetized rats may activate urethral afferents and facilitate the voiding reflex [17]. Serels et al. likewise proposed that an increase in intra-abdominal pressure stretches the pelvic nerves and causes a reflex bladder contraction [18]. Symptoms of SUI and UUI resolved in 92% and 75%, respectively, in women with "stress-induced detrusor instability" after undergoing a bladder neck pubovaginal sling. Fulford et al. proposed an "urethrogenic theory," whereas a reflex bladder contraction may result from urine entering the proximal urethra due to an incompetent bladder outlet [19]. Additionally, McLennan et al. proposed that shorter functional urethral length may allow urine to enter the proximal urethra and cause a reflex detrusor contraction, while Swash proposed that hypermobility of the proximal urethra during increases in intra-abdominal pressure causes peripheral denervation of the pelvic floor musculature, in turn leading to DO [20, 21]. The latter theory has also been considered when evaluating the association of DO and pelvic organ prolapse, as several authors have noted that UUI frequently resolves with prolapse reduction [13, 22, 23].

Additional evidence of a common pathway between the stress and urge components of MUI may be found in the fate of urge symptoms following anti-incontinence surgery. The rate of urgency / UUI resolution after anti-incontinence surgery varies widely (32-74%), while 16-68% may have worsening of their urge symptoms [24, 25]. Additionally, over 20% of women with only SUI may develop *de novo* urgency / UUI following anti-incontinence surgery [26]. A picture of partial obstruction, either before or after surgery, is an appealing theory to explain the aforementioned findings. In Brading's "myogenic" theory, DO is promoted by relative outlet obstruction via increased smooth muscle excitability and electrical coupling [27]. It is certainly possible that UUI, that resolves with prolapse reduction, was likely a result of smooth muscle changes induced by increasing degrees of anterior vaginal wall prolapse. It is also reasonable that bladder neck slings and suspensions improve UUI by restoring competency of the proximal urethra.

Finally, Petros has suggested that his Integral Theory may account for both categories of urinary symptoms [28]. This theory postulates that urinary storage and voiding symptoms, pelvic prolapse, and defecatory dysfunction are linked through the maintenance or loss of tone in three opposing muscle forces / vectors (pubococcygeus, longitudinal muscle of the anus, and levator ani). The symptoms of OAB and abnormal urodynamic parameters, such as intrinsic sphincter deficiency and low flow, are viewed as secondary manifestations of connective tissue damage in the vagina or its suspensory ligaments, rather than separate entities. This hypothesis may account for why reestablishment of vaginal support and repair of SUI with a midurethral sling (MUS) may be associated with a postoperative improvement in UUI in a significant percentage of women undergoing surgery; however, objective validation of these data is by other investigators is limited at this time. Thus, despite the elegant theories, it is not entirely agreed upon at present why certain surgical procedures relieve urge symptoms.

Outcomes of therapy for MUI

Non-surgical, non-pharmaceutical treatment of MUI

While this type of therapy is often referred to as "conservative", we feel that these modalities are effective first-line options and should be offered to all women with MUI. Indeed, behavioral modifications are associated with essentially no adverse events and by themselves may offer a significant improvement in symptom severity and quality of life (QOL). Behavioral techniques include scheduled urination and double voiding, as well as the judicious limitation of fluids. Pelvic floor muscle training (PFMT) has been evaluated in a recent Cochrane database review, and the authors found that PFMT was better than no treatment or inactive control for treatment of MUI [29]. Likewise, after eight weeks, Sar and Khorshid found that those women undergoing PFMT noted significant differences in the 1-hour pad test, episodes of leakage on a 3-day bladder diary, PFM strength, and Incontinence Quality of Life Questionnaire (I-QOL) scores ($p = 0.01$), compared to control group participants [30]. Finally, lifestyle modifications, such as weight loss, may result in improvement of MUI symptoms. Subak et al. recently demonstrated that overweight women who were enrolled in a 6-month weight loss program had a significantly greater improvement in number of weekly incontinence episodes and higher satisfaction with therapy than women offered education only [31].

