The use of voiding studies in the evaluation of women with Overactive Bladder Syndrome

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Table of Contents

Abstract Page 4

Declaration and Copyright statement Page 5

Acknowledgments Page 6

Publications and presentations Page 7

Index of figures and tables Page 9

Chapter One Setting Page 12

Chapter Two Overactive Bladder Syndrome Page 15

Chapter Three Overactive Bladder Syndrome and voiding in women: Current Evidence Page 58

Overall null hypothesis Page 71

Chapter Four Methodology: Page 72

Assessment of lower urinary tract symptoms in women-
History, examination, quality of life and urodynamic studies

Chapter Five The predictive value of pretreatment pressure flow studies Page 93

in women with overactive bladder symptoms treated with antimuscarinics

Chapter Six Effect of prolapse repair on voiding and the relationship Page 105
to overactive bladder and detrusor overactivity- pilot and feasibility study

Chapter Seven A prospective study to assess the effect of prolapse repair Page 121
on voiding and overactive bladder symptoms
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter Eight</td>
<td>The effect of urethral dilatation on pressure flow studies in women with voiding dysfunction and overactive bladder- pilot data</td>
<td>135</td>
</tr>
<tr>
<td>Chapter Nine</td>
<td>A randomised trial of cystoscopy and urethral dilatation versus cystoscopy alone in women with overactive bladder symptoms and voiding dysfunction</td>
<td>150</td>
</tr>
<tr>
<td>Chapter Ten</td>
<td>Conclusions and suggestions for future research</td>
<td>164</td>
</tr>
<tr>
<td>References</td>
<td></td>
<td>170</td>
</tr>
<tr>
<td>Appendix I</td>
<td>Abbreviations used in text</td>
<td>221</td>
</tr>
<tr>
<td>Appendix II</td>
<td>Patient Global Impression of Improvement (PGI-I) and King’s Health Questionnaire</td>
<td>223</td>
</tr>
</tbody>
</table>
Abstract
The aim of this study was to explore the relationship between voiding and overactive bladder (OAB) in women, in order to evaluate whether voiding assessment has any impact on management. This concept was explored within several clinical models. The first study assessed women with detrusor overactivity (DO) undergoing treatment with solifenacin, and identified that women who failed to respond to treatment had a significantly lower pre-treatment maximum flow rate (Qmax) than responders, indicating that urodynamic evidence of differences in voiding can be used to predict treatment response. Prolapse was used as a model of possible elevated urethral resistance. A retrospective analysis of women with OAB and prolapse identified a 53% cure rate for OAB following prolapse surgery, with cure being associated with a significant increase in Qmax and decrease in opening detrusor pressure (ODP). A powered prospective study in the prolapse and OAB population confirmed resolution of OAB symptoms to be associated with an increase in Qmax. Because the relationship between voiding and prolapse is imprecise, the final model used was women with confirmed voiding dysfunction and OAB undergoing urethral dilatation. A retrospective analysis confirmed urethral dilatation to lead to a significant increase in maximum flow rate (when corrected for voided volume), but with a poor cure rate for OAB of 19% at 6 months. Cure of OAB at 6 weeks was associated with a significant increase in Qmax and decrease in PdetQmax. This was followed up with a randomised trial of urethral dilatation and cystoscopy versus cystoscopy alone in women with OAB and voiding dysfunction, which showed urethral dilatation to lead to a higher cure rate for OAB at 6 weeks, but with no long term benefit, and no significant effect on health related quality of life even at 6 weeks. Collectively, these data do suggest an association between voiding parameters and OAB, although the mechanism of this association remains uncertain. Voiding may be a biomarker for another underlying process which affects OAB symptoms. Direct manipulation of the voiding axis in women is poorly defined and future work should focus on the aetiology of voiding differentials in selected women, and whether more targeted correction of these will be effective.
DECLARATION

The work contained within this thesis was predominantly carried out in the Urogynaecology Unit, Department of Obstetrics and Gynaecology, Medway Maritime Hospital, but with some recruitment also from the Department of Urogynaecology at William Harvey Hospital.

All the studies had local ethics committee approval where appropriate, and the women included gave informed consent. All the work in this thesis was my own.

Maya Basu

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Publications and Presentations

The following publications and presentations have been generated from the work contained within this thesis.


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The effect of anterior repair on voiding and the overactive bladder
- Presented by **M Basu** at the UK Continence Society Annual Meeting, 9th-11th April, 2008
- Presented by **M Basu** at the International Urogynaecology Association annual meeting, Taipei, 15th-17th September, 2008

The effect of urethral dilatation on pressure flow parameters in women with voiding dysfunction and overactive bladder.
- Presented by **M Basu** at the UK Continence Society Annual Meeting, 15th-17th April, 2009 (discussed poster)
- Presented at the International Urogynaecology Association annual meeting, Como, Italy, 15th-20th June, 2009
A randomised trial of cystoscopy alone versus cystoscopy plus urethral dilatation in women with voiding dysfunction and overactive bladder symptoms
- Presented by M Basu at the UK Continence Society Annual Meeting, 12\textsuperscript{th}-14\textsuperscript{th} April, 2010
- Presented by M Basu at the International Urogynecological Association meeting, Lisbon, 28\textsuperscript{th} June-2\textsuperscript{nd} July, 2011

The association between voiding and response to treatment with antimuscarinics in women with overactive bladder syndrome
- Presented by M Basu at the British Society of Urogynaecology Annual Research Meeting, 9\textsuperscript{th} November 2011
**List of figures and tables**

Figure 2.1  
The relationship between urgency and other OAB symptoms  
(from Chapple et al, 2005a)  
Page 20

Figure 3.1.  
Nomogram for diagnosis of female bladder outlet obstruction  
(from Blaivas and Groutz, 2000)  
Page 65

Figure 4.1  
Baden Walker classification for pelvic organ prolapse  
Page 76

Figure 4.2  
Pelvic Organ Prolapse Quantification  
Page 76

Figure 4.3  
Example of a bladder diary  
Page 80

Figure 4.4  
Normal uroflowmetry curve  
Page 83

Figure 4.5  
Urodynamic machine and commode at Medway Hospital  
Page 92

Table 4.1  
Comparison of mean voiding parameters from uroflowmetry and pressure flow studies  
Page 89

Table 5.1  
Distribution of PGI-I scores by diagnosis  
Page 98
Table 5.2
Mean pre-treatment pressure-flow parameters in responders and non-responders with 95% confidence intervals Page 99

Figure 6.1
Illustration of retrovesical angle Page 116

Table 6.1.
Age, time to follow up and procedure undertaken Page 111

Table 6.2.
Mean pre- and post-operative values for maximum flow rate in ml/sec. Page 112

Table 6.3.
Mean pre- and post-operative values for voided volume and detrusor pressure at maximum flow and at opening. Page 114

Table 6.4.
Mean pre- and post-operative values for Bladder Outlet Obstruction Index Page 114

Index

Table 7.1
Types of prolapse procedure undertaken Page 127

Table 7.2.
Compartments repaired in Groups 1 and 2 Page 127

Table 7.3
Mean pre- and post-operative values for maximum flow rate (ml/sec) Page 128
Table 7.4
Mean pre- and post-operative values for volume voided and acceleration of flow rate

Table 8.1.
Mean pre- and post-urethral dilatation pressure flow parameters and maximum flow rate centiles for whole cohort

Table 8.2.
Mean pre- and post-urethral dilatation pressure flow parameters and maximum flow rate centiles for patients with symptomatic improvement

Table 9.1
Baseline demographic and clinical characteristics in each group

Table 9.2
Primary outcome measure at 6 weeks and 6 months ("no urgency", taken as response 3 on the UPS)

Table 9.3.
Pre- and post-operative mean voiding parameters for each study group

Table 9.4
Mean scores from the domains of the King’s Health Questionnaire pre and 6 weeks post-procedure

Figure 9.1
Flow of participants through trial
Chapter One

Setting
The work contained within this thesis was predominantly carried out in the Urogynaecology unit at Medway Maritime Hospital between March 2008 and March 2010.

The urogynaecology department at Medway Maritime Hospital is a busy unit which sees and manages a wide range of pelvic floor disorders. Treatments on offer include conservative therapies such as bladder retraining and pelvic floor physiotherapy, primary and secondary suburethral slings, periurethral bulking, Botulinum toxin bladder injections, primary and recurrent prolapse repair (including mesh augmentation), and vault suspension procedures (abdominal sacrocolpopexy/vaginal sacrospinous fixation). The unit carries out approximately 250 prolapse procedures per year.

The unit is staffed by one consultant urogynaecologist, a full time urogynaecology nurse specialist, a pelvic floor physiotherapist, one research fellow and a specialist registrar. Referrals are taken from General Practitioners, as well as other consultants in the Gynaecology department. A “one stop” approach is adopted for new GP referrals, with patients being seen in one of three new patient clinics, at which a full assessment, including urodynamic studies if necessary, is carried out, and a management plan decided. There are further urodynamic clinics throughout the week for follow up studies. The unit carries out approximately 620 urodynamic studies per year.

All new patients are assessed with a urogynaecological history and examination, together with disease specific quality of life and symptom questionnaires. Those with lower urinary tract symptoms (either alone or in combination with symptomatic prolapse requiring surgery) then
undergo urodynamic assessment consisting of uroflowmetry and measurement of post-void residual, followed by filling and voiding subtraction cystometry. Video urodynamics are not carried out as a routine, but are available in the hospital if necessary. Patients requiring investigations such as ambulatory urodynamics or electromyography are referred to a tertiary unit. Complex patients are discussed at a regular urogynaecology/urology multidisciplinary meeting.

The research work detailed in this thesis was carried out whilst the author was both a specialty registrar and then research fellow in the department. The research fellow job plan was purely research based, with no fixed clinical or on-call commitments. Overall co-ordination of all the studies detailed in this thesis was overseen by the author. All patients were recruited by the author from the urogynaecology clinics. The majority of cystometry studies and follow up assessments were conducted by the author. On a small number of occasions when the author was not available, these assessments were carried out by the urogynaecology nurse specialist or the lead consultant. All cystometry traces and reports were checked by the senior urogynaecologist prior to being finalised.
Chapter Two

Overactive Bladder Syndrome
Urinary incontinence is one of the most common chronic healthcare problems affecting women. Although it is not a life threatening condition, it can severely affect quality of life. The treatment and containment of urinary incontinence causes a considerable socio-economic burden for sufferers, their caregivers and society as a whole.

In this chapter, the current evidence surrounding the epidemiology, pathophysiology, impact, treatment and long-term prognosis of the overactive bladder syndrome (OAB) will be examined.

**Definitions and epidemiology**

The International Continence Society (ICS) defined the Overactive Bladder Syndrome in 2002 and more recently in 2010 as “Urgency, with or without urgency incontinence, usually with frequency and nocturia” (Abrams et al, 2002; Haylen et al, 2010). This definition is only applicable in the absence of infection or any other proven pathology. The concept of urgency will be explored further later in this chapter.

Whilst many studies have attempted to elucidate the prevalence of OAB, the true number of women living with these symptoms is difficult to define. Incontinence is one of a number of medical problems subject to the “iceberg phenomenon”, whereby only a small proportion of women with a condition seek help, whilst the greater proportion live with their symptoms in the community. This is either because of embarrassment or lack of knowledge about the condition itself or available treatments (Shaw et al, 2001). A population study across six European countries (France, Germany, Italy, Spain, Sweden and the UK) estimated that 16.6% of the population aged over 40 years had OAB symptoms (Milsom et al, 2001); this was estimated to equate to 22.2 million individuals with OAB in these six countries. Of those with OAB, 60%
had sought medical help, with 27% taking medication at the time of the study. It should be noted that this study was published prior to the 2002 ICS standardisation document. The EPIC study was a large epidemiological study which used definitions from the 2002 ICS standardisation report in telephone interviews to estimate the prevalence of OAB across five Western countries (the UK, Germany, Canada, Sweden and Germany); it reported the prevalence of OAB across these countries to be 11.8% (Irwin et al, 2006). A study by Reeves et al published in 2006 used a health economic model to calculate the prevalence of OAB across 5 European countries (Reeves et al, 2006). The model estimated that in 2000 20.2 million people over 40 years of age suffered from OAB symptoms, of which 7 million had urgency with urgency incontinence. A projection using UN population statistics estimated an increase to 25.5 million people by the year 2020, with 9 million suffering from urgency incontinence. The authors calculated that the total cost of OAB to healthcare systems would be 5.2 billion Euros by 2020. The most recent epidemiological data suggest that OAB affects 68% of adult women in the US, and is associated with significant impairment of health related quality of life, as well as higher anxiety and depression scores (Milsom et al, 2012).

OAB is thought to cause a significant economic burden, with one recent study estimating the disease specific total cost of OAB across the United States as up to $36.5 billion in adults complaining of OAB symptoms “sometimes” (Onukwugha et al, 2009). A paper which used results from a large epidemiological study across Western countries (the UK, Canada, Germany, Sweden, Italy and Spain) in an economic model to calculate direct and indirect annual costs of OAB (Irwin et al, 2009) reported that the total annual direct cost related to OAB, i.e. resulting from the diagnosis and treatment of the condition and its complications, was estimated at $3.9
billion across all 6 countries in the study, and indirect costs resulting from work absenteeism, impaired performance at work were estimated at $1.1 billion. OAB has also been linked to other conditions including urinary tract infections, falls, fractures, depression and skin infections, which have their own associated costs.

**Urgency as the cornerstone of the Overactive Bladder Syndrome**

By definition, urgency is the cornerstone symptom of the OAB Syndrome. In 2002, the definition of urgency was revised by the ICS to “the complaint of a sudden compelling desire to pass urine that is difficult to defer” (Abrams et al, 2002). This definition was upheld in the most recent terminology report from the ICS (Haylen et al, 2010). This definition aims to distinguish normal sensation as the bladder fills from pathological urgency, but will exclude bladder pain syndrome and other similar entities, which are characterised by a gradual rather than sudden increase in sensation. This definition of urgency is based on several assumptions, namely that detrusor overactivity (DO) or urethrovesical dysfunction is the cause, that sensory pathways are intact, that adequate cognition exists for reacting to the sensation and reporting it, and that the symptom is not iatrogenic (Brubaker, 2004). It is of some importance to distinguish normal bladder sensation from pathological urgency. The new definition of urgency is designed to make this distinction. “Urged” is a normal physiological sensation that occurs intermittently throughout the micturition cycle, increases with bladder volume and terminates with a normal void. Chapple et al (Chapple et al, 2005a) raised the question of whether urgency and urge were merely part of a continuum; this would have the implication that normal individuals would experience urgency on occasion. The authors in this consensus paper propose a model where by urgency is always
an abnormal sensation. By definition, urgency is a “sudden” and “compelling” sensation which will always be episodic and usually terminated either by a void or an incontinence episode. Chapple and colleagues liken urgency to a light switch, in that it is either on or off, and can therefore be quantified as episodes, but not graded in terms of severity. A recent study however challenged the assumption that urgency is a single sensation. Forty-eight male and female patients with urgency (as per the ICS definition) were asked to fill in 2 different questionnaires designed to evaluate how urgency was perceived. The authors reported that patients experience at least two different types of urgency- one is an intensification of the normal desire to void, and one is a distinct sensation, which is not defined in the manuscript (Blaivas et al, 2009). These findings should be interpreted with caution however in view of the relatively small number of subjects, and the difficulties stated with developing questionnaires that accurately reflect patients’ experiences of urgency.

Cystometry experiments in healthy subjects have shown that as the bladder is filled, a series of distinct sensations are experienced. A 2002 study of 50 men and women without lower urinary tract symptoms described first sensation, first desire to void, and strong desire to void as reproducible points which occurred in sequence as the bladder volume increased. The volumes at which these sensations occurred varied between individuals, however the ratio between each volume and the volume at strong desire to void was constant (Wyndaele and De Wachter, 2002). This paper also reported overactive detrusor contractions in seven subjects (14%, one man and six women); these were however only associated with sensation in one female volunteer. Other studies of lower urinary tract function in asymptomatic healthy volunteers have also demonstrated overactive detrusor contractions in “normal” women (Robertson et al, 1994). The
significance of such contractions in healthy women, particularly if not associated with abnormal bladder sensation, is unclear.

The key difference between “desire to void” in normal women and women with OAB is the ability to defer voiding. As described in Wyndaele and De Wachter’s paper (2002), even strong desire to void occurs “without the fear of leakage”. At some point during bladder filling, a controlled voluntary void occurs- the point at which this happens varies within each individual depending on circumstances such as the availability of a toilet, other distractions and time availability. In this way, the urge can be suppressed or may resolve.

Women with OAB also experience a desire to void as the bladder fills, however when urgency episodes occur, they are distinguished by the inability of the individual to defer micturition. The sensation of urgency may persist until a void has taken place. With bladder retraining and deferment techniques, the sensation of urgency may eventually be controlled. The figure below illustrates how it is urgency that drives the other symptoms of overactive bladder.

![Fig. 2.1. The relationship between urgency and other OAB symptoms (from Chapple et al, 2005a).](image-url)
Urgency may result in increased frequency of micturition if a void cannot be deferred. Assuming that fluid intake remains constant, this reduced inter-void interval will lead to a lower volume voided per micturition, i.e. lower functional bladder capacity. With deferment techniques, women may adapt to be able to defer a void, meaning that the classical concept of frequency resulting from urgency may not always be found in women with OAB. The concept of “warning time” (Cardozo and Dixon, 2005) refers to the time between the onset of urgency and the void, and can be a reflection of other factors such as pelvic floor and sphincter tone, which may permit enough time for a void to be voluntary. Frequent micturition may also be a learned behaviour in order to avoid incontinence episodes, which will further reduce functional capacity, possibly leading to worsening urgency.

