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# Preoperative Factors as Predictors of Outcome of Midurethral Sling in Women with Mixed Urinary Incontinence

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## 1. Introduction

Mixed urinary incontinence (MUI) presents with characteristics of both stress urinary incontinence (SUI) and urge urinary incontinence (UII). It has been generally assumed to respond less favourably to any type of interventional therapy, whether behavioural, pharmacologic, or surgical as compared with pure stress (effort) or urge urinary incontinence. These patients represent a therapeutic challenge: two pathologies coexist, and treatment of either condition may worsen the symptoms of the other. The result is likely to be a poor response to conservative or surgical interventions. (Chaliha & Khullar, 2004)

The development of midurethral sling (MUS) surgery has become the gold standard for surgical treatment of SUI. There is great variability in data regarding cure rate of MUI following mid urethral sling (MUS) surgery of both the stress and urge components. Moreover, the postoperative course of the urge component after surgery is unpredictable as it may resolve, persist or worsen. There are no consistent predictors for persistent worsening of urge components after sling surgery. While there have been various factors described in the literature to predict who will be more likely benefit, these have not been clearly defined. Further compounding the difficulty is the lack of appropriate tools in delineating the characteristics of a mixed presentation. The poor response to treatment in MUI patients have led investigators to attempt quantifying and comparing dominance of either spectrum to dictate a priority of treatment and quantitatively assess outcome.

Despite such limitations, advance of treatment has allowed more aggressive combined approach to MUI, necessitating the delineation of patient profiles appropriate for each treatment method. Here we will review the current investigations analysing the two distinct pathophysiologies of MUI, as well as the suggested factors determining the outcome following MUS treatment.

## 2. Prevalence of MUI

MUI is the coexistence of stress and urgency urinary incontinence and is defined as involuntary loss of urine associated with the sensation of urgency and also associated with exertion, effort, sneezing or coughing. (Haylen et al., 2010) Mixed incontinence can also be

defined urodynamically as the coexistence of urinary stress incontinence (USI) and detrusor over activity (DO). DO is characterized by involuntary detrusor contractions during the filling phase and is associated with urgency or incontinence. Urge urinary incontinence is the complaint of involuntary leakage accompanied by or immediately preceded by urgency. Investigators, however, often have grouped several different pathologies together under the category of "mixed incontinence." (Khullar et al., 2010) Further compounding the definition of MUI is an acknowledged fact that stress incontinence may also be misperceived as an urgency event. The presence of urine in the posterior urethra may actually induce urinary urgency and eventuate in a secondary episode of detrusor overactivity (stress-induced detrusor overactivity). Therefore, in some individuals, stress incontinence may actually masquerade as MUI due to the significant urgency component associated with spontaneous urinary loss. Urinary frequency is superimposed over this scenario as a behavioral response to the bothersome urinary symptoms. (Dmochowski & Staskin, 2005)

As previously noted, the difficulty in collating the results of different studies primarily lies with a confusion in definition. Epidemiologic studies also vary with reports based on symptoms to those based on urodynamic parameters. While the term "mixed incontinence" remains a clinically useful concept there is debate over the utility of its use for outcomes research. Dooley et al. investigated the discrepancy of prevalence between subjective and objective definitions of MUI. The study showed that in the population of women seeking surgical treatment for stress incontinence, the majority of women fell into the category of MUI when using subjective measures to define the condition. (Dooley et al., 2008) Prevalence rates ranged from 50% to 93% depending on the questions used and severity selected; however, when using objective measures only 8% were diagnosed as having MUI on urodynamics. These data illustrate how such wide variations in prevalence rates for MUI can occur. To date, the appropriate MUI definition has not been agreed upon for either research or clinical care.

Most clinical studies, however, generally approximate the prevalence of MUI as one-third of women with urinary incontinence. (Karram & Bhatia, 1989) Recent incidence data based on urinary symptoms were obtained through the National Overactive Bladder Evaluation (NOBLE) Program, which investigated urinary incontinence in 5,204 adults residing in the United States, 2,735 of who were women. When these survey data were applied to the 2000 US census, the total number of US women with incontinence was estimated to be 14.8 million. Urge, stress, and mixed incontinence each accounted for approximately one-third of cases. (Stewart et al., 2003) The study of medical, epidemiological, and social aspects of aging (MESA), conducted by Diokno et al. reported the prevalence of different types of urinary incontinence in senior citizens aged 60 years. (Diokno et al., 1986) Of the 1,150 randomly sampled non-institutionalized women included in the study, 716 were self-reported as continent and 434 as incontinent. The study found that 55.5% of the incontinent women had mixed stress and urge incontinence, 26.7% had stress incontinence alone, 9% had urge incontinence alone, and 8.8% had other diagnoses.