Pharmaceutical treatment of MUI

It has been traditionally accepted that MUI responds less favorably to any single intervention when compared to either UUI or SUI alone [32]. However, recently published outcomes of medical intervention for MUI have revealed promising results [33]. The MERIT Trial (Mixed Incontinence Effectiveness Research Investigating Tolterodine) was a double-blind, randomized, placebo controlled multicenter, multinational trial (RCT) that enrolled 854 women with symptomatic MUI. After eight weeks, tolterodine ER produced a statistically significant decrease in the weekly UUI episodes compared with placebo (-12.3 *vs.* -8.0; $p < 0.0001$). Other micturition variables improved significantly more with tolterodine ER, while no difference was found between treatment groups regarding the change in the number of SUI episodes. A significantly greater proportion of patients receiving tolterodine ER (*vs.* placebo group) reported improvement in their bladder condition (61% *vs.* 46%; $p < 0.001$) and treatment benefit (76% *vs.* 55%; $p < 0.001$). After eight weeks, the tolterodine ER group had experienced statistically significant improvements (*vs.* placebo group) in 9 of 10 QOL domains. While this study supported the first-line use of anti-muscarinics for MUI, the improvement over placebo was modest. In contrast to earlier

studies, the MERIT trial found no association between the chronology of incontinence and outcomes, suggesting that the etiology of UUI in women with MUI has little influence on the response to therapy with muscarinic receptor antagonists [7, 33]. Previous experience with transdermal oxybutynin (Oxy TDS) likewise revealed a therapeutic benefit in women with MUI [34]. Dmochowski et al. reported on 520 patients (of who approximately 2/3 had concomitant SUI) randomized to Oxy TDS or placebo. At a dose of 3.9 mg daily, a significant improvement in the number of weekly incontinence episodes, mean weekly urinary frequency, mean voided volume, and quality of life was observed. Finally, Kreder et al. reported that tolterodine IR was just as effective in reducing the number of daily incontinence and frequency episodes in women with MUI as in women with UUI alone [35].

Estrogen supplementation as a treatment for both UUI and SUI has been evaluated in two meta-analyses and a systematic review. The Hormones and Urogenital Therapy Committee, which evaluated only six controlled trials out of 166 articles, demonstrated a significant subjective improvement in women with SUI [36]. However, in another meta-analysis of eight controlled and 14 uncontrolled trials, estrogen replacement therapy was found not to be effective in treating the symptoms of SUI, but was useful for symptoms of urgency and frequency [37]. Finally, an outcome of a recent large systematic review indicated that estrogen supplementation is not effective for treatment of SUI or UUI [38]. At the present time, most studies evaluating estrogen therapy for urinary symptoms demonstrate similar outcomes to treatment with placebo and high-quality studies are generally lacking.

Serotonin has been found to impact lower urinary tract function at the level of the spinal cord in several ways. Serotonin inhibits preganglionic parasympathetic outflow to the bladder, suppresses afferent input from the bladder, and enhances urinary storage through facilitation of the urethral sphincter reflexes [39]. Norepinephrine has likewise been implicated in neural regulation of the lower urinary tract [7, 39]. Duloxetine, a serotonin and epinephrine reuptake inhibitor, has been evaluated for treatment of SUI in Phase 2 and Phase 3 trials. In a double-blind RCT conducted in 553 women, duloxetine was associated with significant and dose-dependent decreases in incontinence episode frequency that paralleled improvements observed in the Patient Global Impression of Improvement (PGI-I) scale and the I-QOL [40]. The median incontinence episode frequency decrease with placebo was 41% compared with 54% for duloxetine 20 mg daily ($p = 0.06$), 59% for duloxetine 40 mg daily ($p = 0.002$), and 64% for duloxetine 80 mg daily ($p < 0.001$). One half of the subjects at the 80 mg daily dose had ≥64% reduction in incontinence episode frequency ($p < 0.001$ *vs.* placebo); 67% had ≥50% reduction ($p = 0.001$ *vs.* placebo). Similar statistically significant improvements were demonstrated in a subgroup of 163 subjects who had more severe stress urinary incontinence (≥14 weekly incontinence episodes; 49-64% reduction in incontinence episode frequency in the duloxetine groups *vs.* 30% in the placebo group). Discontinuation rates for adverse events were 5% for placebo and 9%, 12%, and 15% for duloxetine 20, 40, and 80 mg per day, respectively ($p = 0.04$). Nausea was the most common symptom that led to discontinuation and none of the adverse events that were reported were considered to be clinically severe.