The Pathophysiology of Urgency and Overactive Bladder

The overactive bladder exhibits a characteristic set of signs:

- A sudden increase in intravesical pressure at low volumes during filling
- Increased spontaneous myogenic activity
- Fused tetanic contractions
- Altered responsiveness to stimuli
- Changes in smooth muscle ultrastructure

(Chu and Dmochowski, 2006)

Most contemporary experimental models used for the study of mechanisms of urgency rely on the surrogate marker of DO, because of the inability to measure the “desire” to void in animals. This relies on the assumption that DO usually underlies urgency. This issue will be further explored later in this chapter.
Abnormal detrusor contractions may arise either due to malfunction of the detrusor muscle itself (myogenic theory), malfunction of the neural input into the detrusor (neurogenic theory) or malfunction of sensory output from the bladder (afferent dysfunction). In a recent review, Michel and Chapple (2009) state that there is currently insufficient evidence to fully support any of these theories whilst discounting the others. It remains likely that urgency and DO in different patients has different aetiologies.

**Myogenic Theory**

Logically, spontaneous detrusor contractions may arise either directly from the smooth muscle cells or may be triggered by mediators from other cells in the bladder wall. Ultrastructural studies of human detrusor muscle have shown that coupling of smooth muscle cells does occur in asymptomatic volunteers (John et al, 2003), but is up-regulated in patients with urgency symptoms to form limited functional syncytia (Fry et al, 2004; Neuhaus et al, 2005), suggesting increased intra-cellular signalling in the detrusor smooth muscle of individuals with DO which may lead to functional changes. Other histological studies have additionally found patchy denervation of the detrusor muscle together with potassium super-sensitivity in women with DO compared to healthy controls (Mills et al, 2000). There is also evidence that calcium handling in detrusor smooth muscle cells in those with DO is altered, leading to a higher level of intra-cellular calcium (Fry et al, 2002; Derblade et al, 2006). Localised distortions of the bladder wall due to autonomous activity may also contribute to increased bladder sensations and urgency by stimulating sensitive tension receptors in the detrusor smooth muscle. These localised distortions are known as “micromotions”. Physiological experiments in women with increased bladder sensation have shown a higher prevalence of micromotions in the detrusor
smooth muscle than women with normal sensation (Drake et al, 2005). Micromotions can be multifocal with separate areas of the bladder wall contracting independently as modules (Drake et al, 2001). This localised activity is thought to stimulate afferent activity in ascending neurones and may therefore lead to urgency, frequency and reduced functional bladder capacity.

The normal physiological mediator of detrusor contraction is acetylcholine, which acts predominantly via muscarinic receptors M2 and M3. However other factors such as Adenosine Triphosphate (ATP) use ligand gated ion channels to raise intracellular calcium in detrusor smooth muscle fibres (Wu et al, 1999). It has been demonstrated that the relative importance of non-muscarinic mechanisms in causing muscle contractions increases in abnormal bladders (Rap et al, 2005). Other local factors such as nitric oxide may also be of importance (Pandita et al, 2000).

**Neurogenic Theory**

The significance of central nervous system (CNS) malfunction in urgency and urgency incontinence is illustrated by the occurrence of these symptoms in patients suffering strokes, multiple sclerosis and spinal cord injury. These symptoms are thought to occur secondary to impaired inhibition of detrusor tone during the storage phase (Gillespie, 2004). Functional brain imaging using Positron Emission Tomography (PET), functional Magnetic Resonance Imaging (fMRI) and Single Photon Emission Computed Tomography (SPECT) has conferred more information on how the activity of efferent pathways is altered in women with OAB and DO. At small bladder volumes there is abnormal deactivation of limbic regions, which may be in order to suppress unwanted learned emotional reactions (Griffiths and Tadic, 2008). At large bladder volumes with strong sensation but no DO there is evidence of more extensive activation of the
brain globally, including in the limbic system (Griffiths and Tadic, 2008). There is also stronger activation in frontoparietal regions (Griffiths and Tadic, 2008) which are involved in pelvic floor muscle activity (Kuhtz-Buschbeck et al, 2007), and in the lateral somatomotor cortex which is thought to support interoceptive awareness (Critchley et al, 2004). These observations imply excessive emotional arousal, together with the increased activity of pelvic floor muscles and inhibition of the Pontine Micturition Centre in an attempt to maintain continence. In urgency incontinent women certain areas in the orbitofrontal cortex have a reduced response in comparison to normal women, implying either dysfunction or a change resulting from the abnormal responses in the limbic areas (Griffiths, 2007). The same group have carried out imaging on a small number of women with uninhibited detrusor contractions during scanning (Griffiths and Tadic, 2008). They described a decrease in activation of the prefrontal cortex bilaterally and in parts of the limbic system, with no significant change in the activation of the orbitofrontal cortex. This pattern implies a lack of voluntary control of the bladder with ongoing stimulation. There was also a trend toward deactivation of the Pontine Micturition Centre during uninhibited detrusor contractions. A similar response has also been noted in patients with Parkinson’s Disease and neurogenic DO (Kitta et al, 2006). These observations suggest that normal voiding reflexes are not invoked during periods of DO.

**Afferent Dysfunction**

There is increasing evidence that afferent dysfunction may play a significant role in the pathophysiology of urgency and OAB. Dysregulation of afferent pathways can lead to altered micturition signalling within efferent pathways, which may eventually result in overactive bladder behaviour, involuntary detrusor contractions and thus the characteristic symptoms of
OAB. Afferent neurones returning from the bladder travel in the pudendal, pelvic and hypogastric nerves and are comprised of thin myelinated Aδ fibres and non-myelinated C fibres. The Aδ fibre endings are in the smooth muscle and are the most sensitive nerve endings in the bladder, being activated by increasing bladder wall tension secondary to intra-vesical filling. The role of micromotions resulting in excessive activation of these tension receptors has been discussed earlier. The C fibres have their endings in the lamina propria and urothelium and are only activated at greater degrees of bladder distension than Aδ endings. C-fibres are activated also by neurotransmitters and mediators in pathological situations such as inflammation and high osmolality (Habler et al, 1990). Thus C-fibres may be of more importance in women with pathological urgency and OAB. C fibre receptors such as the transient receptor potential vanilloid 1 (TRPV1) and P2X3 (ATP receptor) are modulated by mediators such as Nerve Growth Factor (NGF) and are believed to be of importance in afferent activation in the bladder in women with sensory urgency, although there is conflicting evidence regarding their role in women with DO (Liu et al, 2007; Lui and Kuo, 2007). The emergence of primitive reflexes may also have a role. The neonatal bladder is known to have intrinsic motor activity, e.g. the bladder cooling reflex (BCR), much of which is C fibre mediated. Such reflexes are suppressed once voluntary control of voiding is attained during childhood, by inhibitory descending signals, but are seen to re-emerge in conditions such as spinal cord injury or multiple sclerosis (i.e. where descending inhibitory signalling is lost) (Glahd et al, 2004). It has been suggested that the emergence of such reflexes may play a part in idiopathic DO and OAB (Petersen et al, 1997), although it is notable that a long term follow up of such patients with idiopathic DO demonstrating these reflexes reported that a proportion did go on to develop overt signs of neurological disease (Fall and Geirsson, 1996).
The importance of afferent activity in pathological states can be demonstrated by the use of agents which modulate such activity. Animal studies have shown a reduction in TRPV1 receptor expression and NGF in response to Botulinum toxin A (Ha et al, 2011). Administration of Botulinum toxin A in women with urgency (secondary to both idiopathic and neurogenic DO) leads to chemical denervation, and decreases the expression of TRPV1 and P2X3 receptors (both of which are implicated in afferent signalling) in the urothelium, as well as levels of NGF—this correlates with reduced urgency (Apostolidis et al, 2005; Liu et al, 2009). The C fibre toxin resiniferatoxin (RTX) administered to patients with neurogenic DO has similarly been shown to lead to a decrease in TRPV1 and PGP9.5 (a pan-neuronal marker) immunoreactive nerve fibres, which is associated with symptom improvement. The clinical and urodynamic effect of RTX has also been demonstrated in patients with idiopathic DO (Silva et al, 2002).

The source of the initiating stimulus to the afferent fibres is thought to be the urothelium (Kanai et al, 2006). The cells comprising the urothelium are in close proximity to the afferent nerves and activity in this layer is likely to be intimately involved in signal transmission and modulation, apart from its established barrier function. The urothelium is known to express a variety of ion channels and receptors which respond to chemical as well as mechanical stimuli, by releasing mediators which then stimulate afferent nerve fibres. A variety of urothelial mediators thought to be of importance in afferent dysfunction have been identified. Patients with OAB are known to have higher levels of ATP, NGF, and prostaglandin E2 (PGE2), when compared to normal controls (Yoshida et al, 2004; Kim et al, 2006; Liu et al, 2011). Some of the more important and better understood signalling pathways are discussed below:
Purinergic pathways and ATP

ATP is known to facilitate the non-adrenergic, non-cholinergic component of bladder contraction. It acts on the P2X family of receptors, participating in efferent bladder signalling via the P2X1 receptor on detrusor smooth muscle membranes and in afferent signalling via the P2X2/3 receptors expressed on afferent neurones (Zhong et al, 2003; Ford and Cockayne, 2011). Studies of P2X3 knockout mice reveal detrusor hyporeflexia with a decreased frequency of voiding and an increased bladder capacity (Cockayne et al, 2000). Patients with DO have been found to have substantially elevated levels of P2X3 receptors (Brady et al, 2004) and ATP (Kumar et al, 2010). Bladder distension as well as various physiological insults to the bladder stimulate ATP release (Sadananda et al, 2009), and the presence of ATP-degrading enzymes in rats is seen to prevent activation of P2X receptors and the manifestation of OAB symptoms (Nishiguchi et al, 2005). The same study showed that intravesical introduction of ATP conversely induced DO. A study of human subjects undergoing urodynamic studies showed an inverse correlation between voided volume and levels of ATP in voided urodynamic fluid in both individuals with DO and normal controls, and an inverse correlation between voided fluid ATP levels and first desire to void in those with DO, but not in the control group (Cheng et al, 2010). This suggests that abnormal purinergic signalling may be implicated in modulating early filling sensations in pathological states.

Acetylcholine and muscarinic receptors

Although acetylcholine (ACh) has been classically associated with motor function in the bladder, there is thought to be a non-neuronal release of ACh from the urothelium which leads to modulation of sensory bladder function. This concept is reinforced by studies showing that
antimuscarinic drugs exhibit activity during the bladder storage phase when efferent nerve pathways are silent (Andersson and Yoshida, 2003). The majority of experimental work proving the non-neuronal release of ACh has been carried out in animal models and has shown a distinct storage and release mechanism from the neuronal cells (Lips et al, 2007; Hanna-Mitchell et al, 2007). Yoshida and colleagues carried out a study using strips of bladder tissue from human subjects, demonstrating that removal of the urothelium substantially decreases release of ACh, as well as an age-related and stretch-induced increase in non-nerve evoked ACh release (Yoshida et al, 2006). Further studies using antimuscarinic drugs have suggested that blocking of muscarinic receptors reduces afferent stimulation. Studies examining the effect of oxybutynin on single bladder afferent units from rats have shown a desensitising effect on C fibre afferents (de Wachter and Wyndaele, 2003; de Laet et al, 2006). Similar results have been seen after administration of the M3 selective antimuscarinic darifenacin (Iijima et al, 2007), although a subsequent study by Matsumoto and colleagues (Matsumoto et al, 2010) suggested that it is M2 receptors that mediate cholinergic stimulation of afferent activity. An animal study using different dosing protocols for antimuscarinic drugs following carbachol induced DO showed an increase in bladder capacity and inter-contraction interval, with no accompanying decrease in bladder contractility, suggesting a local inhibitory effect for antimuscarinic drugs. Collectively, the evidence suggests a role for muscarinic pathways in the modulation of afferent signalling, although the exact interaction has yet to be determined.

**Nitric Oxide pathways**

Nitric oxide (NO) is synthesised within the urothelium, and appears to act as an inhibitory transmitter within afferent pathways (Aizawa et al, 2011). Intravesical administration of an NO
substrate and an NO synthase inhibitor lead to inhibition and stimulation of both Aδ and C fibres, respectively. In support of this, in vivo studies have shown a decrease in bladder hyperactivity with administration of PDE5 inhibitors, which potentiate the NO/cyclic GMP pathway (Caremel et al, 2010). Intravesical administration of oxyhaemoglobin, (which decreases NO concentration) to healthy rats leads to an increase in bladder pressure and a decrease in bladder capacity, with the converse being observed with administration of an NO substrate (Pandita et al, 2000).

Adrenergic pathways

The bladder storage phase is predominantly governed by the parasympathetic nervous system, which inhibits parasympathetic nerve mediated detrusor contractions. Noradrenaline release induces detrusor relaxation via adrenergic β3 receptors (Wuest et al, 2009), and β3 receptors are highly expressed in the bladder, particularly in the detrusor muscle and urothelium (Limberg et al, 2010). Administration of β3 receptor agonists to detrusor muscle strips leads to smooth muscle relaxation (Kanie et al, 2012), however possible afferent effects are also suggested by studies showing that β3 agonists have an inhibitory effect on afferent nerve firing (Aizawa et al, 2010), as well as inducing urothelial NO release (Birder et al, 1998).

The selection of appropriate outcome measures- Overactive Bladder versus Detrusor Overactivity

Current treatment models for the symptoms of urgency and/or urgency incontinence, frequency and nocturia have been developed on the assumption that the underlying cause of such
symptoms is DO. Whilst OAB is a diagnosis based on symptoms experienced by an individual, DO is a urodynamic diagnosis defined as the observation of involuntary detrusor contractions during filling that may be spontaneous or provoked. Traditional teaching has been that the bladder is an “unreliable witness”, implying that an objective test of bladder function is necessary to make a diagnosis. Whilst this may be true in some cases, this is based on the assumption that the only pathophysiological mechanism underlying OAB symptoms is the presence of DO. As has been described earlier in this chapter, current evidence suggests that this is not necessarily the case.

Many studies have described the discrepancy between symptoms and urodynamic findings. A study of 843 women with OAB symptoms found that 46% did not have demonstrable DO on a single urodynamic study (Digesu et al, 2003a). A study of 1457 male and female patients with urgency either with or without urgency incontinence, frequency and nocturia reported that 58.2% of women with urgency had DO on urodynamics, and also that 20% of women with DO did not have OAB symptoms. In a multivariate logistic regression model, urgency was the only significant predictor for the presence of DO in women (Hashim and Abrams, 2006).

The observation of a discrepancy between symptoms and urodynamic findings is of interest in interpreting investigation results, however the significance of this is more obvious when one considers how this might affect treatment outcomes. Studies of response to antimuscarinic drugs have sought to evaluate whether the finding of DO on urodynamics determines outcome. An open-label observational study of 352 patients with OAB symptoms (76% with proven DO, 24% without proven DO) found no significant differences in response to oxybutynin between those with DO and those without DO (Malone-Lee et al, 2003).
subjects in a randomised placebo controlled trial of tolterodine were divided into those with DO at baseline and those with no DO at baseline. There was no difference in mean voided volume per void after treatment between the 2 groups in both the placebo and active arms of the trial (Malone-Lee and Al-Buheissi, 2009), indicating that the presence of DO in women with bothersome OAB symptoms did not influence the response to treatment. Similar results have also been described with newer antimuscarinics such as fesoterodine (Nitti et al, 2010). As discussed in the last section, it is becoming clearer that the pathophysiology of OAB is a great deal more complex than previously believed, with increasing evidence that sensory and urothelium derived pathways are of some importance in symptom generation. A study of 74 women with a diagnosis of DO versus 77 with “sensory urgency” (a now defunct diagnosis characterised by increased perceived sensation during filling, early first desire to void, low cystometric capacity) have demonstrated them to have very similar clinical and urodynamic profiles, with the exception of a significantly higher incidence of urgency incontinence in the women with DO (Haylen et al, 2007). The authors of this study concluded that sensory urgency is part of the same spectrum of bladder dysfunction as DO, perhaps representing an earlier manifestation. This would provide a possible explanation for the existence of OAB symptoms in the absence of DO. In addition, one of the principles of good urodynamic practice is to note whether the patient’s symptoms have been reproduced during the test- if they have not, it may be the case that the individual does have DO which has simply not been demonstrated because the urodynamic test merely represents a “snapshot” of their bladder function.

Urgency, together with associated incontinence, is known to be the most bothersome component of the overactive bladder syndrome, as well as being regarded as the driver for the other symptom components (Chapple et al, 2005). Therefore the aim of any therapeutic
intervention in OAB is essentially to treat urgency. Despite this, the subjective nature of urgency has lead to it rarely being used as an outcome measure in published studies. Surgical and drug trials tend to use bladder diary based measures as an end-point presumably on the assumption that these are surrogate measures of the urgency experienced by an individual. There are various other factors that may affect frequency and nocturia such as drinking habits and defensive voiding; thus, not directly assessing urgency risks inaccurate evaluation of research data. The development of several validated tools to measure urgency (and also distinguish it from normal bladder sensation) has increased its feasibility for use as an outcome measure. A recent review of tools used to measure urgency in clinical trials of the antimuscarinic drug solifenacin concluded that urgency should be the primary endpoint for future studies of OAB and DO (Abrams et al, 2011).

**Management Principles in Women with OAB**

The principles of management of a woman presenting with urgency and/or urgency incontinence are based on the basic escalating measures of conservative, medical and interventional. A greater understanding of the role of detrusor contractions and sensory disturbance in the disease process, as well as increasing availability of urodynamic studies, has lead to a treatment model based on lifestyle modifications and behavioural measures, in combination with pharmacotherapy, which aims to modulate the detrusor muscle and urothelial activity.
Conservative Measures and Behavioural Therapy

Women with urgency symptoms and/or detrusor overactivity are thought to benefit from simple advice regarding fluid intake, avoidance of caffeine and weight loss (if applicable). However, the evidence base for this in the literature is limited when compared to that which exists for other therapies.