The limitations of comparing MUI in epidemiologic studies to MUI in clinical settings may also be due, in part, to the fact that they require purely symptom based assessments. Thus, one would expect that evaluations of MUI in clinical samples would be superior as they tend to employ a combination of subjective and objective evaluation. Unfortunately, the variation in prevalence rates for MUI in these settings is equally broad. Lemack and

Zimmern investigated 128 women reporting lower urinary tract symptoms and found that 26.6% had mixed incontinence, 20.3% had stress incontinence, 13.3% had urge incontinence, 14.1% had urgency and frequency symptoms, and 10.1% had vaginal prolapse. (Lemack & Zimmern, 1999) However, when symptoms were matched with urodynamic findings they correlated in less than 50% of the time.

Urodynamic studies, which provide objective evidence of the type of urinary incontinence, have shown that between 8% and 56% of women with urinary disorders have proven mixed incontinence. Digesu et al. reported rates of DO in a population of stress predominant MUI was 11%. (Digesu et al., 2008) Dooley reported that the proportion of women diagnosed with MUI ranged from a low of 8.3% using only the urodynamic-based definition. (Dooley et al., 2008) Chou et al. suggested that patients may mistake the urge component for the "fear of leaking for urge", in explaining the discrepancy between subjective and objective diagnoses. (Chou et al., 2008)

The absence of a universal definition of mixed incontinence has made it difficult to compare findings from studies. Whether it is defined urodynamically or symptomatically, incontinence associated with both stress and urge is considered mixed in nature. Ideally, a reproducible instrument that would clearly segregate stress versus urge symptoms and assess the magnitude of bother for a particular patient would best define the MUI presentation; however, this entity is yet to be defined.

Another difficulty in estimating the population of MUI is the varying degrees of severity in what constitutes the urge component. In a recent, randomized study to investigate the treatment of mixed incontinence in women, Bump et al. found that 31% of patients had mixed urinary incontinence symptoms. (Bump et al., 2003) These women had more severe baseline urinary incontinence than did those with USI in terms of frequency of incontinence and impairment of quality of life. Surprisingly, the baseline severity of incontinence was less in women with urodynamically proven mixed incontinence than in those with USI. The authors performed a comprehensive nationwide survey in Korea and found 40.8% of patients aged 30-79 years reported urinary incontinence. (Choo et al., 2007) Pure stress incontinence only consisted about half of this population (22.8% overall), while the remainder reported mixed symptoms. Of note, patients with mixed symptoms reported a higher degree of impact on daily activities, social life and mental symptoms. More patients with mixed symptoms reported an insult on the overall quality of life (43.8%) compared to pure stress symptoms (28.3%). Furthermore, these patients reported a higher likelihood to seek medical attention for their problems (19.1% vs. 25.8%).

Other than semantic aspects of this question, patients may also significantly vary in their pathophysiology. This is more evident in the diverse presentation of these components pertaining to age or race. Nygaard and Lemke reported that stress incontinence occurs in a higher degree in older women (i.e., 40%). (Nygaard & Lemke, 1996) In studies of Scandinavian women, the rates of SUI peaked at approximately 60% in patients who were in their fifth decade (40-49 years). Urge incontinence began to increase in the sixth decade of their life and peaked at approximately 20% between 80 and 89 years. Racial differences have in fact been reported in a few studies. Bump identified mixed incontinence in up to 17% of African American subjects compared with only 11% of whites. (Bump, 1993) A larger proportion of white women, however, were found to have USI (61%) compared with African American women (27%).