A subsequent phase 3 trial recruited 683 women with SUI predominance and ≥7 weekly incontinence episodes (IEF) [41]. Mean baseline IEF was 18 weekly and 436 subjects (64%) had a baseline IEF of ≥14. There was a significant decrease in IEF with duloxetine *vs.* placebo (50% *vs.* 27%, $p < 0.001$) with comparably significant improvements in QOL (11.0 *vs.* 6.8, $p < 0.001$). Of women on duloxetine, 51% had a 50-100% decrease in IEF *vs.* 34% of those on placebo ($p < 0.001$). These improvements with duloxetine were associated with a significant increases in the voiding interval compared with placebo (20 *vs.* 2 minutes, $p < 0.001$) and they were observed across the spectrum of incontinence severity. The discontinuation rate for adverse events was 4% for placebo and 24% for duloxetine ($p < 0.001$), with nausea being the most common reason for discontinuation (6.4%). Nausea, the most common side effect, was typically mild to moderate and transient, usually resolving after one week to one month. Of the 78 women who experienced treatment-emergent nausea while taking duloxetine 58 (74%) completed the trial. In light of these outcomes, duloxetine is the first agent to show efficacy as a sole therapeutic option for SUI. While widely available in other countries, duloxetine is not currently approved by the U.S. Food and Drug Administration.

Outcomes of surgery in the treatment of MUI

Surgical intervention for MUI has been traditionally approached with some trepidation owing to the concern that these procedures may be associated with significant failure rates from aggravation of preexisting urgency or UUI, or development of *de novo* storage symptoms [42]. Despite the valid concerns, evidence is gradually emerging that several categories of anti-incontinence procedures may be effective in treating both the stress and urge components of MUI. After Burch colposuspension, up to 80% of women experienced a resolution of DO, [3, 43] although both of these studies were retrospective in nature and study populations included women with pure SUI and MUI. Langer et al. evaluated 30 women with combined SUI and DO who underwent colposuspension and the proportion of women with symptoms of DO decreased significantly from 73.3% preoperatively to 33.3% following surgery [44]. On the other hand, in a study comparing 2-year outcomes after colposuspension, significantly more women with pure SUI were cured compared to women with MUI (95% *vs.* 75%), suggesting that a preoperative urge component may have a deleterious effect on the efficacy of this procedure [45].

Since McGuire and Savastano suggested that DO was not a contraindication to pubovaginal sling surgery for SUI, several retrospective studies have concluded that bladder neck slings are effective in resolving preoperative urge symptoms (69% and 41% of autologous and cadaveric allograft slings, respectively) [19, 46, 47]. Additionally, Barnes et al. observed that 45% of their patients with preoperative UUI experienced resolution of these symptoms after treatment of prolapse and occult SUI with a bladder neck sling [48]. The wide range of cure rates after surgery should be interpreted cautiously due to the variations in definitions of cure, procedural differences, and different lengths of follow-up.