There is a general consensus that modifying fluid and caffeine intake is of benefit in patients with OAB (Hashim and Al Mousa 2009). A reduction in daily fluid intake of 25% is associated with a significant improvement in OAB symptoms (Hashim and Abrams, 2008). A study of 12 patients with OAB reported a lower threshold for bladder sensation and a lower bladder capacity during filling cystometry when ingestion of a caffeinated drink was compared to ingestion of water (Lohsiriwat et al, 2011).

Bladder retraining involves gradually increasing intervals between voiding in the hope of rediscovering central control of continence using an operant learning model. This allows higher centres in the brain to suppress the dominant stimuli which precipitate detrusor contraction via a voluntary pathway. There are four different schedules for bladder retraining: prompted voiding, timed voiding, habit retraining and bladder drill. Patient education on fluid intake and monitoring with regular bladder diaries are an intrinsic part of the process. There is limited evidence concerning the role of bladder retraining. A systematic review undertaken in 2004 reviewed data from 5 trials with a total of 467 women. The evidence showed no significant benefit for bladder retraining when compared to no treatment. When added to other treatments, e.g. physiotherapy, bladder retraining was associated with a significant benefit in the short term which was not sustained at 3 months’ follow up. The available evidence for its use as an adjunct to antimuscarinic treatment was similarly equivocal. The trials used for the analysis were subject
to high levels of bias, had small numbers and there were wide confidence intervals around the point estimate of the effect size (Wallace et al, 2004). A study of in-patient management consisting of bladder retraining and antimuscarinic therapy for patients with symptoms refractory to out-patient management showed significant improvements in inter-void interval, incontinence episode frequency and nocturia episodes (Majumdar et al, 2010). Outpatient instruction on bladder retraining is more usual, and has been suggested to lead to significant reductions in incontinence episodes (Fantl et al, 1991), however compliance may be suboptimal outside of a trial setting (Visco et al, 1999). When combined with antimuscarinic therapy, the results are similarly mixed. A randomised trial of tolterodine with bladder retraining versus tolterodine alone with 501 women and a follow up period of 24 weeks found significant improvements in bladder diary variables in women treated with tolterodine and bladder retraining versus those treated with tolterodine alone, although no difference in urgency or urgency incontinence episodes (Mattiasson et al, 2003). Another similar study identified no differences in symptom scores, health related quality of life or bladder diary variables between the study groups, although patient satisfaction was higher in the tolterodine plus bladder retraining group (Zimmern et al, 2010). It should be noted however that there was no difference in the measured fluid intake between the 2 groups, which may reflect a problem with instruction or compliance rather than technique. A study of patients previously treated with antimuscarinics reported high treatment satisfaction and improvement in bladder diary variables following a 16 week treatment protocol consisting of tolterodine plus either self-administered or individualised behavioural intervention (Klutke et al, 2009). A further randomised trial of tolterodine and bladder retraining versus tolterodine alone, using discontinuation of drug therapy at 8 months as a primary outcome measure, found no significant differences between the treatment groups (Burgio et al, 2008).
However secondary outcome measures including incontinence episode frequency, symptom scores and patient satisfaction, favoured the tolterodine plus bladder retraining group.

Pelvic floor muscle training (PFMT) has long been regarded as an effective adjunct in the treatment of stress incontinence, but is less commonly used in urgency and urgency incontinence. There is very little in the literature to support its effectiveness. A randomised trial of tolterodine alone versus tolterodine with a simple pelvic floor exercise regimen found no difference in treatment outcome (Millard et al, 2004). Instruction on pelvic floor contraction to manage urgency episodes and prolong voiding intervals is likely to be of some use as part of a bladder retraining programme, but this has not been subject to evaluation in the literature. The specific role of pelvic floor muscle training may be to permit the deferment of a void in the context of an urgency episode. PFMT is recommended by the International Consultation on Incontinence (ICI) (Abrams et al, 2013) for this reason.

Pharmacotherapy

The basis of drug treatments for OAB/DO is blockade of cholinergic stimulation to the detrusor muscle. The detrusor muscle is supplied by the parasympathetic nerves via spinal segments S2, S3 and S4. The micturition reflex is activated by myelinated Aδ fibres which lead to an increase in efferent outflow resulting in detrusor contraction. The predominant neurotransmitter at the nerve endings on the detrusor muscle is acetylcholine acting via muscarinic M3 receptors. Blocking of these receptors leading to a reduction in spontaneous detrusor contractions (Andersson and Yoshida, 2003) is the classical concept that underpins virtually all pharmacotherapy for DO. However, antimuscarinics are known to act mainly in the storage phase by decreasing urgency and increasing functional capacity (Andersson, 2004),
meaning that there must be release of acetylcholine somewhere in the bladder during this phase. There is now increasing evidence that antimuscarinic drugs may also have sensory mediated effects via the urothelial pathways discussed earlier in this chapter, and that muscarinic receptor function in women with OAB may be distinct from that in those without OAB.

Muscarinic receptors have been identified throughout the bladder, including in the urothelium (Tyagi et al, 2006), lamina propria and interstitial cells (Mukerji et al, 2006; Grol et al, 2009) and the detrusor smooth muscle (Tyagi et al, 2006) and associated structures. Antimuscarinic drugs are competitive antagonists for all receptor subtypes (i.e. M1-M5), but with variable selectivity. The release of acetylcholine during the storage phase from the nerves and urothelium leading to an indirect or direct effect on afferent nerves and consequent contractile activity seems to be enhanced in individuals with DO (Drake et al, 2005; McCarthy et al, 2009). This resulting spontaneous contractile activity of the detrusor smooth muscle during the storage phase is known to generate afferent signals (so called “afferent noise”), and this may also contribute to symptom generation in OAB/DO. Animal studies have confirmed that antimuscarinics act via C and Aδ fibre mediated mechanisms. Administration of tolerodine to resiniferatoxin (a C fibre toxin) and non-resiniferatoxin treated rats with neurogenic DO showed an increase in bladder capacity in the non-resiniferatoxin treated rats only (Yokoyama et al, 2005). Similar studies using darifenacin (Iijima et al, 2007) and oxybutynin (De Laet et al, 2006) have shown effects on both C and Aδ fibre afferent pathways. In human subjects, tolerodine has been shown to increase current perception threshold values of sensory nerves when compared with placebo (Vijaya et al, 2012). This increase in sensory perception threshold has been shown to be associated with clinically significant improvements in OAB symptoms (Kenton et al, 2010).
The detrusor contains all 5 muscarinic receptor subtypes, although the M2 and M3 subtypes are the most predominant. Immunohistochemistry studies have demonstrated an increase in M2 and M3 receptors in the lamina propria in humans with idiopathic DO which correlates with clinical measures of urgency (Mukerji et al, 2006), although other studies have shown M3 receptor mRNA expression to be reduced in those with idiopathic DO when compared to healthy controls (Mansfield et al, 2007). Human studies using receptor antagonists with varying degrees of selectivity suggest that bladder contractions occur predominantly via the M3 receptor (Fetscher et al, 2002). Similar results have been found in animal studies (Tong et al, 1997; Lai et al, 1998; Sellers et al, 2000). Comparison of the muscarinic receptor subtype affinities for a range of selective antagonists in detrusor muscle strips pre-treated with carbachol (as a muscarinic agonist) from women with OAB/DO and controls showed that this mediation of contractile activity is via M3 receptors in the OAB and non-OAB states, and that patients with DO also show an increased sensitivity to muscarinic receptor stimulation (Stevens et al, 2007).

Antimuscarinics are the recommended first line medical treatment for OAB symptoms (Andersson, 2004). The aims of treatment are to decrease urgency episodes, incontinence episode frequency and number of voids per day, ultimately leading to improvements in clinical parameters and quality of life. The choice of drug is a balance between clinical efficacy and adverse effects.

**Oxybutynin**

Oxybutynin is a tertiary amine which has antimuscarinic effects on smooth muscle, including the bladder. Oxybutynin has muscle relaxant and local anaesthetic effects in addition to an anti-muscarinic action. It is selective for M1 and M3 receptors over M2 receptors.
Oxybutynin is available in immediate release (IR), once daily extended release (ER), transdermal, gel, elixir and vaginal ring preparations. The IR form has an onset of action within 30-60 minutes of administration with peak effects at 3-6 hours. Randomised control trials have shown oxybutynin IR to be superior to placebo in terms of reduction of voiding episodes and incontinence episodes (Moore et al, 1990; Tapp et al, 1990), however in normal clinical practice, the marked adverse effects, particularly dry mouth, are frequently dose limiting, and only a minority of patients are able to persist with treatment beyond 6 months (Kelleher et al, 1997a). The side effects are principally caused by metabolites of oxybutynin. These difficulties highlighted a need for modified formulations and drug delivery systems to overcome these side effects. The ER formulation was approved by the US Food and Drug Administration in 1999. Published evidence suggests that there are no significant differences in efficacy between IR and ER oxybutynin (Salvatore et al, 2005), however the ER formulation is better tolerated with a lower incidence of dry mouth (Anderson et al, 1999). Transdermal forms of drug delivery using topical patch formulations of oxybutynin have been developed to further overcome adverse effects caused by hepatic metabolites such as N-desethyloxybutynin, which has been shown to be most associated with dry mouth (Appell et al, 2003). There have been several large controlled trials evaluating the use of transdermal oxybutynin. One Phase 3 study randomised 520 subjects to transdermal oxybutynin or placebo (Dmochowski et al, 2002). Those randomised to oxybutynin reported significantly fewer incontinence episodes per week (p=0.016) as well as improvements in health-related quality of life scores. A recent large, open label, multicentre study sought to assess health-related quality of life and safety with the oxybutynin transdermal system (Sand et al, 2006). 2878 individuals with a diagnosis of OAB were enrolled and treated with oxybutynin transdermal 3.9mg/day for less than 6 months. There were statistically
significant improvements in 9 of 10 domains in the KHQ. 16.5% of participants discontinued the study due to treatment related side effects, although none of these were due to dry mouth. A head to head trial of 76 volunteers compared IR oxybutynin to transdermal oxybutynin (Davila et al, 2001). Each was found to be similar in terms of efficacy, with over 20% of patients in each group becoming totally dry. In terms of side effects, 94% of patients in the IR group reported dry mouth, as compared to 32% in the transdermal group. In this trial, no patients discontinued therapy because of dry mouth or similar anticholinergic side effects. Of course, a class of adverse effect that is unique to transdermal oxybutynin is skin reactions, which may render it unsuitable for certain patients. These range from mild erythema to severe cutaneous reactions which may lead to treatment discontinuation. Transdermal oxybutynin gel is a more recent development. Advanced Transdermal Delivery gel technology is a type of formulation used to allow enhanced passive skin permeation for various drugs, with the advantage that it permits greater flexibility of dosing and is associated with less skin irritation (Alberti et al, 2005). Initial trial data has been positive. A randomised controlled trial (RCT) of oxybutynin gel versus placebo in 789 men and women with overactive bladder reported a significant decrease in urgency incontinence episodes and micturition frequency, with a 6.9% rate of dry mouth in the treatment group (versus 2.8% in the placebo group) (Staskin et al, 2009). Subsequent RCTs in female populations have confirmed these findings (Sand et al, 2012).

The oxybutynin intravaginal ring was developed in the last decade as an initial alternative delivery method to avoid intra-hepatic first pass metabolism. It consists of an oxybutynin silicone elastomer core encased in a non-medicated silicone sheath (Woolfson et al, 2003). The development of transdermal and cutaneous gel alternatives has subsequently rendered it a less
acceptable option for patients. Oxybutynin is also available in a liquid form intended for paediatric use (Schroder and Thuroff, 2010).

**Tolterodine**

Tolterodine was launched in 1998 in an attempt to introduce a drug with higher bladder selectivity, and thus fewer antimuscarinic side effects. In vivo studies have shown tolterodine to be bladder selective leading to a longer and more pronounced effect on the bladder than on salivary glands (Stahl et al, 1995). As with oxybutynin, both twice daily IR and a once daily ER formulations are available.

IR tolterodine has peak serum concentrations at 1 to 2 hours after administration. The efficacy and acceptability of tolterodine was evaluated in a pooled analysis of 4 studies including 1120 patients. The studies looked at tolterodine 1 and 2mg twice daily versus placebo, and tolterodine 2mg twice daily versus oxybutynin 5mg three times daily and placebo. It was found that both the tolterodine and oxybutynin treatment arms significantly reduced incontinence episodes and increased volume voided at micturition. Tolterodine 2mg bd was equally as efficacious as oxybutynin 5mg tds, but tolterodine at either dose was significantly better tolerated than oxybutynin (Appell1997)

The extended release, once daily formulation of tolterodine (4mg) was developed with the aim of improving patient compliance and convenience. It has peak serum concentrations at 2 to 6 hours after administration and demonstrates sustained release over 24 hours, leading to more stable serum concentrations. The effectiveness of tolterodine ER relative to tolterodine IR and placebo was assessed in a double-blind, multicentre randomised controlled trial involving 1529
participants over 12 weeks (van Kerrebroek et al, 2001). It was found that both the IR and ER formulations significantly reduced the number of urgency incontinence episodes per week (p=0.0005 and p=0.0001, respectively), but ER tolterodine was 18% more effective than IR tolterodine (p<0.05). The rate of dry mouth for patients taking tolterodine ER was 23 % lower than those taking tolterodine IR (p<0.02). All other adverse effects were seen with similar frequency in all the groups, including the placebo arm. Interestingly, despite the higher rates of dry mouth in the IR arm, the withdrawal rates for each arm of the study were essentially the same (ER 5%, IR 5%, Placebo 6%). A longer term study has shown that tolterodine ER maintains similar efficacy and favourable incidence of side effects over longer treatment periods of up to a year (Kreder et al, 2002).

**Fesoterodine**

Fesoterodine is a pro-drug of tolterodine, which has been developed in response to the need for formulation of tolterodine with flexible dosing capability. Fesoterodine is rapidly hydrolysed by non-specific ubiquitous esterases to 5-hydroxymethyl tolterodine, which is the active metabolite of tolterodine (Nilvebrant et al, 2002). Fesoterodine can be administered in 2 doses, 4mg and 8mg. Pharmacokinetic studies have shown that plasma concentrations are dose proportional (Malhotra et al, 2008). The efficacy and tolerability of fesoterodine have been evaluated in a number of RCTs. A 12 week study of fesoterodine 4mg (with the option for dose escalation at week 2) once daily versus placebo in 883 subjects showed significant improvements in urgency and urgency incontinence episodes, micturition frequency and Urgency Perception Scale (UPS) and Patient Perception of Bladder Condition (PPBC) scores (Dmochowski et al, 2010). The benefits of fesoterodine above placebo have been shown to be dose dependent.
(Khullar et al, 2008), and patient determined dose escalation is associated with the same efficacy and tolerability as remaining on a 4mg dose (Staskin et al, 2011). Open label extensions of 12 week RCTs have shown sustained improvements in health related quality of life and OAB symptoms at 12 and 24 months (Kelleher et al, 2011; Scarpero et al, 2011). There have also been several head to head studies of fesoterodine versus tolterodine. A 2008 study of fesoterodine versus tolterodine versus placebo showed improved bladder diary variables and quality of life in both active drugs versus placebo; fesoterodine was found to be superior to tolterodine in terms of reductions in urgency incontinence and urgency episodes (Chapple et al, 2008a). A study of 2417 subjects randomised to fesoterodine 8mg, tolterodine ER 4mg or placebo reported similar results at 12 weeks (Kaplan et al, 2011).

_Trospium Chloride_

Trospium is a quarternary amine with predominantly peripheral antimuscarinic activity, leading to smooth muscle relaxation in the bladder. It is thought to lack CNS side effects since it is unlikely to cross the blood brain barrier (Staskin et al, 2010), and so has particularly been advocated for use in the elderly. Also pertinent to this, is the fact that up to 80% of trospium is excreted unchanged in the urine and it does not undergo metabolism by the cytochrome P450 mechanism, meaning that interaction with other medications is unlikely (Chapple, 2010). A phase 3 study of a total of 658 patients randomised to trospium or placebo showed it to significantly decrease urgency symptoms- an effect that was seen at the end of week one, and was sustained throughout the 12 week study period (Rudy et al, 2006). Dry mouth was the most common side effect (19.8% in trospium group, placebo 5.2%). The overall discontinuation rate due to adverse effects was 7.3% in the treatment arm (versus 4.6% in the placebo group); the
most common reason for discontinuation was dry mouth. Another study of 523 patients found similar results in terms of efficacy and adverse effects, but also used quality of life as an outcome measure. Trospium was found to significantly improve health related quality of life as measured by the incontinence impact questionnaire at 12 weeks (Zinner et al, 2004).

Trospium is also available in an extended release once daily preparation. A pooled analysis of two RCTs containing a total of 1165 subjects with OAB symptoms reported a significantly greater reduction in micturition episodes (-1.9 versus -2.7, p< 0.001) and urgency incontinence episodes per day (-1.8 versus -2.4, p< 0.001) in patients taking trospium ER versus placebo (Staskin et al, 2009). A subanalysis of subjects from these trials aged over 75 years also showed significant reductions in micturition frequency and urgency incontinence episodes above placebo, together with low adverse events overall, and no CNS related adverse events in the group taking trospium (Sand et al, 2011).