### 3. Proposed mechanism of mixed urinary incontinence

There are several theories of DO in MUI. The most commonly proposed mechanism attributes MUI primarily to triggering of an involuntary bladder contraction. (Serels et al., 2000) Detrusor overactivity is, however, often not identified in many patients undergoing analysis for OAB wet symptoms. As previously noted, the underlying source of mixed incontinence may be detrusor overactivity associated with SUI which may represent a reflex stimulated by urine entering the proximal urethra during stress events. (Dmochowski & Staskin, 2005) This supposition has been shown to correlate with certain urodynamic factors including diminished urethral functional length in patients with urethral instability. Urethral instability instigates a bladder contraction response (detrusor overactivity), which is a normal physiological event. Webster et al. reported on a series of 73 patients with cystometrically diagnosed detrusor overactivity in combination with SUI. (Webster et al., 1984) A third of these patients had a period of electromyographic silence immediately preceding an unstable detrusor contraction. They concluded that the unstable contraction may have been induced by a urethral event and, therefore, was not a primary bladder abnormality.

There is a possibility that mixed symptoms may be due to a more severe form of stress component rather than two separate mechanisms for urge and stress incontinence (Bump et al., 2003); or that DO is caused by a weak urethral sphincter mechanism, resulting in funnelling of the proximal urethra. Major et al. identified that patients with detrusor overactivity had thinner urethral longitudinal smooth muscle layers and lower MUCP. (Major et al., 2002) McLennan et al. demonstrated that the functional urethral length was significantly shorter in patients with urethral instability. (McLennan et al., 2001) This shortened functional length may allow urine to enter the urethra, as there is less of a barrier, resulting in a weak urethral sphincter mechanism, which leads to funneling of the proximal urethra. When intra-abdominal pressure is increased, urine enters the proximal urethra, producing sensory stimulation and resulting in a reflex bladder contraction. (Fulford et al., 1999) This "urethrogenic" theory has also been supported by observations that patients with detrusor overactivity have significantly lower MUCP on urethral pressure profilometry, as well as lower angle of deflection measured by Q-tip cotton swab test. (Awad & McGinnis, 1983; Kim et al., 2010) The authors compared urodynamic characteristics, as well as physical examination findings in a retrospective study of 241 patients who were diagnosed with urinary incontinence. We found that patients with mixed incontinence showed lower Q-tip angle ( $28.6^\circ$  vs.  $42.1^\circ$ ) and lower MUCP (44.1cmH<sub>2</sub>O vs. 54.7cmH<sub>2</sub>O), in addition to higher symptom severity and lower bladder capacity. (Kim et al., 2010)

There are several possible explanations why UUI may improve after MUS surgery. One particular explanation is that MUS prevents urine from entering into the upper posterior urethra with increases in intra-abdominal pressure thereby avoiding reflex urgency. (Koonings et al., 1988; Minassian et al., 2008) Another possible explanation is that MUS may stabilize urethral overactivity, both statically and dynamically. (Kim et al., 2010) The current MUS are generally designed to be applied in a tension free manner at the urethra, theoretically providing a kinking axis, rather than a pressure aided coaptation of the urethra. Such mechanisms underscore the beneficial effects that MUS may provide to the urgency symptom per se, rather than an incidental improvement through relief of stress symptoms.



#### 4. Outcome of midurethral sling in resolution of mixed urinary incontinence

The presenting symptoms of patients may be a guide to the approach to MUI. In those cases where either the stress or urge symptoms predominate, the most bothersome symptom should be approached first to potentially lessen the impact of the secondary symptom. Older surgical literature implies that patients with significant stress symptoms preoperatively, even if detrusor over activity is present, have a greater likelihood of success than those patients with a significant preoperative urge. The use of history (inclusive of symptomatic appraisal) associated with physical examination demonstrating (or not) stress incontinence may be very helpful in assessing the relative contributions of stress and urgency symptoms as well as the other potential insensate urinary loss that some patients experience. (Dmochowski & Staskin, 2005) Once the patient's initial response to the primary intervention is determined, further therapies can be recommended for persistent symptoms or for secondary symptoms, should those symptoms remain problematic. For instance, patients with mixed symptoms with a strong urge component and definable but less severe stress component could undergo therapy specially defined to ameliorate the urgency symptoms including anticholinergic use followed by neuromodulation (and/or botulinum toxin) and a secondary intervention for the bladder outlet, should persistent stress symptoms remain bothersome. Similarly, patients with predominant stress symptoms could undergo intervention for SUI with secondary interventions for UUI depending upon the results of the primary intervention and persistence of bothersome urinary symptoms. Therefore, the approach to MUI should be based on symptomatic segregation, with therapy promulgated on the basis of the most bothersome symptom and secondary interventions reserved for either persistence of the primary symptom or bother arising from the less prominent initial symptom. In those individuals with relatively equal bother, or who are unable to segregate their symptoms, the initial guideline to therapy may become apparent only after beginning more intensive evaluation (such as urodynamic studies). Alternatively, conservative or minimally invasive intervention may be initiated to establish response, followed by more intensive intervention for nonresponse. Ideally, patients should be informed about which symptoms may persist or become problematic post-intervention.