Surgical results are gradually emerging regarding the effect of mid urethral slings (MUS) on DO and MUI. In a prospective study with 4-year follow-up, Rezapour and Ulmsten reported a subjective cure of MUI in 85% of women after undergoing tension-free vaginal tape (TVT, Gynecare, Ethicon); however, urodynamics were not performed postoperatively and women with significant DO were excluded from the study [10]. Other groups have also reported substantial rates of MUI resolution after TVT surgery, but these cure rates have typically been significantly lower than those for women with pure SUI. Jeffry et al. reported similar objective cure rates (89%) for women with pure SUI and MUI; however, the subjective cure rate (66%) was significantly lower and was attributed to the 26% of women developing *de novo* urge symptoms [49]. In two retrospective, single institution studies with 5-year follow-up, cure rates for women with MUI compared with pure SUI were lower (54.9% *vs.* 81%) and (67% *vs.* 84.5%) [50, 51]. The authors of the latter study noted that ≥50% of the women with preoperative urinary urgency had successful resolution; however, women with DO had a less satisfactory outcome. At a minimum follow-up of six

years, Deffieux et al. likewise reported a higher cure rate in women with pure SUI than MUI after TVT (80% *vs.* 37%) [52]. Conversely, at a minimum follow-up of five years, Doo et al. observed similar cure rates in women with pure SUI and MUI after TVT (78% *vs.* 72%, p >0.05) [53]. Also, some authors have suggested that the resolution of DO symptoms after TVT may not be durable with longer periods of follow-up. In a questionnaire-based study of 112 women with MUI, Holmgren et al. observed a subjective cure rate of 60% at four years of follow-up (compared with 85% cure rate for women with pure SUI) [54]. The cure rate for MUI declined to 30% at four to eight years of follow-up, and the decline was attributed to symptoms of DO.

Several studies from a group in Illinois have compared the resolution of DO symptoms between different types of slings. In a retrospective analysis, Botros et al. found that DO resolved in significantly more women after MUS than after allograft bladder neck sling (38% *vs.* 15%, p <0.001) [55]. The rates of resolution of DO and subjective UUI between retropubic (TVT and SPARC, American Medical Systems) and transobturator (Monarc Subfascial hammock, American Medical Systems) MUS was also evaluated [56]. There was no difference in the rates of DO resolution among the three groups (40% *vs.* 48% *vs.* 32%, p = 0.39) at a follow-up of three months; however, the authors did observe a threefold increase in resolution of UUI symptoms for the transobturator sling over the retropubic MUS and bladder neck slings. Gamble et al. evaluated 305 women with MUI and preoperative DO, 112 of whom underwent bladder neck sling, 105 transobturator MUS, and 88 TVT [24]. Evaluation with postoperative urodynamics revealed that women who underwent bladder neck sling had the lowest rate of DO resolution compared to the other groups.

Can we predict which women with MUI will benefit from surgery?

A common gestalt to the surgical approach to MUI has been to first treat the component that most significantly impacts the woman's QOL. While sound in theory, this approach may be challenging for several reasons. First, there are currently no validated screening tools that quantitatively define the impact of the urge or stress component of MUI. Second, treating the urge component with non-surgical means may lead to a significant improvement in QOL and potentially reduce a woman's desire for further treatment. Furthermore, some women with MUI may require individual treatment modalities for each component. It is important then to ascertain whether predictive factors exist that may identify those women with MUI whose urge component is likely to benefit from anti-incontinence surgery.