**Solifenacin**

Solifenacin is a phenylethylamine derivative and was developed as an M3 selective antimuscarinic. A Phase 3 trial found solifenacin to be significantly superior to placebo in terms of incontinence episode reduction and urgency symptoms. Of patients who were incontinent at the start of the trial, 50% were fully dry at the end of the 12 week study period. As with all of the other medications, the most frequently reported side effect was dry mouth, although this was reported to be mild in severity. The incidence at a 5mg once daily starting dose was 7.7% and at a 10mg dose was 23% (Cardozo et al, 2004). This study did not however, assess impact on quality of life. A longer term open label study which was an extension of 2 phase 3 studies showed that 81% of participants were willing to continue with solifenacin over a treatment
period of 40 weeks. The pooled data showed significant improvements in 9 of the 10 domains of the King’s Health Questionnaire (KHQ), although patient satisfaction had dropped to only 48% after 40 weeks’ treatment (Haab et al, 2005). Other studies have also identified positive long term effects on quality of life (Kelleher et al, 2005). A pooled analysis of four phase 3 trials containing 1783 subjects reported continence rates of over 50% in women taking solifenacin, with significant reductions in urgency incontinence episodes above placebo (Cardozo et al, 2006). Stratification of the population by baseline symptom severity or age did not affect this finding. A randomised placebo controlled trial in 863 patients taking solifenacin 5mg rising to 10mg if necessary or placebo, reported superior efficacy in terms of reduction in severe urgency episodes (using a validated urgency scale) with or without urgency incontinence (Cardozo et al, 2008). Another RCT evaluated bladder diary variables as well as “warning time” (the time from first sensation to voiding) in patients taking solifenacin or placebo, and reported a significant increase in warning time in the solifenacin group compared to the placebo group (increase of 31.5 seconds versus 12.0 seconds) (Karram et al, 2009). Published data indicate that solifenacin is also effective in patients with mixed incontinence. A subgroup analysis of subjects with mixed urinary incontinence from four phase 3 RCTs of solifenacin found significant improvements in urgency and incontinence episodes, micturition frequency and voided volume both in subjects with mixed incontinence and urgency incontinence above placebo (Kelleher et al, 2006). The reduction in total incontinence episodes suggests that the increase in voided volume did not lead to a worsening of the stress urinary incontinence symptom component.
**Darifenacin**

Darifenacin is a tertiary amine derivative and is another M3 selective muscarinic receptor antagonist. It is known to have a higher degree of selectivity for the M3 over the M2 receptor when compared to other anticholinergics, with some selectivity for the M1 receptor (Napier and Gupta, 2002). A double blind randomised crossover study showed darifenacin to be as effective as oxybutynin in terms of urodynamic outcome, but superior in terms of salivary side effects (Chapple and Abrams, 2005). A pooled analysis of Phase 3 studies involved 1059 participants (85% women) who were randomised to darifenacin 7.5mg, 15mg or placebo, after a 4 week washout period. Darifenacin was found to have significant, dose dependent positive effects on urgency symptoms, incontinence and bladder capacity (Chapple et al, 2005c). The most common side effects were dry mouth and constipation, although these led to few discontinuations (Darifenacin 7.5mg 0.6% of patients, darifenacin 15mg 2.1% of patients, placebo 0.3% of patients). There were no cardiovascular or CNS side effects associated with darifenacin treatment. A 2 year open label study showed that this favourable efficacy and safety profile was maintained over a longer treatment period (Haab et al, 2006).

**Propiverine**

Propiverine is a well established antimuscarinic which also has an inhibitory effect on cellular calcium influx, thereby decreasing muscular spasm (McKeage, 2013). RCTs of propiverine 20mg once daily versus placebo in adults with OAB showed propiverine to have significant beneficial effects on urgency episodes, incontinence episodes and bladder diary measures (Lee et al, 2010; Gotoh et al, 2011). However, a recent meta-analysis of efficacy and
adverse effects found propiverine to have an unfavourable ratio of efficacy to side effects (Buser et al, 2012).

**Choice of Drug**

As can be seen, there is an increasing number of drugs available for the treatment of OAB symptoms and DO. A recent meta-analysis of 73 trials of antimuscarinic medications found all of the drugs to be safe and efficacious. All, apart from oxybutynin IR, were well tolerated, and no drug was associated with increases in any serious adverse events. There were significant differences in terms of withdrawal rates and efficacy outcomes (Chapple et al, 2008b). However, comparison of different drugs using this type of meta-analysis carries certain problems, mainly relating to the heterogeneity of the trials and different methodology and patient populations. With this in mind, a number of head-to-head studies have been carried out, although these should also be interpreted with caution. The OPERA (overactive bladder: performance of extended release agents) trial compared Oxybutynin ER with Tolterodine ER in 790 women (Diokno et al, 2003). Oxybutynin ER was found to be significantly superior to tolterodine ER in terms of reduction in frequency (p=0.003) and urgency incontinence episodes (p=0.03). Both groups had a low incidence of adverse effects and comparable discontinuation rates, although dry mouth was more common in the oxybutynin group (p=0.02). The ACET (Antimuscarinic Clinical Effectiveness Trial) study again compared oxybutynin ER and tolterodine ER (Sussman et al, 2002). In contrast to the OPERA trial, this trial showed tolterodine 4mg once daily to be superior to oxybutynin ER 5 or 10mg and tolterodine 2mg in terms of patient perception of improvement in bladder symptoms (p<0.01). Incidence of dry mouth was significantly lower in the tolterodine group.
The Solifenacin (flexible dosing with 5 and 10mg od doses) and Tolterodine 4mg od as an Active comparator in a Randomised (STAR) trial aimed to compare the effectiveness and side effect profile of the two newer anticholinergics solifenacin and tolterodine ER (Chapple et al, 2005b). The investigators found solifenacin, with a flexible dosing regimen, to be superior to tolterodine ER in terms of urgency (p=0.035), urgency incontinence (p=0.001) and overall incontinence (p=0.006). 59% of incontinent patients in the solifenacin group became continent at the study’s end, compared with 49% in the tolterodine ER group (p=0.006). Discontinuation rates due to side effects were 3.5% in the solifenacin group and 3.0% in the tolterodine ER group. Discontinuation rates due to lack of efficacy were 2.0% in the tolterodine group versus 1.2% in the solifenacin group.

Discontinuation rates for antimuscarinic drugs are generally high. A study of over 1000 women taking antimuscarinics for OAB symptoms reported continuation rates of just 18.2% at 6 months, with 5.5% being symptom free (Kelleher et al, 1997a). This poor long term persistence may have been reflective of the limited available drugs for OAB at the time. A more recent large population based analysis of adults using OAB medications in the US reported that only 66% persist with medications in the long term with predictors of discontinuation being unawareness of adverse effects, non-efficacy and poor understanding of dosing (Brubaker et al, 2010). A secondary analysis of the same population found that patients themselves report lack of efficacy and tolerability as reasons for discontinuing medication (Benner et al, 2010). The most commonly reported adverse event in the 2008 meta-analysis was dry mouth (29.6% with treatment versus 7.9% with placebo) (Chapple et al, 2008b), however only oxybutynin IR had a significantly higher withdrawal rate than placebo across the trials.
One essential question is whether any of these trials are actually of any help in deciding which antimuscarinic to use in a particular patient. For example, the 2 trials comparing oxybutynin ER to tolterodine ER outlined above reported opposite results in terms of efficacy. It is debatable whether trial data can actually help clinicians in practice when they are often so conflicting. It is also important to remember that what clinicians deem to be important in determining a drug’s efficacy may differ significantly from the opinion of individual patients. It is arguably more important therefore, to place more emphasis on patient perceived outcomes and quality of life than absolute numbers in terms of voiding episodes, incontinence episodes, etc. A major factor in the choice of drug is obviously the side effect profile. Indeed, this seems to be the driving force behind new drug development for OAB symptoms. It is clear that with each new generation of antimuscarinic, the incidence of side effects is dropping. Drug trials in urinary incontinence are arguably a “false” situation, thus the true efficacy and acceptability of a drug is only really seen once it is in use in real life situations. This is highlighted by the relatively large placebo response that is a characteristic of trials of drugs for lower urinary tract symptoms (Chapple et al, 2008b). Clearly, improvements in the placebo group are related to coincidental patient factors, regression to the mean or intrinsic elements of the study design. Participation in a RCT protocol may be highly intensive with frequent interaction with study investigators and clinical staff. Completion of patient diaries and quality of life questionnaires may give the patient better insight into their condition. Participating in the trial protocol may thus confer behavioural interventions that benefit the patient and will, in themselves, lead to improvements in quality of life. Similar placebo responses have been seen in the duloxetine trials for stress incontinence (Mariappan et al, 2007).
Ultimately, the choice of drug for a particular patient is a balance between efficacy and side effect profile. Some patients may be willing to trade off a rapid onset of action against a higher incidence of side effects, for example taking oxybutynin IR to ensure that they are dry for a social engagement or work event. Drug treatment should be tailored to each patient’s lifestyle and symptom profile.

**Potential Novel Drug Targets**

Current pharmacological management of OAB symptoms is based on muscarinic receptor blockade. As has been discussed earlier in this chapter, the occurrence of antimuscarinic side effects can have a significant impact on patient compliance. Advances in understanding of the physiology of bladder function during both the storage and voiding phases has allowed the exploration of a number of new targets for OAB drugs, which may have improved efficacy and tolerability than current available medications.

The majority of non-antimuscarinic drug development has focused on beta adrenoreceptor pathways. Beta adrenoreceptor agonists have been found to act during the storage phase to reduce detrusor muscle tone and modulate afferent nerve activity, such that storage symptoms are improved (Michel et al, 2011). Animal studies of YM178, a selective $\beta_3$ adrenoreceptor agonist, demonstrated suppression of induced detrusor contractions during filling (Takasu et al, 2007). This drug has been further developed into a formulation suitable for human subjects with OAB (Mirabegron). Results from phase 3 trials of mirabegron in European, Australian and North American populations have shown favourable effects on bladder diary variables with good tolerability (Nitti et al, 2011; Khullar et al, 2011). Mirabegron was approved for clinical use in post-menopausal women in Japan in 2011, and was later approved by the US...
Food and Drug Administration (FDA) in 2012. It was launched in the UK in 2013 and is licensed for the treatment of OAB in women over the age of 18.

The role of cyclic adenosine monophosphate (cAMP) pathways in detrusor smooth muscle relaxation has lead to interest in this pathway as a potential target for novel pharmacotherapies. cAMP is broken down by phosphodiesterase (PDE) enzymes, meaning that inhibition of these enzymes will increase cAMP levels and perhaps potentiate detrusor smooth muscle relaxation. In vitro studies of the effect of a PDE4 inhibitor on human detrusor muscle strips demonstrated a reduction in phasic contractile activity (Oger et al, 2007). This effect was similar in strips with and without urothelium. Suppression of DO in animal models of bladder outlet obstruction (BOO) has also been demonstrated with administration of a PDE4 inhibitor (Nishiguchi et al, 2007). These very early studies do indicate the potential for new drugs based on modulation of cAMP pathways, but the development of such molecules for women with OAB does not seem to be imminent.

**Non-drug therapies for OAB**

Conservative management and pharmacotherapy remain the mainstay of treatment for OAB symptoms. However there is a subset of patients with more intractable symptoms, who fail to respond to multiple therapies. For these patients, other, more invasive, treatments have been developed.

*Botulinum neurotoxin type A (BoNT-A)*

This is a neurotoxin produced by the bacterium *Clostridium botulinum* and is one of the most poisonous substances known to man. It is known to bind to peripheral cholinergic
terminals and inhibit acetylcholine release at the neuromuscular junction by irreversibly cleaving the SNAP-25 protein (Dolly, 2003). The clinical effects of treatment with BoNT-A will therefore persist until regrowth of new motor endplates has occurred—this will typically be a few months (Tincello, 2011). Seven distinct botulinum toxins (A-G) have been isolated, but it is botulinum toxin A that is of most interest to the medical community. In addition to the motor effects, it has been shown to inhibit afferent nerve mediated bladder strip contractions (Smith et al, 2002), and decrease expression of urothelial mediators (Ha et al, 2011) and receptors associated with afferent function (Apostolidis et al, 2005).

There are 2 preparations of BoNT-A in use for urinary tract complaints at the present time, each with differing dosing protocols: Dysport (Ipsen), otherwise known as aboBoNT-A, and Botox (Allergen), otherwise known as onaBoNT-A. It is injected cystoscopically into the detrusor muscle at multiple sites. Although initial studies described sparing the trigone due to the risk of vesico-ureteric reflux, randomised evidence now suggests that including the trigone is associated with higher efficacy and no significant difference in voiding dysfunction or reflux (Manecksha et al, 2011).

The use of BoNT-A in the management of women with OAB symptoms secondary to idiopathic DO is now more commonplace, although there is limited RCT evidence to support its use. Evaluation of outcomes in a non-neurogenic context is generally in patients with symptoms refractory to antimuscarinic therapy. There have been many prospective non-randomised studies published reporting good outcomes in terms of improvements in symptom scores, quality of life and urodynamic parameters, but these papers are limited by small numbers (Rapp et al, 2004; Kessler et al, 2005; Schulte-Baukloh et al, 2005; Rajkumar et al, 2007; Jeffrey et al, 2007). The first RCT evaluating BoNT-A was published in 2007 and included 34 patients with idiopathic
DO who were randomised to receive onaBoNT-A or placebo. BoNT-A administration was associated with a significant increase in maximum cystometric capacity, and a decrease in micturition frequency and urgency incontinence episodes, with these benefits persisting at 24 weeks post-injection (Sahai et al, 2007). Another small RCT of 22 patients reported similar results (Flynn et al, 2009). Tincello and colleagues have recently published the results from a study of 240 women randomised to 200u onaBoNT-A or placebo with a 6 month follow up, they describe a more than 50% reduction in urgency and urgency incontinence in the BoNT-A group and a 31% continence rate versus a 12% continence rate in the placebo group. The incidence of voiding difficulty requiring self-catheterisation was 16% (Tincello et al, 2012). A recent dose finding (onaBoNT-A 50 to 300u) RCT of 313 patients with OAB identified a dose dependent increase in maximum cystometric capacity in those in the onaBoNT-A arm (Rovner et al, 2011). 57.1% of those who received 300u onaBoNT-A were dry, compared to 15.9% of those who received placebo. A similar dose finding study identified 100u of onaBoNT-A as the dose which balances efficacy with the risk of adverse effects such as voiding dysfunction (Dmochowski et al, 2010). Another study randomised 99 participants with OAB to 50, 100 or 150u of onaBoNT-A or placebo- a similar efficacy was found with 100u and 150u injections, with a lower risk of a significant post-void residual in the 100u group (Denys et al, 2012). Makovey and colleagues stratified outcomes from BoNT-A by indication and identified higher efficacy in those receiving BoNT-A because of antimuscarinic intolerability than those receiving it due to inefficacy (86% dry versus 60% dry, p= 0.02) (Makovey et al, 2011).

The effect of BoNT-A injections is not thought to be permanent, meaning that repeated treatments may be necessary. An analysis of 100 patients who underwent repeated injections (up to 5) showed that improvements in OAB symptoms are maintained after repeated injections, and
that the mean inter-treatment interval is 322 days (Dowson et al, 2012). Similar results on health related quality of life have been reported with repeat injections (Game et al, 2011). There is limited evidence to suggest that the benefits of BoNT-A are seen in women with OAB symptoms, but without proven DO, although this should be treated with caution as patient numbers are small (Kanagarajah et al, 2012).

Dowson et al described a 37% drop-out rate after 2 injections, with the most common reasons being lack of efficacy (13%) and not wishing to perform intermittent self catheterisation (ISC). Urinary retention requiring catheterisation is the most commonly described side effect following BoNT-A administration. A large US RCT of BoNT-A in women with OAB was terminated early due a 43% rate of urinary retention in the active group (Brubaker et al, 2008). Other RCTs have described BoNT-A related rates of ISC to be between 15 and 20% (Dmochowski et al, 2010). Use of BoNT-A in neurogenic DO patients has been associated with muscle weakness (Wyndaele and van Dromme, 2002), but this has not been described in idiopathic patients.

It should be noted that although two preparations of BoNT-A are in use, the majority of the available published studies have used onaBoNT-A. The active botulinum toxin molecule is identical between the two preparations, but the attached haemagglutinin complex is different. This means that evidence on onaBoNT-A cannot necessarily be directly extrapolated to aboBoNT-A. There are currently no published randomised studies evaluating the use of aboBoNT-A in patients with refractory DO. There are pharmacological differences between the two preparations, which are reflected in distinct dosing protocols.
Neuromodulation

Neuromodulation is an increasingly popular treatment option for women with refractory OAB symptoms. The concept is based on stimulation of pelvic nerves in order to decrease uninhibited detrusor contractions. Various animal studies have demonstrated that stimulation of the pudendal nerve or sacral nerve roots decreases detrusor contractions during filling (Tai et al, 2007; Tai et al, 2011). Human studies have confirmed that sensory input via the pudendal nerve inhibits DO (Ohisson et al, 1989). Stimulation of afferent nerves is thought to increase the inhibitory stimuli to the efferent nerves, leading to a decrease in contractility. Overall, neuromodulation appears to work at several levels to restore the balance between excitatory and inhibitory regulation at various locations in the peripheral and central nervous systems (Al-Shaiji et al, 2011).

The two types of neuromodulation in common use in urogynaecological practice are percutaneous posterior tibial nerve stimulation (PTNS) and sacral nerve stimulation (SNS).

PTNS has the advantage that it is a minimally invasive and office based treatment. It involves the placement of a small needle over the medial malleolus in order to electrically stimulate the posterior tibial nerve. The end result is stimulation of the S3 spinal cord root via the peroneal nerve. Initial small studies showed a 50% cure or improvement rate with few complications (Amaenco et al, 2003). There have subsequently been 2 RCTs evaluating outcomes. The SUmiT trial evaluated PTNS against sham therapy in 220 adults with OAB symptoms, and reported a 54.5% cure/improvement rate with PTNS versus 20.9% with sham, and no serious adverse events (Peters et al, 2010). An RCT of PTNS versus tolterodine showed an 80% subjective cure or improvement rate with PTNS versus 54.8% with tolterodine, with similar objective outcomes (Peters et al, 2009).
SNS involves implantation of a pulse generator which stimulates the S3 nerve roots. It is a two stage process. Stage 1 involves an initial screening test in order to identify patients who will have an adequate response to treatment. This consists of placement of a temporary lead (either a unilateral tined lead, or bilateral percutaneous leads), often under fluoroscopic guidance, which is then connected to an external stimulator. The initial screening test lasts for 7 days, during which a minimum 50% improvement in bladder diary variables will be deemed adequate to justify progression to stage 2. This consists of insertion of an implantable pulse generator (IPG), which is tunneled and implanted under the skin and connected to the S3 nerve root unilaterally via a tined lead. The battery life of an IPG is limited with second generation devices lasting for 3 to 5 years. A 2006 systematic review of available RCTs and case series evaluating SNS for urgency incontinence described an overall 80% cure or improvement rate in the RCT subjects (n=120), and a 67% cure or improvement rate in the case series patients. The authors described an overall reoperation rate of 33% (Brazzelli et al, 2006). White and colleagues described the most common adverse events as pain and trauma at the IPG site, infection, haematoma and lead migration (White et al, 2009). A 5 year follow up of patients with an IPG after a successful stage 1 showed a gradual decline in efficacy, with 87% success at 1 month to 62% at 5 years (Groen et al, 2011). Overall the evidence on SNS is limited by small numbers, and it is obviously a more invasive treatment than the others described here. However, success rates seem to be good, and it may be an acceptable option for women with refractory symptoms.