The role of surgery in the treatment of mixed incontinence had been historically considered highly controversial due to a high failure rate, from symptomatic or asymptomatic DO. (Stanton et al., 1978) More recently, several studies have concluded that an effective pubovaginal sling can cure stress incontinence and may also have benefit for urge symptoms. Langer et al. reported the results of a study of 30 women with mixed incontinence who underwent Burch colposuspension. (Langer, 1988) The proportion of patients with symptoms of DO decreased significantly from 73.3% before to 33.3% after surgery. In all, 50% of patients had marked improvement in clinical symptoms of DO. Normal cystometric findings were present postoperatively in 60% of patients, and only 40% had evidence of DO on postoperative urodynamic assessments. Ulmsten et al. evaluated the effect of TVT in 80 women suffering from MUI. (Ulmsten et al., 1996) They demonstrated that at a mean of 4 years, both SUI and UUI were cured in 85% of patients, significantly improved in 4%, and unchanged or worse in 11%. They concluded that TVT could be used to treat women patients with MUI. This study excluded patients with significant detrusor overactivity; therefore, the population was somewhat selected. Anger and Rodriguez reported that surgical intervention for patients with mixed incontinence resulted in

incontinence resolution rates ranging from 20 to 70%. (Anger & Rodriguez, 2004) They concluded that those patients with predominant symptoms should have the primary symptoms initially managed. They further concluded that persistent symptomatology may not require secondary therapy and intervention for symptomatic persistence should be based on patient bother. In the study by Segal et al. (Segal et al., 2004), the improvement rate of the irritative subscales in the Urinary Distress Inventory for patients with MUI was 87.8%.

On the other hand, several studies have presented that these results were only transient. Several studies report good cure rates of stress component (85–97%) and lower (30–85%) and declining cure rates of urge incontinence over time following MUS in MUI. Holmgren et al. presented initial good cure rates of TVT, with up to 60% at 4 years, for MUI which did not persist after 4 years, decreasing to 30% cure rate from 4 to 8 years. (Holmgren et al., 2005) There seems to be no significant difference in the overall subjective and UUI cure between tapes used by retropubic (TVT) or transobturator routes. Colombo et al. (Colombo et al., 1996) assessed women who underwent Burch colposuspension. These investigators retrospectively compared findings from 44 women with mixed incontinence and matched controls with USI. At the 2-year follow-up point, the cure rate for stress incontinence was significantly lower in the group with mixed incontinence than in the group with stress incontinence alone (75% vs. 95%,  $P$  0.02). One study reported that the overall cure rate was lower in women with MUI (55%) as compared with women with SUI only (81%) at 5-year follow-up after surgery. (Ankardal et al., 2006) They found type of incontinence was the only independent variable found to influence surgical outcome. In another study, when cure rate was defined as stress and urge indices of two or less (episode of incontinence one to four times a month or less), the observed subjective cure was 60% at 7 months and 53.8% at 38 months. But on the other hand, when cure was defined as complete dryness, the subjective cure rate dropped to 35.9% at 7 months and 28.4% after 38 months. (Kulseng Hanssen et al., 2007)

Another pitfall in the interpretation of these data is the discrepancy between subjective and objective determination of treatment success. Karram and Bhatia reported results in 52 women, 27 of whom underwent surgery (i.e., modified Burch colposuspension procedures). (Karram & Bhatia, 1989) Cure, defined as complete subjective relief of incontinence plus objective evidence of the disappearance of both stress incontinence and DO on repeat urodynamic testing, was achieved in 59% of the patients who underwent the surgery. Another 22% of surgically treated patients had improvement, defined as complete subjective relief of symptoms with objective evidence of the persistence of incontinence at the time of testing, or adequate relief of symptoms, such that the patient did not desire any further therapy. Of the 25 patients treated medically, 32% achieved cure and 28% were markedly improved. In another study that assessed TVT in women with either USI or mixed incontinence, the objective cure rate (89.3%) was similar for both types of incontinence, but the subjective cure rate was 66%, a significant difference ( $P$  0.05), for objective versus subjective evaluations. (Jeffrey et al., 2001) The lower subjective value was attributed to patients with de novo urge symptoms.