Symptom presentation and predominance

The population of women with MUI is heterogeneous, with either the SUI or UUI component often occurring first or one of the two components typically being predominant. In a series of 46 women with MUI undergoing colposuspension, Scotti et al. observed that 56.5% of their patients had resolution of UUI, but women who developed SUI first had a significantly higher UUI resolution rate (78.6% *vs.* 22.2%) [43]. Lewis et al. found that women with urge predominant MUI were more likely to have lower urodynamic bladder capacities and demonstrable DO on UDS (70% *vs.* 26%), with higher amplitude contractions occurring at lower bladder volumes [57]. Likewise, Digesu et al. retrospectively evaluated 1,626 women with MUI and classified them according to the most severe symptom using the King's Health Questionnaire (KHQ) [58]. In those women with stress predominant MUI, 82% had urodynamic SUI, while in those with urge predominant MUI, 64% had DO (p <0.05). In women who had equally severe UUI and SUI, 46% had DO while 54% had urodynamic SUI. The authors concluded that the relative severity of symptoms from a symptom questionnaire significantly was able to distinguish between different urodynamic diagnoses.

Kulseng-Hanssen et al. prospectively evaluated the effect of TVT surgery on symptom resolution in 1,113 women with MUI [59]. Across all groups, SUI was cured in 87% and 83% of women at 7 and 38 months, respectively and women with stress predominant MUI had significantly better subjective and objective outcomes at both follow-up intervals than women with urge predominant MUI. The same group also determined that women with stress-predominant MUI had a better cure rate after TVT than women who were equally bothered by SUI and UUI [60]. Based on these results, the authors suggested counseling women with urge predominant and stress predominant MUI differently.

Presence of preoperative DO

The literature is divided regarding the association of preoperative DO and worse surgical outcomes, and currently there is no consensus on whether DO should be addressed prior to anti-incontinence surgery in women with MUI. Women with MUI and no DO on UDS reportedly have MUI resolution rates of 72-87% after colposuspension, bladder neck sling, or TVT, approaching those reported for women with pure SUI [10, 12, 61]. In their study comparing resolution of DO after bladder neck slings and TVT, Botros et al. and Paick et al. both determined that the presence of preoperative DO was a significant risk factor for postoperative DO [55, 62]. However, in a prospective study of stress-predominant women randomized to colposuspension or autologous sling, Nager et al. found that women with DO did not have significantly worse overall or SUI-specific success rates than women without DO [63]. Furthermore, based on a 3-day frequency volume chart and a validated questionnaire, Choe et al. found that after TVT women with DO had a significantly higher MUI resolution rate than women without DO (36.8% *vs.* 18.1%, p = 0.021) [64].

While the association of DO and lower MUI cure rates is not currently clear, the presence of high pressure DO is likely a risk factor for lower MUI cure rates. Lockhart et al. found that women with an absolute rise in detrusor pressure >25 cm H_2O during episodes of DO had poorer surgical outcomes than women with lower-amplitude DO [65]. Likewise, Schrepferman et al. observed in women with preoperative DO that complete resolution of urge symptoms occurred in 91% of those with low pressure DO, compared to only 28% of those with high pressure DO [66]. Thus, it may be prudent to counsel extensively or avoid surgery altogether in those women with high-amplitude DO.

Other urodynamic indices may also have a role in predicting outcomes after surgery for MUI. Duckett and Basu reviewed a pressure-flow study in 35 women with mixed DO and urodynamic SUI before and after TVT [14]. They observed that persistent postoperative DO symptoms were associated with a significantly decreased maximum flow rate and a significantly higher detrusor pressure at maximum flow. Women with persistent DO on cystometry had a significantly lower maximum flow rate before TVT as compared to women without persistent DO. Women with resolution of DO were more likely to have better flow rates before TVT than women who were not cured of DO. The authors felt that these findings suggested that partial obstruction is a potential reason for persistent DO after TVT.

The choice of anti-incontinence procedure

Although colposuspensions, bladder neck slings, and MUS are effective in treating the stress component of MUI, the impact on symptoms of DO may vary by procedure. Botros et al. determined that women receiving a transobturator MUS (8%) had a signifi-

cantly lower incidence of *de novo* UUI compared to TVT (33%) and SPARC (17%) [56]. The rates of persistent UUI and urodynamic DO were not significantly different between the three groups. Botros et al. also found that women who underwent bladder neck sling had more *de novo* UUI (62% *vs.* 29%), persistent urodynamic DO (85% *vs.* 62%), and persistent UUI (78% *vs.* 62%) than those who underwent TVT / SPARC procedures [55].