**Surgery**

Surgical options for urgency symptoms refractory to other treatments are highly specialised and include augmentation (clam) cystoplasty and urinary tract diversion procedures.
The long term course of OAB

As has been described earlier in this chapter, knowledge on the pathophysiology of OAB is increasing, leading to the availability of a larger number of treatment options. Until recently, there has been a lack of evidence in the literature on the natural history of OAB, and this is an important consideration when counselling patients regarding treatment options. Garnett and colleagues conducted a follow up of 267 women with OAB symptoms and DO, who had first been evaluated more than 10 years previously. They identified no significant differences in OAB symptoms at follow up, with 88% demonstrating persistent DO on urodynamic testing, and a decrease in voided volume and flow rate, together with an increase in the number and magnitude of involuntary detrusor contractions during filling (Garnett et al, 2009). A longitudinal study of 386 women over 3.5 years showed OAB to be a dynamic chronic condition, with periods of stability, remission and progression over time, with an annual incidence rate of 5.3% and annual remission rate of 4.6% (Heidler et al, 2011), however this study did have a high drop out rate (50%) and was characterised by a population who were not seeking medical help for their symptoms, meaning that the generalisability of this study to urogynaecology patient populations may be limited. A further population based longitudinal study from Sweden examining OAB symptoms in 1081 women over a 16 year period identified significant increases in prevalence of urgency incontinence, frequency and nocturia, but also remission rates of 34 and 43% for incontinence and OAB, respectively, and persistent incontinence in 66% (Wennberg et al, 2009). 28% of women with OAB dry at baseline had developed OAB wet at the 16 year follow up. A study with a larger population of 2284 women between 40 and 60, but a shorter
follow up time of one year, reported a 10% incidence and a 28% remission of lower urinary tract symptoms (Moller et al, 2000).

Whilst the studies discussed do report differing rates for incidence, persistence and remission of OAB symptoms, they do all indicate that OAB is a dynamic condition, with an overall high persistence rate. This should be considered when counselling patients, particularly those taking antimuscarinic medications which may be long term, or considering other therapies such as botulinum toxin or neuromodulation. This fact also highlights the importance of long lasting life-style changes to manage the symptoms caused by OAB

**Summary**

As has been discussed in this chapter, OAB is a common and debilitating condition with a significant socioeconomic burden. Management requires a multidisciplinary approach, with conservative measures such as bladder retraining being an important adjunct to pharmacotherapy. Recent advances in our understanding of the pathophysiology of OAB, particularly the role of afferent dysfunction, have stimulated the investigation of new drug targets, which will hopefully offer patients more options in terms of treatments. Pharmacotherapy is characterised by high discontinuation rates due to adverse effects or lack of efficacy, and the treatment options for refractory symptoms are generally more invasive with higher risks of complications. The next chapter focuses on a possible explanation for lack of efficacy of treatments in certain women, who may have other clinical factors driving their OAB symptoms.
Chapter Three

Overactive Bladder Syndrome and voiding in women: current evidence
The aim of the work described in this thesis is to explore the hypothesis that there is an association between OAB symptoms and voiding parameters in women, and therefore to gauge whether assessment of the voiding phase is of any value in women with OAB. This would only be the case if evaluation of voiding either had the potential to allow prediction of outcome for OAB treatments, or could be used to guide management. If these assumptions were proven, this would provide novel insight into the pathophysiology of OAB, as well as being of importance for any clinician managing women with this condition.

In this chapter, the rationale for examining this theory will be described, and the current evidence on the association between voiding and OAB in women will be summarised.

The stimulus to focus on the concept of voiding and OAB came from an earlier study evaluating the predictive value of pressure flow studies for the resolution of OAB and DO in women with mixed incontinence (i.e. urodynamic evidence of DO and stress incontinence, USI) treated with a tension free vaginal tape (TVT) (Duckett and Basu, 2007). In this study, a population of 35 women with mixed incontinence (i.e. urodynamically proven stress incontinence plus detrusor overactivity) who underwent insertion of a TVT were evaluated with filling and voiding cystometry pre- and post-surgery. The aim of the study was to compare voiding studies before and after TVT insertion in women with mixed DO and USI, in order to ascertain whether voiding studies can predict persistent OAB and DO post-operatively. The mean time to follow up evaluation was 27 months. Subjective outcomes were recorded using the symptom domain of the KHQ. Of the 35 women, 18 (51%) had no OAB symptoms at follow up, and 16/35 (46%) had no urodynamic evidence of DO. No women complained of stress urinary incontinence (SUI) at follow up, however the objective cure rate for USI was 92%. On analysis of the pressure flow data, women with persistent OAB were found to have a significant fall in
maximum flow rate ($Q_{\text{max}}$) following TVT insertion (from 20.0 to 14.0 ml/sec, $p=0.027$). There was no significant change in $Q_{\text{max}}$ post-operatively in women who were cured of OAB (from 25.4 to 19.7 ml/sec, $p=0.147$). Changes in detrusor pressure at maximum flow ($P_{\text{det}}Q_{\text{max}}$) did not reach statistical significance, however a trend towards an increase in women with persistent OAB (from 48.4 to 55.9 cmH$_2$O, $p=0.176$) and a decrease in those who were cured of OAB (from 53.9 to 45.1 cmH$_2$O, $p=0.463$), was observed. The post-operative $P_{\text{det}}Q_{\text{max}}$ was significantly higher in those with persistent OAB ($p=0.04$). The pre-operative $Q_{\text{max}}$ was significantly lower in women with persistent DO after TVT (19.3 versus 26.9 ml/sec, $p=0.022$). None of the women in the cohort developed post-operative voiding dysfunction, i.e. needed long term catheterisation. There were no significant baseline differences or changes in any other pressure flow parameters. A secondary analysis of these data demonstrated a significantly higher pre-operative opening detrusor pressure (ODP, defined as $P_{\text{det}}$ at the commencement of flow) in women with persistent DO (33 cmH$_2$O versus 16 cmH$_2$O) in those with persistent DO compared to those with normal urodynamics (Panayi et al, 2009). ODP is considered to be a surrogate marker of urethral resistance, which demonstrates good test-retest reliability (Digesu et al, 2004).

The results from this study suggested an association between voiding function and the persistence of OAB symptoms and DO. The mechanism of cure for OAB in 51% of participants is unclear, but may involve denervation secondary to the dissection required to place a TVT. The periurethral dissection performed during placement of the TVT may denervate the urethra, perhaps by disrupting branches of the pudendal nerve entering the urethra laterally. It is possible that the dissection may damage a theoretical pacemaker area in this region. Unfortunately there are no neurological investigations that can currently test this theory (S Elneil, personal communication). An alternative explanation for this phenomenon is that mixed incontinence in
some women may be a reflection of habitual frequent voiding in order to reduce SUI episodes by keeping the bladder empty. This behaviour can lead to a reduction in bladder capacity with consequent development of urgency. In such women, it can be speculated that cure of SUI relieves the need for this behaviour, with consequent cure of frequency and urgency.

At the time of publication of this study, there was very little in the literature examining the role of voiding and OAB/DO in women, meaning that the implication of these findings was unclear. One possible explanation for the results was that a significant fall in flow rate following TVT placement provided a mechanical stimulus for ongoing OAB symptoms/DO, rather than allowing any beneficial effect of the dissection to take place. However, even the role of the TVT in causing “obstruction” is unclear, with transperineal ultrasound studies showing that the TVT does not kink or physically obstruct the urethra in unstressed circumstances. The TVT was designed to be a “tension free” procedure (Ulmsten et al, 1996). Any conclusions from this study regarding the aetiology of the association between voiding parameters and persistent OAB/DO were therefore somewhat speculative, and the basis for this series of studies was to further explore this association.

**Male Bladder Outlet Obstruction and OAB/DO**

The relationship between increased outlet resistance and DO has been more extensively studied in men with bladder outlet obstruction (BOO) secondary to prostatic hypertrophy. Large population based urodynamic studies of men with lower urinary tract symptoms and benign prostatic hypertrophy have confirmed an independent association between the presence of BOO and DO, with the prevalence of DO increasing continuously with the grade of BOO (Oelke et al, 2008; Oh et al, 2011).
Long term follow up of men who have undergone a trans-urethral resection of prostate (TURP) for lower urinary tract symptoms suggestive of BOO have shown a sustained improvement in symptom scores post-operatively (Thomas et al, 2005; Masumori et al, 2010). The available data suggest an association between pre-operative urodynamic parameters suggestive of BOO and symptomatic relief (Thomas et al, 2005), with urodynamic evidence of detrusor underactivity being associated with higher post-operative symptom scores.

Extrapolation of the evidence on the association between male BOO and OAB symptoms to women cannot be carried out since fundamental differences in voiding mechanics exist between men and women. The presence of a prostate in men and the role of the pelvic floor in women make direct comparisons difficult. Differences in voiding can be caused by either differences in the contraction strength of the detrusor muscle, or by changes in the resistance of the bladder outlet to flow. The association between DO and BOO in men may be caused by overactivity of the detrusor muscle in order to overcome a down-stream element of obstruction, with evidence showing that men with prostatic obstruction have a DO-related facilitation of bladder contractility (Cucchi et al, 2005). It can be speculated that the underlying basis for the association between voiding parameters and persistent OAB in the original TVT and mixed incontinence study may involve a similar aetiology. However, if one is to exclude women with iatrogenic alterations in voiding parameters (i.e. women having undergone continence procedures), the possible association between voiding and OAB again becomes an unknown quantity.
**Female Voiding Parameters**

Women are known to void at significantly lower pressures than men, with many voiding by way of urethral relaxation or abdominal straining alone, meaning that definitions of BOO used for men cannot be applied to women. There is no accepted urodynamic definition for voiding dysfunction based on voiding parameters. The latest ICS/IUGA standardisation report on female pelvic floor dysfunction defines voiding dysfunction as being characterised by “an intermittent and/or fluctuating flow rate due to involuntary intermittent contractions of the periurethral striated or levator muscles during voiding in neurologically normal women” (Haylen et al, 2010). BOO is described as being characterised by a reduced urine flow rate and/or raised post void residual, with an increased detrusor pressure (Haylen et al, 2010). Because of the lack of numerically defined limits for voiding parameters, there is an inherent heterogeneity in the published research on female voiding. Voiding dysfunction has been defined as a flow rate below the 10th centile (based on the Liverpool nomograms) on free flow studies (Haylen et al, 1990), but it should be noted that this definition has not been applied to populations of women with lower urinary tract symptoms. As previously mentioned, alterations in voiding can be either due to underactivity of the detrusor muscle itself, or bladder outflow obstruction. BOO is often associated with symptoms of frequency and urgency in women, whereas detrusor underactivity tends to be more associated with classical voiding symptoms. It has been noted that the amplitude of the detrusor contraction will tend to increase to cope with any downstream obstruction (Groutz et al, 2000). As will be explained later in this chapter, there are other molecular changes which occur in response to BOO, which may also be associated with the development of OAB symptoms. The questions of whether more subtle differences in voiding may have prognostic value in women undergoing treatment, and whether attempted treatment of
potential outflow obstruction is associated with symptomatic relief will be addressed in the experimental chapters.

The concept of female BOO is far less well established than in men. There are 2 major studies which have studied BOO in large populations of women, with strict definitions used to make the diagnosis. Groutz and colleagues evaluated a population of 887 women with voiding symptoms (hesitancy, weak/intermittent stream, incomplete emptying, straining). They defined BOO as a free flow rate of less than 12 ml/sec in repeated studies with a $P_{\text{det}}Q_{\text{max}}$ of 20 cmH$_2$O or more. 6.5% of the population met the criteria for diagnosis of BOO, with the aetiologies including previous continence surgery (26%), severe genital prolapse (24%), and urethral stricture/narrowing (13%). 16% of the obstructed women had no identifiable cause. The mean free $Q_{\text{max}}$ in the obstructed women was 9.4 +/- 3.9 ml/sec, and the mean $P_{\text{det}}Q_{\text{max}}$ was 37.2 +/- 19.2 cmH$_2$O. Symptoms of frequency and urgency were common in addition to obstructive symptoms in these obstructed women, with 92% of the cohort complaining of these symptoms with or without urgency incontinence or nocturia (Groutz et al, 2000). The same group attempted to construct a nomogram for female BOO. They identified 50 women with diagnosed BOO (using the same definitions as the previous study plus radiographic evidence of outlet obstruction in the presence of a sustained detrusor contraction of at least 20 cmH$_2$O) from a database of 600 women (i.e. incidence of obstruction 8.3%). These 50 women were age-matched with 50 unobstructed controls, and patient and urodynamic characteristics compared between the 2 groups. The nomogram was constructed using the free flow $Q_{\text{max}}$ (to avoid any influence of the pressure catheter on voiding) and the maximum detrusor pressure (so that women unable to initiate voiding could also be included). The resulting nomogram has 4 zones from unobstructed
to severely obstructed, and these grades of obstruction correlate with lower urinary tract symptom scores (Blaivas and Groutz, 2000).

**Fig 3.1. Blaivas/Groutz nomogram for female BOO (Blaivas and Groutz, 2000)**

**Voiding parameters and DO/OAB in women**

Although clinically obstructed women do complain of OAB related symptoms, there is limited evidence of more subtle differences in urodynamic parameters between women with and without DO/OAB without clinical evidence of obstruction. Whilst such women cannot always be said to be “obstructed” (based on the Blaivas nomogram), these differences may be of interest in terms of decision making in women with OAB symptoms. Various studies have assessed differences in voiding parameters between women with different diagnoses. A study of age related changes in urethral function indentified significantly increased opening and closing detrusor pressures in women with DO versus those with stable bladders (Wagg et al, 1996). These differences were found across all age ranges and suggest that women with DO have increased urethral resistance. Other authors have directly studied urethral function in the presence of DO. Analysis of urethral pressure profile (UPP) studies from women with different urodynamic diagnoses has indicated a
decrease in functional urethral length and pressure transmission ratios with bladder filling in women with DO (Chaliha et al, 2005). This indicates an association between DO and abnormal urethral function. A later study evaluating 223 urethral resistance pressure (URP) measurements and urodynamic traces from women with DO or USI found higher URPs and opening detrusor pressures in women with DO than those with USI ( Digesu et al, 2007a). The same authors have also reported higher $P_{\text{detQ}_{\text{max}}}$ and lower $Q_{\text{max}}$ values for women with DO compared to those with USI (Digesu et al, 2004). A study defining obstruction as a $Q_{\text{max}}$ of less than 15ml/sec with a $P_{\text{detQ}_{\text{max}}}$ of over 40cmH$_2$O reported a higher incidence in 25 women with idiopathic DO (in the absence of pelvic organ prolapse and neurological problems) than 40 controls with “anatomic” incontinence (36% versus 15%) (Kayigil et al, 2007). Collectively, the available data on pressure flow parameters in women with DO suggest a trend towards higher urethral resistance, both when measured directly, and indicated indirectly by lower $Q_{\text{max}}$, and higher $P_{\text{detQ}_{\text{max}}}$ and ODP. The implications of these data are limited by the fact that each study compares parameters in women with DO versus those with USI, with no studies directly comparing women with DO with normal controls; it is therefore an extrapolation to suggest that DO is associated with more obstructive voiding parameters. It may be the case that urethral resistance is low in women with USI as one would expect, but “normal” in women with DO. It is also unclear whether this association is due to an aetiological role for increased urethral resistance in women with DO/OAB, or whether urethral resistance is increased as a result of OAB symptoms, i.e. due to repeated attempts to resist urgency incontinence episodes.

Ultrasound studies of the lower urinary tract also provide some insight into the possible anatomical association between increased outlet resistance and OAB/DO in women. The use of ultrasound measurement of bladder wall thickness has been suggested as a non-invasive method
of screening for DO. A cut off of 5mm has been reported as correlating with a urodynamic diagnosis of DO (Khullar et al, 1996), although estimates of specificity and sensitivity are highly variable, with specificity varying between 78-89% and sensitivity varying between 40 and 84% (Latthe et al, 2010). It may be that increased bladder wall thickness in some women with DO is as a result of hypertrophy caused by repeated contraction of the detrusor against a downstream obstruction caused by increased urethral resistance, although direct evidence to make this link is lacking.

**Molecular and cellular changes associated with Bladder Outlet Obstruction**

Chapter 2 contained a full discussion of the underlying cellular and molecular changes associated with DO and OAB. Studies using animal models of obstruction have provided evidence for similar cellular and molecular changes which are thought to occur as a result of outlet obstruction. These common changes may provide some insight into the pathophysiology of the clinical features seen in women with elevated outlet resistance and OAB. Detrusor muscle strips from outlet obstructed bladders in both humans and animal models show a pattern of denervation and decrease in nerve mediated responses similar to that seen in patients with DO (Gosling et al, 1986; Harrison et al, 1987; Harrison et al, 1990). This pattern of denervation has been shown to lead to an enhanced response to acetylcholine (Sibley, 1987). These changes have also been seen in association with evidence of oxidative stress in a guinea pig model of outlet obstruction (de Jongh et al, 2009), and there is evidence to suggest that this denervation may be caused by tissue ischaemia and hypoxia secondary to distension of the bladder (Azadzoi et al, 1996). Animal models of urethral obstruction have also shown alterations in the number of
detrusor muscle contractile units responding to stimulation (van Koeveringe et al, 1993), as well as a higher instability of membrane potential, which can cause cell depolarisation with the net result that detrusor muscle in obstructed bladders is more irritable whilst synchronous activation of contractile units is damaged (Seki et al, 1992).