Appropriate case selection is of utmost importance in order to get good results after surgery. Cure rate of MUI is better in a group of women with predominant SUI symptoms in comparison to a group with predominant UUI symptoms. (Kulseng Hanssen et al., 2007) The effect of detrusor overactivity on urodynamics associated with MUI on outcomes is not

as clear as the majority of studies did not include urodynamically proven MUI. MUI implies a component of detrusor dysfunction that may be motor or sensory and is associated with superimposed urethral sphincteric underactivity. Rates of incontinence improvement in pharmacologic studies are approximately 70% although a substantive percentage of these patients are improved, not cured. Potential pharmacologic approaches to the treatment of mixed incontinence include antimuscarinic agents, estrogen replacement therapy (for postmenopausal women), and dopamine, serotonin, and norepinephrine reuptake inhibitors. (Khullar et al., 2010) Electrical stimulation is another conservative measure that could potentially be used for the treatment of MUI. (Sand, 1996) Surgery should be considered after failed medical management, proper work up, and careful counselling about the lower overall success rates of around 55%.

### **5. Preoperative risk factors for mixed urinary incontinence**

Though various factors have been described in the literature to predict the persistence of urge components following incontinence procedures, no single predictor has presented consistent value between studies. Earlier studies, investigating Burch colposuspension, suggested precedence in patient symptom history were indicative of symptom predominance within a mixed profile of incontinence, and consequently better outcomes for patients with precedent stress symptoms. Scotti et al. investigated 82 women who underwent Burch colposuspension. (Scotti et al., 1998) They found that patients with a history of stress symptoms preceding the onset of urge symptoms showed higher cure rates compared to antecedent urge patients (78.6% vs 22.2%,  $p < 0.001$ ). Langer et al. also showed similar results, also with Burch colposuspension. However, these results have not been reproduced in recent MUS procedures. (Langer, 1988)

Urodynamic studies would appear to have predictive benefit for some patients with mixed symptoms in elucidating the gravity of urethral dysfunction (stress component) and any associated detrusor dysfunction. (Lin et al., 2004) Certain aspects of detrusor dysfunction, such as high-pressure detrusor overactivity, have been suggested to be indicative of outcome, though investigators varied in their use of its reference value. The authors retrospectively reviewed 279 patients with MUI who underwent MUS with at least 2 years of follow up. (Kim et al., 2008) Patients were divided into patient with a predominance of bother symptoms and a predominance of DO, where DO patients were further divided into patients with high pressure DO and low pressure DO with a reference level of 15cmH<sub>2</sub>O of maximum detrusor pressure at which involuntary contraction occurs during filling cystometry. We found that patients with high pressure DO showed improvement of urge symptoms in 70% compared to 91.4% for patient with low pressure DO ( $p = 0.03$ ). These factors also seemed to affect resolution of stress components as patients with high pressure DO showed lower resolution rates than low pressure DO patients (90% vs. 96.6%,  $p = 0.04$ ). In a retrospective study of 51 patients, Panayi et al. found that higher opening detrusor pressure, lower volume at DO during cystometry and higher detrusor pressure were predictive of persistent DO. (Panayi et al., 2009) Schrepferman et al. evaluated 84 women undergoing a pubovaginal sling surgery for MUI. (Schrepferman et al., 2000) Of those patients, 69 had urgency symptoms. Urgency was related to defined motor urge (as established on urodynamic testing) in 41 women. Twenty-eight patients experienced sensory urgency (urge symptoms with/ without urodynamic findings). Complete resolution