The use of questionnaires as predictive measures

As the presence of DO and other urodynamic indices may not correlate well with subjective symptoms, some authors have suggested the use of validated questionnaires to differentiate between mixed symptoms. Digesu et al. concluded that the KHQ significantly distinguished between different urodynamic diagnoses, while Lemack and Zimmern found that specific items from the UDI-6 could correlate with urodynamic findings, such as DO [58, 67]. Thirty of 36 women who answered that UUI was bothersome were found to have DO, which was significantly higher than the incidence of DO in women who did not report this complaint. Sinha et al. administered the MESA preoperatively and six months after TVT and found that symptom-based improvement on MESA scores related well with the basic outcome measures for SUI and UUI used by the British Society of Urogynecology database [68]. Further investigation into the role of validated instruments in predicting postoperative outcomes is justifiably warranted.

CONCLUSIONS

The identification of an ideal treatment modality for mixed urinary incontinence MUI is challenging due to difficulty in defining the entity and the lack of coordination between subjective symptoms and urodynamic findings. Furthermore, treatment may necessitate the employment of several modalities, as successful treatment of UUI may make SUI symptoms more prominent and treatment of SUI may be associated with *de novo* or persistent symptoms of DO. What cannot be debated is that non-pharmacological, non-surgical therapy with behavioral and lifestyle modification and PFMT is the first-line therapy, and should be incorporated in the treatment algorithm, for all women with MUI. Pharmacological therapy, most commonly with muscarinic receptor antagonists, is effective in addressing the urge component of MUI, and may often provide sufficient QOL benefit to diminish the impact of the stress component.

Although most of the studies are retrospective in nature and have relatively short-term follow-up, the literature appears to support the use of surgical intervention for select women with MUI. The recent long-term outcomes after the TVT procedure reveal 37-72% rates of MUI resolution; however, these rates may not be durable and may decline with longer follow-up. While outcomes of transobturator MUS continue to mature, there is some indication that the rates of de novo and persistent DO symptoms may be lower after these procedures compared with both bladder neck slings and retropubic MUS.

Women who develop SUI first, and those with stress-predominant MUI, appear to have better outcomes than women with urge predominance; however, outcomes remain difficult to predict in women with equal stress and urge predominance. No definitive conclusions can be drawn regarding the relationship of DO and resolution of MUI; however, women with low-pressure DO appear to have better outcomes than women with high-pressure DO. While not an ideal surrogate for subjective urge symptoms, urodynamics remains useful in the evaluation of women with MUI. Emerging evidence regarding the utility of validated questionnaires, such as MESA, UDI-6, and the King's Health Questionnaire, to assess the predominance of the stress and urge components may lead more practitioners to employ these tools in the evaluation of women with MUI. In conclusion, the majority of the data regarding the optimal treatment for the woman with troublesome MUI is hardly definitive. Many women may require multiple treatments and should undergo extensive counseling and informed consent prior to undergoing any type of anti-incontinence surgery.

Certainly current definitions of MUI place great emphasis on the bladder centric nature and causation of mixed urinary symptomatology. Other complicating factors may however compound or produce urinary urgency. Posterior compartment prolapse and uterosacral laxity is associated with urinary urgency and urinary symptoms have been found to resolve with intervention for these posterior compartment deficits [69, 70]. Indeed, UDS abnormalities may resolve with restoration of anatomic configuration [70].

Additionally, the concept of urinary urgency and aberration of the normal reflex arc has been called into question with several recent authors concluding that urgency may indeed be reflective of early activation or other abnormality of an otherwise normal mechanism [71-74].

Clearly, more clinical and definitive basic science work must be done to better elucidate the contributing factors and causations for the urge component of mixed incontinence.

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