There is increasing evidence that afferent pathways are remodelled in response to outlet obstruction. In a rat model of urethral obstruction, significant hypertrophy of afferent neurones (Steers et al, 1991a) as well as elevated levels of NGF has been observed (Steers et al, 1991b). These changes are only partially reversed with relief of obstruction, indicating variable plasticity of this remodelling. Immunisation to NGF in the same model prevents obstruction induced neuronal hypertrophy, as well as reducing urinary frequency, indicating that cytokine mediated mechanisms may be responsible for the symptoms associated with outlet obstruction (Steers et al, 1996). Elevated Nitric Oxide synthase in spinal bladder afferents has also been noted following urethral obstruction, providing further support for this concept (Zvara et al, 2004).

Indirect evidence of remodelling of afferent pathways has been shown in a study of 111 patients who underwent an “ice water test” (bladder instillation of water at 0°C at 50 mls/min; positive result indicated by presence of uninhibited detrusor contractions in response to this). A positive ice water test indicates an enhanced C-fibre mediated spinal micturition reflex which indicates afferent dysfunction. This study demonstrated a significantly higher proportion of patients with clinical evidence of obstruction having a positive ice water test, than those with normal bladders (Chai et al, 1998), indicating enhanced activity of spinal micturition reflexes in patients with outlet obstruction. Studies of bladder weight and smooth muscle structure in a rat model of outlet obstruction have shown no significant changes following outlet obstruction and the subsequent development of DO (Schroder et al, 2003), which may indicate that the clinical
features associated with DO following outlet obstruction are mainly due to sensory, rather than motor dysfunction.

Clearly these studies rely heavily on animal models of urethral obstruction which are produced by tying off the urethra. This produces an extreme degree of obstruction which will be an inherently poor surrogate for female BOO. Nevertheless, the pattern of change seen in these animal models may be present at lesser degrees in women with outlet obstruction and therefore provide some insight into the possible aetiological link between BOO and OAB symptoms.

Summary

The evidence discussed in this chapter does seem to suggest an association between bladder outlet obstruction (particularly iatrogenic following continence procedures) and OAB symptoms. The development of female obstruction nomograms has gone some way to improving the definition of “normal” and “obstructed” female voiding. There is evidence to suggest that differences in voiding parameters do exist between women with OAB and DO, and women with stable bladders. Models of urethral obstruction do indicate that changes in nerve density and responses, muscle contractile activity and particularly afferent function, occur in response to outlet obstruction. In the previous chapter, the importance of these mechanisms in the pathophysiology of OAB symptoms and DO was discussed, and it may be the case that they represent the final common pathway by which clinical obstruction leads to OAB symptoms.

Gross BOO is women is relatively uncommon however. Given that there may be an association between voiding function and outlet resistance and OAB symptoms in such women, the next question to be addressed would be whether more subtle differences in voiding function
(in the absence of clinical BOO) are associated with OAB symptoms, and also whether attempts to decrease outlet resistance and improve voiding parameters will lead to an improvement or resolution of symptoms. If these theories were proven, it would imply that routine assessment of the voiding phase should be a component of the assessment package for women with OAB.

The question of whether differences in voiding function in women with OAB are important clinically in terms of management is the basis of this thesis. Graded differences in urethral resistance cannot be produced in human subjects, therefore a number of clinical models of variable urethral resistance have been selected to explore the relationship between voiding and OAB.

- The initial study will use an unselected population of women with OAB treated with antimuscarinic drugs to assess whether voiding parameters can be used to predict response to treatment
- A population of women with symptomatic pelvic organ prolapse and OAB will be evaluated to assess whether voiding parameters can be altered by surgical repair, and whether cure of OAB can be predicted using voiding parameters
- Women undergoing urethral dilatation to reduce outlet resistance will be evaluated to determine whether this leads to any change in voiding function, and whether such changes are associated with symptomatic relief
OVERALL NULL HYPOTHESIS

Routine evaluation of the voiding phase of urodynamics is of no value in the evaluation of women with Overactive Bladder symptoms
Chapter Four

Methodology:

Assessment of lower urinary tract symptoms in women—history, examination, quality of life and urodynamic studies
The studies described in this thesis each have a different objective and evaluate voiding and OAB from within a number of different clinical models. However, certain aspects of Methodology are common to each study, and will be described here. History, examination, assessment of quality of life and objective evaluation of bladder function using urodynamic studies permit a global assessment of an individual woman’s symptoms, together with the impact of these symptoms on her lifestyle.

The assessment of all the subjects who took part in this series of studies followed the same structured format of a full history and examination, quality of life assessment and urodynamic studies. In this chapter, each of these components of patient assessment will be described.

**HISTORY AND EXAMINATION**

A thorough history of the patient’s urinary symptoms is best conducted in an interview setting, using the patient’s own terminology. As a general principle, the patient’s most bothersome symptom should be first discussed, followed by an enquiry for the presence of other associated urinary symptoms. This is so that treatment can be directed towards the most troublesome symptom. For each symptom, the impact on an individual’s daily activities can be assessed. The duration of symptoms can discriminate between transient and well established symptoms, and any adaptive behaviour (in the case of long-standing symptoms) can be enquired after. It is important to systematically ask about all urinary symptoms, as some women may be too embarrassed to volunteer information without being directly asked.

Symptoms can be grouped into storage, voiding and sensory disorders. Urinary incontinence is a failure of storage and is defined as the complaint of any involuntary loss of
urine (Haylen et al, 2010). Evaluation of any provoking factors for incontinence, such as exertion, running water, “key in the door”, etc, may help in differentiating between SUI and OAB symptoms, and asking whether urine loss is continuous or intermittent will also assist in forming a differential diagnosis. The severity of the incontinence can be estimated by asking about the number of pads used per day. Urgency severity can be quantified using severity scales such as the Urgency Perception Scale (Cardozo et al, 2005)

Specific urinary symptoms are listed below (all definitions Haylen et al, 2010):

Storage

- **Urgency**: “a sudden and compelling desire to pass urine that is difficult to defer” (unable to “hold on”)

- **Urgency incontinence**: “involuntary leakage of urine that is accompanied by, or immediately preceded by urgency” (being unable to make it to the toilet on time and leaking)

- **Frequency**: the number of times a woman voids during waking hours (often defined by the patient as voiding too often during the day)

- **Nocturia**: waking 1+ times during the night to void (must discriminate between being woken up by the need to void, and voiding because patient is awake anyway)

- **Nocturnal enuresis**: loss of urine occurring during sleep

- **Stress urinary incontinence**: involuntary loss of urine with raised abdominal pressure (exertion, effort, coughing, sneezing)
- Mixed urinary incontinence: stress urinary incontinence plus urgency incontinence

- Coital incontinence: involuntary loss of urine with coitus (penetration/orgasm)

- Insensible incontinence: urinary incontinence with woman unaware of how it occurred

Voiding

- Hesitency: difficulty in initiating micturition

- Straining: muscular effort (usually via valsalva) used to initiate, maintain or improve urinary stream

- Incomplete emptying

- Post-micturition dribble: involuntary loss of urine immediately after finishing passing urine

- Slow stream

Sensory

- Urethral pain: can occur at rest or with passing urine (= dysuria)

- Bladder pain: felt suprapubically or retropubically, and classically increases with bladder filling; can persist even after voiding

As well as urinary symptoms, there are several other symptoms of pelvic floor dysfunction which must be asked about. These include prolapse symptoms (“something coming down”, sensation of bulge/lump/dragging in the vagina), dyspareunia and vaginal dryness, haematuria, recurrent urinary tract infections, obstructed defecation symptoms (in association with prolapse
symptoms) and any history of childbirth injury. It is important to enquire after fluid intake (including caffeine and carbonated drinks specifically), as this may impact on OAB symptoms. This can be more accurately assessed using a bladder diary.

An obstetric and gynaecological history should be taken for parity, menstrual function, and previous surgery. Past medical history should include any conditions which may affect urine production (e.g. congestive cardiac failure, diabetes) or storage/voiding (e.g. neurological disorders), as well as conditions leading to chronically raised intra-abdominal pressure (e.g. constipation, chronic cough). A drug history aims to identify any medications affecting urine production or storage.

Examination should always start with an abdominal inspection and palpation to identify any surgical scars or the presence of a full bladder or pelvic masses. Inspection of the vulva and vagina will reveal the presence of vulvovaginal atrophy or excoriations. A bimanual examination is used to assess the size and mobility of the uterus, as well as to rule out any adnexal masses. Pelvic floor muscle strength can be assessed during a digital vaginal examination, and can be graded according to the modified Oxford scale (Laycock, 2003). Genital prolapse is assessed in the left lateral position at maximum valsalva using a Sims speculum. The two grading or scoring systems which have been used in this thesis are the Baden Walker classification (Fig 4.1) and the Pelvic Organ Prolapse Quantification (POP-Q) system (Fig 4.2)
Fig. 4.1 Baden Walker classification for prolapse (I-IV)

Fig. 4.2 Pelvic organ prolapse quantification
Stage 1: Most distal part of prolapse descends to less than 1cm inside hymen
Stage 2: Most distal part 1cm from hymen (proximal or distal)
Stage 3: Most distal part more than 1cm outside hymen (but no more than within 2cm of total vaginal length)
Stage 4: Complete eversion or extension to within 2cm of total vaginal length
**QUALITY OF LIFE ASSESSMENT**

Quality of life is associated with the World Health Organisation definition of health (Kelleher, 2010), which refers to a state of physical, emotional and social well-being, and not simply the absence of disease. Urinary incontinence is usually a non-life threatening condition, and therefore quality of life impairment is the fundamental end result which impacts on patients. Assessment of quality of life at baseline and after any treatments for incontinence is thus an important part of clinical evaluation in urogynaecology. Health related quality of life questionnaires are multi-item questionnaires that usually evaluate different aspects (or domains) of a patient’s life, e.g. social life, work life, personal relationships, etc. The score for each of these domains represents the degree of impairment of an individual’s functioning within that particular activity.

There are a large number of different instruments available for assessing health related quality of life in women with lower urinary tract symptoms, and a full discussion of their use is outside of the scope of this thesis. Evaluation of patients in this series of studies was undertaken using the King’s Health Questionnaire, KHQ (Kelleher et al, 1997). This validated questionnaire consists of 3 parts. The first contains two questions measuring general health and overall health related to urinary symptoms. The second consists of 19 questions divided into seven domains of quality of life. The third consists of 11 questions evaluating the bother of urinary symptoms. The KHQ is presented and discussed further in Appendix 2.
URODYNAMICS

Much of the basis of the series of studies described in this thesis centres around the assessment of voiding parameters in women being treated for OAB symptoms. The direct assessment of lower urinary tract function can be achieved by urodynamic investigations, which involve measurement of physiological parameters in real time. Urodynamics can be used to investigate all aspects of lower urinary tract dysfunction, however this chapter will focus on the urodynamic evaluation of voiding and OAB symptoms used throughout this thesis.

The term “urodynamics” was first used by D.M. Davis in 1954 (Davis, 1954). Initially it referred to the hydrodynamics of the upper urinary tract, but soon encompassed “the physiology and pathophysiology of urine transport from the kidney to the bladder as well as its storage and evacuation”. In the early 1970s the first sophisticated laboratory techniques combining dynamic investigations of both the upper and lower urinary tracts were introduced by Miller (Miller, 1967). These investigations were later advocated in Europe by Bates, Whiteside & Turner-Warwick. The measurement of intravesical and urethral pressures was first described by Dubois in 1876, but it was not until 1927 that the term “cystometer” was first used by Rose. In 1948 Talbot first described “stable” and “unstable” cystometric recordings (Talbot, 1948), and in 1961 Enhorning established the pathophysiology of stress incontinence by concurrent measurement of urethral and bladder pressure.

The aim of urodynamics is to reproduce symptoms whilst recording physiological measurements, so as to delineate the underlying pathophysiology of these symptoms. This clearly requires the initial formulation of a clinical question, based on a careful history and examination, together with the use of adjuncts such as a frequency volume chart which will give important information on micturition frequency and nocturia episodes, functional capacity and
fluid intake. The use of a diary has been found to be more accurate than patient recall (Stav et al, 2009). A minimum of three days is optimal to gain meaningful information (Palnaes et al, 1998), although a four day diary has been found to be as accurate as a seven day diary (Schick et al, 2003). Recording of additional information such as bladder pain, urgency or incontinence episodes will enhance the usefulness of this record (See Fig 4.3).

<table>
<thead>
<tr>
<th>DATE/TIME</th>
<th>LIQUID INTAKE</th>
<th>VOLUME OF URINE</th>
<th>LEAKS</th>
<th>PAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0100</td>
<td>150</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0115</td>
<td>250</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0200</td>
<td>50</td>
<td></td>
<td></td>
<td>P</td>
</tr>
<tr>
<td>0300</td>
<td>Glass of juice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>100</td>
<td></td>
<td></td>
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<td>20</td>
<td></td>
<td></td>
<td>P</td>
</tr>
<tr>
<td>1500</td>
<td>Glass of tea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1600</td>
<td>150</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1800</td>
<td>Glass of tea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1900</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
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<td>2000</td>
<td>Glass of water</td>
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<tr>
<td>2300</td>
<td>Glass of water</td>
<td>150</td>
<td></td>
<td>P</td>
</tr>
<tr>
<td>2400</td>
<td>150</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Differences in bladder diary variables have been identified between women with different urodynamic diagnoses, with women with DO tending to have more frequent, smaller volume voids than those with USI (Parsons et al, 2007). The value of a frequency volume chart lies in the objective evidence of day to day bladder function, which can be used to assess response to interventions, together with information on functional capacity which can be used to guide filling volumes at urodynamics.

In 2002, the International Continence Society published standardisation guidance on performing urodynamic investigations (Schafer et al, 2002). All urodynamic investigations carried out in the studies in this thesis were carried out according to the standards set out in this document, and these standards will be discussed in this chapter. In the standardisation document, three main elements to Good Urodynamic Practice were described:
- A clear indication for and appropriate selection of, relevant test measurements and procedures
- Precise measurement with data quality control and complete documentation
- Accurate analysis and critical reporting of results

(Schafer et al, 2002)

**Uroflowmetry**

This is a non-invasive and inexpensive first line screening test for women with lower urinary tract dysfunction. Women should be provided with a private area for this investigation, and asked to void when they feel a normal desire to void. This is to ensure an adequate voided volume and also to ensure that the void is representative of a normal void. The voided volume may be compared to voids from a bladder diary to check if the volume voided is typical of an individual.

The recording obtained from uroflowmetry will give both quantitative information on the flow rate and a graphical representation of the flow pattern. The flow rate is defined as the volume of fluid expelled via the urethra per unit time and is expressed in millilitres per second (ml/s). This should be interpreted in the context of the volume voided, the position of the patient during micturition, and whether the bladder filled naturally or via a stimulated diuresis. The following specific parameters will be recorded:

*Maximum flow rate* \(Q_{\text{max}}\) (ml/s)

*Voided volume* (mls)

*Flow time* (the time over which the measurable flow occurs) (s)
Average flow rate (voided volume divided by flow time) (ml/s)

Time to maximum flow (The elapsed time from onset of flow to maximum flow) (s)

The investigation will usually be completed with ultrasonographic determination of post-void residual volume.

Currently available flowmeters use several different principles. The weight transducer flowmeter calculates the weight of fluid voided to assess voided volume, and measures the weight increase over time to calculate flow rate parameters. The spinning disc flowmeter has a disc which rotates at a constant speed, and calculates the power needed to maintain this speed when urine falls onto it. The power needed to maintain the disc rotation is proportional to the flow rate. Finally, some flowmeters will use a pressure transducer to measure the hydrostatic pressure of a column of urine. Most flowmeters will produce a printout of flow over time together with the flow parameters described above. This should be reviewed carefully by the clinician performing the test, since the software in the flowmeter will not be able to distinguish an artificially high flow rate caused by artefact.

A normal uroflow pattern is of a smooth arc shaped flow rate curve with a high amplitude. This is produced by relaxation of the bladder outlet and contraction of the detrusor smooth muscle. Pathological alterations in either the strength of the detrusor contraction or the relaxation of the bladder outlet will lead to changes in the shape and height of this curve, although diagnosis of such pathologies is not possible using uroflowmetry alone (Chou et al, 2000).
The ICS recommends the following technical standards for uroflowmetry: a range of 0-50 ml/s for Qmax, a range of 0-1000mls for voided volume, a maximum time constant of 0.75 seconds, and an accuracy of +/- 5% relative to full scale. Graphical scaling should be standardised such that one millimetre should equal 1 second on the x axis, and 1 ml/s or 10ml volume voided on the y axis. For routine clinical measurements, accuracy for flowrate values should be to the nearest full ml/s and for volume to the nearest 10mls. Curves should be electronically smoothed to remove spike artefacts (Schafer et al, 2002)

Urine flow rates are known to be strongly dependent on voided volume (Haylen et al, 1990), and as such, should usually be interpreted with reference to nomograms such as the Liverpool nomogram, which provides a centile value for a given flow rate and voided volume (Haylen et al, 1989). A flow rate of less than the 10th centile for volume is taken as abnormal. The centile value can be calculated using the formula below:

\[
100 \times \text{NORMSDIST}((\ln(Q_{\text{max}}) - (0.51136 + 0.50457 \times \ln(\text{voided volume})))/0.33966)\]

This formula has previously been used to convert flow rate data (Dietz and Haylen, 2005), and will be used in the studies reported later in this thesis.
In the context of voiding disturbances in women, uroflowmetry has been found to have a high specificity and negative predictive value for diagnosis (Constantini et al, 2003), and has also been suggested to be predictive of post-operative voiding dysfunction following continence procedures (Wheeler et al, 2008).