or improvement in urge symptoms occurred in 24 (58.5%) patients with urodynamically demonstrated motor urge incontinence, and an additional 7 (17.1%) patients were improved. In those patients with sensory urgency, only 11 (39.3%) patients were cured, and 9 (32.1%) patients were improved. Additionally, in those patients with urodynamic motor urge overactivity, 21 of 23 (91.3%) patients were cured, and 2 (8.7%) patients were improved if low pressure overactivity was present. High-pressure instability was associated with a cure in only 5 (27.8%) patients, and improvement in another 5 (27.8%) patients. The investigators used 15 cm of water as a cutoff for low-pressure versus high-pressure motor overactivity of the bladder. They suggested that patients with low-pressure motor urgency are more likely to experience resolution than those with high-pressure. Despite the fact that the International Continence Society no longer utilizes motor versus sensory urgency, the application of this trial is limited; however, these findings are interesting and provocative for potential subsequent clinical trials. Finally, on the basis of the symptoms present, Scotti et al. reported that high-pressure detrusor overactivity presented commonly with stress symptoms is a significantly poor prognostic indicator with pressures of 25cmH<sub>2</sub>O or greater being consistent with poor surgical results. (Scotti et al., 1998)

Recently, Paick et al. evaluated factors that might predict persistency of urge incontinence in patients after undergoing tension-free vaginal tape (TVT) procedures. (Paick et al., 2007) They evaluated 274 patients of which 73 had mixed urinary symptoms. They found cure rates for stress incontinence to be different (78.1% for the mixed symptom group versus 95.5% for the pure group). Their analysis revealed that maximal urethral pressure was associated with a greater risk of persistent urge symptoms, suggesting that profound urethral dysfunction may be contributory to persistent symptoms after TVT. These findings are again intriguing and suggest the possibility that urethral dysfunction and resultant effects upon the severity of SUI may affect detrusor function. This paper gives further support to the fact that correction of the low-pressure outlet may benefit at least some individuals with detrusor overactivity although the overall benefit may be less than that experienced by patients with only SUI.

Other studies have failed to find significant predictive value for successful treatment of MUI in urodynamic studies. Houwert et al. retrospectively reviewed 437 patients who received MUS, in which the diagnosis of MUI itself was also used as a factor in analysis. (Houwert et al., 2009) Results showed that a diagnosis of MUI, a history of previous incontinence surgery and the presence of detrusor overactivity was predictive, while urodynamic parameters failed to suggest insight to outcomes in multivariate analyses. However, relative symptom components are most frequently reported as predominant and nonpredominant (assuming a rough estimate of percentage contribution). As noted previously, this method can be inaccurate and begs the need for better methods of symptom quantification. Given the confusing terminology for both patients and surgeons of what constitutes MUI, as well as the higher failure rate of surgical outcomes, treatment should be individualized based on clinical scenario along with urodynamic findings.

## 6. Conclusion

Recent advances in surgical treatment for stress urinary incontinence have provided effective resolution with limited morbidity. However, preoperative components of urgency complicate the treatment outcomes in a significant number of patients. Detrusor overactivity

and urgency symptoms represent a separate and distinct pathophysiology, of which the possible occurrence or persistence must be addressed before management of stress incontinence symptoms. Several studies have suggested high pressure detrusor overactivity or maximal urethral pressure during preoperative urodynamic studies may implicate a higher rate of treatment failure in mixed urinary incontinence. Other studies have suggested insights into the predominance or antecedence in urgency symptoms may be indicative of treatment difficulty. Currently, no definite conclusions have been reached. Future studies require a cohesive approach in determining risks and treatment methods, while clinically, patients should be warned of risks and possibility of continued medical treatment associated with mixed symptoms.

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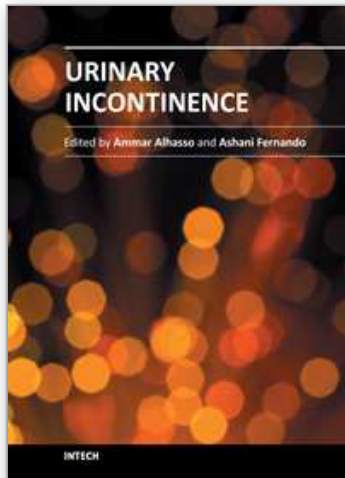
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Management strategies are framed within a multidisciplinary team structure and as such a range of specialists ranging from psychologists, specialist nurses, gynaecologists and urologists author the chapters. There are some novel methods outlined by the authors with their clinical application and utility described in detail, along with exhaustive research on epidemiology, which is particularly relevant in planning for the future.

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