**Filling Cystometry and Pressure Flow Studies**

Cystometry analyses the pressure volume relationship of the bladder and is used to study the storage and voiding phases of bladder function. Unlike uroflowmetry, these investigations are invasive, and as such should not be performed without a clear indication. Three key recommendations were laid down in the ICS standardisation document:

- “A good urodynamic investigation should be performed interactively with the patient. It should be established by discussion with the patient that the patient’s symptoms have been reproduced during the test;
- There should be continuous and careful observation of the signals as they are collected, and the continuous assessment of the qualitative and quantitative plausibility of all signals;
- Artefacts should be avoided, and any that occur should be corrected immediately.”

  Schafer et al, 2002

During cystometry, the pressures within the bladder (intravesical pressure) and within the abdomen (usually by measuring the pressure in the rectum) are measured concurrently. In simple terms, pressure is measured by a water column with a catheter placed in the bladder/rectum, with the height of the column in centimetres above the bladder giving the
pressure within the bladder (in centimetres of water, cmH2O). Modern urodynamic systems will use pressure transducers for accurate measurement of pressure. Intravesical pressure will reflect both the pressure generated by the detrusor muscle and also changes in abdominal pressure. The electronic subtraction of abdominal pressure from intravesical pressure calculates the detrusor pressure, thus eliminating any intravesical effects of changes in abdominal pressure. It should be noted that this calculation of detrusor pressure will also be influenced by any changes in abdominal pressure which are not transmitted intravesically (e.g. rectal contractions), meaning that the detrusor pressure measurement should always be interpreted with reference to the intravesical and abdominal pressure measurements at the time.

The urodynamic studies carried out for the studies in this thesis used external strain gauge transducers, which record pressure waves transmitted from the patient by fluid filled catheters. These are based on recording the strain exerted on a metal diaphragm by transmitted pressure changes, which is then converted into an electrical signal.

All cystometry studies performed for this thesis utilised a 6 French transurethral double lumen intravesical catheter (for filling and pressure transduction) for intravesical pressure measurement, and a rectal balloon catheter for abdominal pressure measurement. The role of the balloon is to allow a small fluid volume at the catheter opening and avoid blockage with faecal material. It will also prevent pressure artefacts arising from contact between the catheter tip and the wall of the rectum. A balloon is not necessary for the vesical catheter because of the absence of solid material in the bladder.

In order to ensure correct measurement of pressure, the transducers should first be set to zero, calibrated and finally a pressure reference level established. The ICS recommends the convention that transducers are set such that zero pressure is equivalent to the surrounding
atmospheric pressure. These steps are taken following flushing of the catheters with fluid, in order to fill the catheters, eliminate bubbles (which could affect pressure measurements as they disrupt the column of water through which pressure is transmitted) and check for leaks. The transducer domes themselves should also be flushed and filled with fluid. The ICS has defined the reference level for external transducers and fluid filled catheters as the superior border of the symphysis pubis, meaning that transducer height should be adjusted to this level before commencing the investigation.

There are a number of recommended quality control tests which should be undertaken before filling cystometry commences, in order to allow for correction of any problems. The aim is to ensure the recording of perfect signals at the beginning of the study in order to avoid artefacts. The minimum recommendations for quality control are listed below:

- Resting values for abdominal and intravesical pressures are within the range of: supine 5-20 cmH₂O, sitting 15-40 cmH₂O, standing 30-50 cmH₂O. If standards have been followed, the detrusor pressure should by definition be near zero, as both recorded pressures should be almost identical

- The abdominal and intravesical pressure signals are “live”, with minor variations caused by breathing or talking being similar for both signals

- Coughs are used to ensure that the abdominal and intravesical pressure signals respond equally. Coughs immediately before and after voiding should also be used.

  (Schafer et al, 2002)

The infusion fluid used in these studies was sterile normal saline at room temperature, although water and obviously x-ray contrast media for video urodynamic studies may also be
used. Low temperature fluid is known to provoke detrusor contractions (Geirsson et al, 1993), and should not be used for routine cystometry studies. The bladder filling rate is known to affect bladder compliance. The ICS defines three categories of filling from 10-100ml/min; all studies in this thesis were performed with a filling rate of 50 mls/min. This rate was chosen to avoid provocation of detrusor contractions caused by fast filling (a theoretical possibility in women without DO), whilst also avoiding prolonging the time taken to complete the investigation.

During filling, the central principle of aiming to reproduce the patient’s symptoms should not be forgotten. There are certain parameters that should be observed during filling. Note should be made of bladder sensation, with the volume at which markers such as first desire to void, strong desire to void and urgency occur being noted. Although sensory disturbance is now not defined as a urodynamic diagnosis, these parameters can be useful in interpreting a patient’s day to day symptoms and bladder diary variables. The activity of the detrusor muscle should also be observed during filling. A normal detrusor will remain quiescent (i.e. with a pressure of near zero) during filling, even if provocative manoeuvres (see later) are undertaken. This reflects the ability of the detrusor to relax and increase in size without any significant changes in pressure. Detrusor overactivity is defined as the occurrence of involuntary detrusor contractions during filling, which may be spontaneous or provoked (Haylen et al, 2010). DO may or may not be accompanied by symptoms of urgency or urgency incontinence, and note should be made of such accompanying events. Provocation manoeuvres which may be undertaken include running water, handwashing and postural changes. The presence of USI (the involuntary leakage of urine during filling cystometry, associated with increased intra-abdominal pressure, in the absence of a detrusor contraction) should also be noted during filling, and at capacity. Cystometric capacity is the bladder volume at the end of filling. Maximum cystometric capacity is the volume at which
the patient feels that micturition can no longer be delayed, and will often be indicated by the
volumes on a patient’s bladder diary. Patients undergoing urodynamic studies for the studies in
this thesis were filled to 500mls, or less if the patient requested termination of filling. In all
patients, the first 100mls was infused with the patient supine. The remainder of the filling phase
occurred with the patient standing.

The final phase of cystometry is voiding cystometry, also known as the pressure flow study. The patient is asked to void into a flowmeter with the catheters still in place. This gives
information on the flow rate and pattern, with the additional recording of intravesical, abdominal
and detrusor pressure during the voiding phase, which allows for better definition of voiding
function and dysfunction than uroflowmetry. As before, privacy is of importance to ensure a
successful void. A number of parameters are measured during the pressure flow study:

*Premicturition pressure* (the detrusor pressure immediately before the initial contraction)
*Opening time* (the time elapsed from the initial increase in pressure to the onset of flow)
*Opening pressure*  (the detrusor pressure recorded at the onset of flow)

*Maximum pressure*

*(Detrusor) Pressure at maximum flow*

*Closing pressure* (the detrusor pressure recorded at the end of flow)

*Contraction pressure at maximum flow* (the difference between pressure at maximum flow and
the premicturition pressure)

*Flow delay* (the delay in time between a change in pressure and a measured change in flow)

(Haylen et al, 2010)
Normal voiding in women is achieved by an initial voluntary urethral relaxation, followed by a sustained detrusor contraction, which leads to complete bladder emptying over a normal time span (Haylen et al, 2010). The magnitude of the detrusor contraction will tend to increase to overcome any degree of outflow obstruction, with the opening pressure more specifically being a measure of the pressure needed to initiate flow and therefore a surrogate for urethral resistance. Detrusor underactivity is said to occur if the detrusor contraction is unable to empty the bladder or to maintain a normal flow rate for a given voided volume. Some women will void by urethral relaxation in the absence of a detrusor contraction. Following a void, note should be made of the volume voided with reference to the volume of fluid infused, such that an estimate of residual volume may be made. The presence of the 6F urethral catheter during voiding does have a measurable effect on voiding parameters. Comparison of flow rates from women with and without a 6F urethral catheter has shown a significant difference in Qmax, even when corrected for volume voided, as shown in the table below:

<table>
<thead>
<tr>
<th></th>
<th>Uroflow study</th>
<th>PFS study</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qmax (mls/sec)</td>
<td>25.1</td>
<td>12.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Voided volume (mls)</td>
<td>156.4</td>
<td>380.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Flow rate centile</td>
<td>45.3</td>
<td>12.6</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Table 4.1 Comparison of mean voiding parameters from uroflow and pressure flow studies

(Duckett et al, personal communication)

Pressure flow studies in women have been found to have good reproducibility and reliability with minimal inter-observer variation (Digesu et al, 2003). The measurement of
pressure will allow differentiation of clinical voiding difficulties due to detrusor undertactivity or BOO, however for the purposes of this thesis, differences in voiding parameters before and after various interventions for OAB will be assessed with a view to analysing their relationship to outcome, and evaluating the possible relationships between voiding function and the diagnosis of OAB.

**Summary**

Assessment of women with lower urinary tract symptoms should begin with a careful symptom assessment and formulation of a clinical question. A clinical examination to assess for external urogenital abnormalities (such as vulvovaginal atrophy), pelvic masses, urethral and bladder neck mobility, demonstrable incontinence, and pelvic organ prolapse is an essential step prior to undertaking initial investigations. The use of a bladder diary will give a useful estimate of day to day functional bladder capacity together with both day and night-time micturition frequency. The aim of urodynamic studies is to reproduce the patient’s symptoms, such that the underlying pathophysiology can be delineated. Carrying out urodynamic studies with reference to set quality control and technical standards is of paramount importance, in order to allow for accurate and reproducible information. The filling phase may reveal urodynamic diagnoses such as DO and USI, and the voiding phase allows evaluation of detrusor function during flow.

**Summary of specific method for urodynamics**

All urodynamic studies in this thesis were conducted using a Dantec Duet Logic urodynamic system (See Figure 4.3), with a 6F double lumen intravesical catheter for filling and pressure measurements, a rectal balloon catheter for abdominal pressure measurements, and a
rotating disc flowmeter. Prior to filling, an unintubated free flow study was performed, with the post-void residual being checked using Doppler planimetry. Filling cystometry was carried out with normal saline (stored at room temperature) at an infusion rate of 50mls/min. The first 100mls of filling was undertaken in the supine position, and the remainder of the filling phase was carried out with the patient standing. Provocative manoeuvres were undertaken during filling and subtraction was checked with coughs prior to filling, after every 100mls infused, and at the end of filling. Patients were observed for urodynamic stress incontinence (leaking on cough or valsalva in the absence of a detrusor contraction) whilst supine after 100mls had been infused, and again at cystometric capacity (provoked with coughing, valsalva, heel bounces). Patients were filled to 500mls (unless their bladder diary indicated a higher functional capacity), unless they requested termination of filling due to pain or severe urgency. A voiding pressure flow study was undertaken at cystometric capacity with the vesical and rectal pressure lines still in place.

Over 90% of the urodynamic studies carried out for this work were undertaken by the author, with the remaining being undertaken by the Urogynaecology Nurse Practitioner. All equipment is calibrated and serviced regularly, and all urodynamic traces are reviewed by the senior consultant. All urodynamic studies were carried out to a standardised protocol. For logistical reasons, paired urodynamic studies in the same patient could not be done at the same time of day each time.
Fig 4.5 Urodynamic machine and commode at Medway Hospital
Chapter Five

The predictive value of pre-treatment pressure flow studies in women with overactive bladder symptoms treated with antimuscarinics
Introduction

Initial management of OAB symptoms in women consists of conservative measures such as bladder retraining and modification of fluid intake. Women who experience persistent symptoms following these treatments will then usually be commenced on pharmacological therapy to control their symptoms.

Pharmacological agents for OAB are based on blockade of muscarinic receptors. The predominant type of muscarinic receptor found in the lower urinary tract is the M3 receptor (Andersson, 2011), and it is this receptor that was thought to be responsible for the overactive detrusor contractions seen in women with OAB symptoms. However, it is known that antimuscarinics act mainly during the storage phase by increasing bladder capacity and decreasing urgency, and parasympathetic nerves tend to be quiescent during this phase (Andersson and Yoshida, 2003). M3 receptors are found in the urothelial and suburothelial tissue (Hawthorn et al, 2000), and it has been demonstrated that the effects of antimuscarinic drugs are also mediated via effects on afferent pathways (Iijima et al, 2007; Boy et al, 2007).

Whilst antimuscarinics have proven efficacy, their use is limited by adverse effects related to effects on muscarinic receptors outside the lower urinary tract. This has led to the development of M3 selective medications such as solifenacin succinate. Solifenacin has demonstrated good efficacy and tolerability in multicentre placebo controlled trials (Cardozo et al, 2004; Chapple et al, 2004), and was also shown to be superior to tolterodine in terms of reduction of micturition frequency and urgency episodes (Chapple et al, 2005b). A more recent study using urgency as an end-point found solifenacin to lead to a 70% reduction in urgency episodes per 24 hours (Cardozo et al, 2008).
It is unclear why some women fail to improve with drug treatment. It may be that if another factor in addition to muscarinic receptor medicated symptoms is present, this will render medications less effective or ineffective. For example, both OAB and interstitial cystitis cause the patient defined symptom of urgency, but each has a distinct pathophysiology (Clemens et al, 2011). Other factors which may give rise to OAB symptoms without underlying DO include constipation/faecal loading, pelvic masses (including fibroids), medications including diuretics, diabetes, tumours or stones in the bladder, pregnancy and urinary tract infection. Various studies have indicated that increased urethral resistance may be of aetiological importance in women with OAB and detrusor overactivity (Duckett and Basu, 2007; Panayi et al, 2009), but these studies have examined this in the context of surgical interventions for lower urinary tract symptoms. Since the majority of women referred with OAB symptoms will be treated with antimuscarinics, it would be of benefit to be able to identify pre-treatment factors which may cause a higher risk of treatment failure. This study was designed to explore the hypothesis that increased urethral resistance (measured by reduced flow rates or increased voiding pressures) is important in the failure of women to respond to antimuscarinic therapy. The aim of this study was to identify whether there is any difference in pre-treatment voiding parameters between women who respond to solifenacin succinate 5mg versus those who do not respond.

Null Hypothesis

Pre-treatment voiding cystometry parameters are not predictive of response to treatment with solifenacin in women with overactive bladder symptoms.
Patients and Methods

This was a prospective observational study. The study population consisted of women with overactive bladder symptoms which had proved refractory to conservative measures (i.e. bladder retraining, fluid intake modification, caffeine reduction) with urodynamic evidence of DO. These data were collected between October 2008 and April 2010. The primary outcome measure was the change in OAB symptoms 6 weeks after commencing treatment with solifenacin, as defined by the Patient Global Impression of Improvement score (PGI-I) (see Appendix 2) A score of 1 or 2 (“very much better” or “much better”) was taken as a marker of treatment success, with 3 or higher being regarded as unsuccessful. Exclusion criteria were:

- Stress predominant mixed urinary incontinence- since persistent stress incontinence could make evaluation of improvement difficult to assess

- Prior treatment with antimuscarinics- since this may affect baseline continence, bias treatment response and alter urodynamic parameters

- Patients having undergone previous continence surgery- since this may affect voiding

- Patients with neurological disorders affecting urinary function or haematuria of unknown origin

- Patients unwilling to consent to urodynamics

All participants underwent an initial assessment with a full urogynaecological history and examination, urinalysis, and King’s Health Questionnaire (Kelleher et al, 1997b). All had previously been given advice regarding fluid intake and bladder retraining. Those with persistent symptoms underwent filling and voiding cystometry as per ICS guidelines, using normal saline
at room temperature through a 6F double lumen catheter at a filling rate of 50 ml/min. Provocation manoeuvres were undertaken throughout filling and at cystometric capacity.

Participants with proven DO were offered a course of solifenacin succinate 5mg od, together with further written advice regarding fluid and caffeine restriction and bladder retraining. Outcome measures were evaluated at 6 weeks after commencing treatment. Women who had discontinued solifenacin due to side effects were excluded from the analysis.

Pre-treatment voiding parameters were entered into a database. The Bladder Outlet Obstruction Index (BOO-I) was calculated for baseline data using the formula $P_{deq}Q_{max} - 2$(maximum flow rate). The BOO-I was described by Blaivas as a surrogate index of outlet obstruction in women. A BOO-I of over 40 is considered as indicating a woman who is obstructed, with a value of between 20 and 40 being equivocal and under 20 unobstructed. Statistical analysis was undertaken using a Mann Whitney U test to evaluate any differences between women who had responded to medication versus those who had not.

Under current UK regulations, this study was classified as a Service Evaluation and therefore exempt from formal ethical approval.

Results

During the study period 200 sets of pre-treatment cystometry data were collected. 6 women stopped the solifenacin prior to the 6 week follow up visit and were excluded from the analysis. Of the remaining 194 women, 94 had DO only on pre-treatment urodynamics and 96 had mixed incontinence (i.e. urodynamic stress incontinence together with detrusor overactivity). The mean age of participants was 51.3 years (range 22-79), the mean Body Mass Index (BMI) was 29.4 (range 20-41) and the mean parity was 2.1
In the cohort as a whole, 78/194 women (40.2%) reported a significant improvement in OAB symptoms (i.e. PGI-I 1 or 2 ticked) at the 6 week follow up visit. Women with DO were more likely to report an improvement in their overall symptoms than women with mixed USI and DO (46/94, 49%, versus 33/96, 34% p=0.05, chi-square test). The distribution of PGI-I scores by diagnosis is shown in table 5.1.

<table>
<thead>
<tr>
<th>PGI-I</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>DO (n=94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>17.0</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>31.9</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>23.4</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>24.5</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>2.1</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>Mixed (n=96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>14.6</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>19.8</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>35.4</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>26.0</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>3.1</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 5.1. Distribution of PGI-I scores by diagnosis

**Voiding Parameters**

Comparison of pressure flow parameters between responders and non-responders, both for the whole cohort and by urodynamic diagnosis, is shown in table 5.2. In women with DO, women who failed to respond to solifenacin had a significantly lower pre-treatment maximum flow rate than those who did respond. There was no corresponding difference in voided volume or PdetQmax. There were 2 women in the DO group and 3 women in the mixed group who voided without a detrusor contraction, i.e. by pelvic floor relaxation only.
Table 5.2. Mean pre-treatment pressure flow parameters in responders and non-responders (95% confidence interval) with p-values from Mann Whitney U test (*= p < 0.05 taken as significant)

<table>
<thead>
<tr>
<th></th>
<th>Responders</th>
<th>Non-responders</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Whole cohort, n=194</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q&lt;sub&gt;max&lt;/sub&gt; (ml/s)</td>
<td>19.9 (17.6-22.2)</td>
<td>19.2 (17.3-21.1)</td>
<td>0.63</td>
</tr>
<tr>
<td>P&lt;sub&gt;detQ_max&lt;/sub&gt; (cmH20)</td>
<td>44.0 (39.2-48.9)</td>
<td>41.8 (37.8-45.8)</td>
<td>0.49</td>
</tr>
<tr>
<td>Voided volume(mls)</td>
<td>324 (288.1-359)</td>
<td>299 (269.1-328.4)</td>
<td>0.29</td>
</tr>
<tr>
<td>BOO-I</td>
<td>-0.73 (-7.8-6.3)</td>
<td>0.54 (-5.4-6.4)</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Detrusor overactivity, n=94</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q&lt;sub&gt;max&lt;/sub&gt; (ml/s)</td>
<td>18.7 (15.8-21.6)</td>
<td>14.2 (12.7-18.3)</td>
<td>0.02*</td>
</tr>
<tr>
<td>P&lt;sub&gt;detQ_max&lt;/sub&gt; (cmH20)</td>
<td>46.8 (40.3-53.2)</td>
<td>42.2 (36.2-48.2)</td>
<td>0.17</td>
</tr>
<tr>
<td>Voided volume(mls)</td>
<td>314 (265.1-363.2)</td>
<td>268 (220.7-314.9)</td>
<td>0.19</td>
</tr>
<tr>
<td>BOO-I</td>
<td>3.33 (-6.0-12.6)</td>
<td>7.71 (-1.2-16.6)</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Mixed Incontinence, n=96</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q&lt;sub&gt;max&lt;/sub&gt; (ml/s)</td>
<td>21.6 (18.1-25.0)</td>
<td>22.1 (19.6-24.6)</td>
<td>0.82</td>
</tr>
<tr>
<td>P&lt;sub&gt;detQ_max&lt;/sub&gt; (cmH20)</td>
<td>40.3 (32.7-47.9)</td>
<td>41.5 (36.1-47.0)</td>
<td>0.80</td>
</tr>
<tr>
<td>Voided volume(mls)</td>
<td>337 (285.2-388.6)</td>
<td>324 (286.4-361.2)</td>
<td>0.69</td>
</tr>
<tr>
<td>BOO-I</td>
<td>-6.52 (-17.2-4.2)</td>
<td>-5.26 (-13.0-2.50)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

**Discussion**

This study has demonstrated that women with DO who experience an improvement in urinary symptoms with solifenacin have a higher pre-treatment maximum flow rate than those who do not respond, with no corresponding correlation between treatment response and other pressure flow variables. This may indicate that voiding parameters are of some importance in the prediction of treatment success in women with OAB and DO.

Female voiding is regarded as a complex interaction between detrusor contraction, pelvic floor relaxation and the resistance of the urethra to flow. There was no difference in detrusor pressure at maximum flow between responders and non-responders, as well as no significant
between group difference in the proportion of women voiding by pelvic floor relaxation only. The results from this study would therefore seem to suggest that women with higher outlet resistance are less responsive to treatment with antimuscarinic medication. Other studies have identified factors which may render patients less responsive to treatment with antimuscarinic drugs. Women with pelvic organ prolapse are known to be more likely to have OAB symptoms (de Boer et al, 2010). This may be due to several reasons which will be discussed in detail later in this thesis. These reasons include the possible association between OAB and changes in voiding caused by prolapse, and trigonal distorsion leading to changes in afferent function. Antimuscarinics have been shown to be less efficacious in women with anterior vaginal wall prolapse, with the response rate being less than half that of women with no anterior wall prolapse (Salvatore et al, 2007). The authors speculate that this finding is explained by distorsion of the trigone leading to increased afferent activity. Other studies later in this thesis have identified an association between resolution of OAB symptoms following prolapse repair and an increase in maximum flow rate and decrease in detrusor pressure at maximum flow (see chapters 6 and 7), thus it may be speculated that anterior wall prolapse may lead to disordered voiding which in turn causes OAB symptoms. In women with prolapse, it may well be a combination of each of these suggested aetiologies which leads to OAB symptoms more difficult to treat with medications.

Other authors have evaluated whether the presence of DO on urodynamics prior to treatment is associated with any differences in response to treatment. A 2009 study of women with OAB treated with tolterodine demonstrated no difference in subjective and objective outcome variables between women with DO versus those with “normal” urodynamics (Malone-Lee and Al-Buheissi, 2009), although positive urodynamics were predictive of a greater
improvement in certain quality of life domains. Similar results have also been reported for fesoterodine, with this study also confirming that a favourable dose-response relationship is independent of the presence of DO (Nitti et al, 2010). The presence of DO is therefore not predictive of treatment response to antimuscarinics, which is in keeping with the fact that OAB is a clinical rather than urodynamic diagnosis, a fact borne out by large population studies showing that almost half of women with OAB symptoms do not have DO on urodynamics (Digesu et al, 2003a).

An analysis of paired urodynamic data from 80 women with OAB treated with tolterodine demonstrated that there was a higher baseline ODP in non-responders than responders (Wagg and Malone-Lee, 2003). Opening detrusor pressure is a reproducible pressure flow parameter which has been described as a surrogate marker for urethral resistance (Digesu et al, 2004), and this finding would therefore support the present hypothesis that women who have a higher resistance to flow prior to treatment are less likely to respond to antimuscarinics. The tolterodine study also reported that there was no difference in voiding parameters between baseline values and those after 4 weeks of treatment with tolterodine, indicating that drug treatment does not alter voiding, at least in the short term.

Although these data suggest an association between urethral resistance and treatment failure, a cause and effect relationship cannot be established without further study. It could be postulated that this association may merely be a reflection of differing symptom severity between responders and non-responders. However studies have failed to prove any link between urodynamic parameters and symptom severity (Wagg et al, 1998) and solifenacin has been proven to be equally efficacious in women with severe OAB symptoms (Millard and Halaska, 2006). The increased urethral resistance may be secondary to hypertrophy of the striated portion
of the urethral sphincter as a learned response secondary to urgency and urgency incontinence episodes. Alternatively, it may be the case that women with a functional increase in urethral resistance have more refractory symptoms since the effect of “obstruction” leads to ultrastructural changes in the bladder including denervation, altered membrane potentials and upregulation of afferent pathways (Seki et al, 1992; Harrison et al, 1987; Steers et al, 1991), all of which may make symptoms more difficult to treat.

It is noteworthy that the relationship between voiding parameters and treatment outcome was only seen in the subset of women with isolated DO, and not in those with mixed incontinence. Treatment outcomes were also inferior in those with mixed incontinence, which is in contrast to other published studies (Kelleher et al, 2006). Women with mixed incontinence are known to have urethral resistance indices and flow rates which are intermediate between those with DO and those with USI (Digesu et al, 2004), which may explain why flow rate measurements were less predictive of treatment outcome in this group of women. The lesser response in women with mixed incontinence may also reflect the 2 distinct pathologies present in women with mixed DO and USI as opposed to isolated DO.

There are certain limitations to this study. The patient population, although large, was heterogenous and other factors which may be responsible for the different outcomes were not studied. However the populations studied were relatively large and unselected making small variations in the different samples less important. Prolapse was not formally assessed although the relationship with voiding is imprecise. The presence of prolapse was obviously a constant factor in each individual subject over the 6 week study period as none underwent any form of additional intervention. The primary outcome measure was assessed at 6 weeks’ follow up, as it was felt that the maximum therapeutic benefit of the drug alone (with no additional benefit from
(bladder retraining) would be seen at this point, although there are no data in the literature to support this supposition. The longitudinal effects of drug treatment may have been seen more clearly with a longer follow up period. The differences in the maximum flow rates were relatively small in the group of women with DO (18.7 vs 14.2 ml/sec) and there was overlapping of the confidence intervals. Therefore although this study may be very useful in delineating the aetiology of OAB, it may be less useful in a day to day practical management of individual patients. The PGI-I scale provides a global assessment of improvement and does not assess individual symptoms e.g. severity of urgency and has previously been used predominantly in studies of stress incontinence. Although it was originally validated for SUI studies, it has been validated for the assessment of women with urgency (Tincello et al, 2013). This instrument was able to delineate differences in outcome to allow the demonstration of significant differences in flow rates. The complexity of symptom interaction may explain why no difference was demonstrated in patients with mixed USI and DO. It should be noted that the differences in flow rates were not accompanied by significant differences in voiding pressures, therefore one must be cautious regarding any discussion of bladder outlet obstruction. Detrusor underactivity may be associated with reductions in flow rates, but this is unlikely in this cohort since voiding pressures were relatively high. It may be that differences in $P_{\text{det}}Q_{\text{max}}$ are smaller and less clinically relevant in this context. Potential reasons for this are unclear.

Although the results of this study may well be useful in pre-treatment counselling of women with OAB commencing on antimuscarinics, it is unclear whether interventions to decrease urethral resistance in women with lower flow rates will lead to improved efficacy. This has been explored in the context of the alpha-1 adrenoceptor blocker tamsulosin, which has been used “off label” for OAB symptoms in women on the basis of similar use in men with
obstruction from benign prostatic hyperplasia. Tamsulosin was shown to have no benefit over placebo in women with OAB symptoms (Robinson et al, 2007), however this was in an unselected population of women in terms of voiding function. Tamsulosin also has no muscarinic receptor activity, meaning that a direct effect on urgency is unlikely. It is not known however, whether an intervention to reduce urethral resistance in selected women would then increase the likelihood of a positive response to antimuscarinics. A potential risk of such a strategy however may be worsening incontinence due to relative urethral incompetence, particularly if OAB symptoms fail to be controlled with a subsequent drug treatment.

This study has demonstrated an association between lower urinary flow rates and non-response to antimuscarinic therapy in a model using women with DO and OAB symptoms. This would imply a positive association between the level of urethral resistance and treatment response to pharmacological agents in women. As discussed previously, creating clinical models of elevated urethral resistance in female human subjects is difficult. The creation of animal models by tying off the urethra obviously cannot be carried out in human subjects. The findings of this chapter do indicate an association between voiding and OAB symptoms, which is worthy of further exploration. Women undergoing surgical treatment for pelvic organ prolapse and those undergoing urethral dilatation as a direct manipulation of the voiding axis may be suitable surrogate models to explore this relationship further. The remaining experimental chapters of this thesis detail a series of experiments designed to evaluate the association of voiding function with OAB within these clinical models.
Chapter Six

Effect of prolapse repair on voiding and the relationship to overactive bladder and detrusor overactivity- pilot and feasibility study
Introduction

Pelvic organ prolapse is a prevalent problem which affects 50% of parous women with 20% of these being symptomatic (Digesu et al, 2005). Large epidemiological studies have estimated that 11% of women will have had an operation for prolapse by the age of 70, with a risk of requiring further surgery for prolapse or incontinence (either of the same or different compartment) of up to 29% (Olsen et al, 1997).

Pelvic organ prolapse can include anterior vaginal prolapse (cystocele), posterior vaginal prolapse (rectocele or enterocele), apical prolapse (vault/uterine prolapse) and perineal descent. The anterior vaginal wall is the most common compartment to prolapse, however unicompartmental defects are unusual, with most women presenting with multicompartmental prolapse. The socioeconomic, psychological and physical impacts of prolapse are considerable. Case control studies have shown women with prolapse to have higher depression scores (Ghetti et al, 2010), as well as lower scores on validated body image and quality of life questionnaires (Jelovsek et al, 2006). This psychological and quality of life impairment has been shown to be reversible with both surgical and non-surgical treatment (Ghetti et al, 2010; Fayyad et al, 2008; Patel et al, 2010).

Epidemiological studies have attempted to quantify the co-existence of overactive bladder symptoms and prolapse. One study reported that 68% of women with prolapse also complain of urgency, with 50% suffering from urgency incontinence (Ali et al, 2006). 41% of a cohort of women with severe prolapse were reported to have DO (Rosenzweig et al, 1992). Other authors have reviewed the literature on the co-existence of prolapse and overactive bladder and used data from observational studies to calculate the relative risk of OAB symptoms in women with prolapse (de Boer et al, 2010). These studies included a total of 12514 women.
They identified an increased prevalence of OAB symptoms in women with prolapse compared to those without prolapse. The largest study in this review covered a population of 5489 women, with a calculated relative risk for OAB symptoms in women with prolapse of 5.8 (Tegerstedt et al, 2005).

Despite the suggestion of an association of urinary symptoms with prolapse there has been little research to identify how the conditions are linked and if there is any link to be found. Both OAB and prolapse are more common in older women, meaning that their co-existence in the same patient may merely reflect their prevalence as separate entities. If there were an aetiological connection between prolapse and OAB, one might expect OAB symptoms to improve with treatment of prolapse. Previous work has suggested that there is an association between voiding and the presence of OAB and DO, with women with higher pre-operative maximum flow rates being more likely to experience resolution following insertion of a retropubic mid-urethral sling for stress urinary incontinence. It has been demonstrated that women with prolapse have lower maximum flow rates on urodynamic evaluation than controls (Wall and Hewitt, 1994; Long et al, 2002). Women with complete vault prolapse have additionally been found to have an elevated detrusor pressure at maximum flow on voiding cystometry (Wall and Hewitt, 1994). A study of women with anterior compartment prolapse identified a decrease in flow rates that increased in magnitude with increasing degrees of prolapse (Romanzi et al, 1999). Other studies have had conflicting results however, with the presence of prolapse leading to no significant difference in maximum flow rates when compared to a control group (Rosensweig et al, 1992; Schimpf et al, 2007), although the study by Schimpf and colleagues reported a trend toward higher post-void residual measurement in women with anterior wall prolapse versus women with no prolapse, which may imply some effect of anterior
compartment prolapse on voiding function. Alternative explanations may be that anterior compartment prolapse leads to a urinary “sump” which is unable to drain due to its position relative to the bladder neck, or afferent dysfunction due to distorsion of the trigone (Salvatore et al, 2007). An anterior compartment prolapse may lead to reduced flow rates due to increased urethral resistance secondary to anatomical kinking. Studies of urodynamic parameters have shown increased maximum urethral closure pressures (MUCP) in women with prolapse (Rosenzweig et al, 1992; Bai et al, 2003).

If the presence of a prolapse does indeed lead to alterations in voiding, this is a possible aetiological basis for the relationship between overactive bladder symptoms and prolapse. Thus correction of prolapse and restoration of anatomy might be expected to lead to resolution of overactive bladder symptoms. The aim of this pilot study was therefore to establish whether prolapse repair leads to resolution of overactive bladder symptoms, and whether resolution of overactive bladder symptoms is associated with any change in voiding parameters.

**Null Hypothesis**

Anterior repair is not associated with relief of overactive bladder symptoms or measurable changes in voiding function.

**Methods**

This was a retrospective observational study. 67 women with known DO who had undergone an anterior repair operation (either alone, or in combination with repair of other compartments) between April 2003 and February 2007 were identified from departmental records. The primary outcome measure was presence or absence of overactive bladder
symptoms post-operatively, with the secondary outcome measures being pressure flow study parameters post-operatively.

Inclusion criteria were symptomatic anterior wall prolapse (Grade II or above) with confirmed DO on cystometry. All patients were undergoing prolapse surgery as the primary indication but were found to have DO when cystometry was performed. Only women with lower urinary tract symptoms are routinely offered cystometry at our Centre. Exclusion criteria included women with prolapse but the absence of DO on cystometry and women with coexistent USI. Women with USI were treated with a concurrent midurethral tape and as this would be expected to alter voiding they were excluded. Women with neurological disorders or bladder pathology identified at cystoscopy were also excluded. The study was restricted to patients undergoing an anterior repair as this was felt to be more likely to be associated with changing in voiding. All cystometry studies were performed when the patient was not taking antimuscarinics.

All the women in the study group were assessed pre-operatively with a detailed urogynaecological history and examination. Urogenital prolapse was examined for with the patient in the left lateral position and graded as 0-IV, according to the Baden-Walker Halfway system (Baden and Walker, 1982). Women with lower urinary tract symptoms underwent twin-channel subtraction cystometry as described in chapter 4. All pre-operative cystometry studies were carried out by a urogynaecology nurse specialist. Prior to the prolapse repair, women were offered antimuscarinics for their urinary symptoms.

All women underwent a standard fascial anterior repair. Clamps were placed beneath the external urethral meatus and at the innermost point of the prolapse to mark out the extent of the repair. A longitudinal incision was made in the vaginal epithelium between the clamps. Forceps were placed along the incised vaginal skin edges and the pubocervical fascia was carefully
dissected away from the vaginal epithelium. Two or more buttress sutures were placed laterally into the fascia and then tied in the midline using No. 1 vicryl. The redundant vaginal tissue was excised and the vaginal edges opposed using No 1 vicryl continuous locking sutures. A cystoscopy was performed in all women.

A size 14F foley catheter was left in situ to drain the bladder and removed on day 2 and a vaginal pack was removed on day 1. Each patient had a single dose of prophylactic antibiotic (Co-amoxiclav or cefuroxime) intra-operatively.

Post-operative assessment was undertaken at 2-3 months and then at a later date in a research clinic. Patients were assessed using a KHQ, PGI-I, clinical examination and repeat filling and voiding cystometry. A patient was considered cured of DO if there were no spontaneous detrusor contractions noted during the filling phase of cystometry. A patient was considered to be cured of OAB if she did not document urgency in the symptom domain of the King’s quality of life questionnaire and denied overactive symptoms on direct questioning (denied frequency, nocturia, urgency and urgency incontinence). Rises in detrusor pressure during filling, evidence of urodynamic stress incontinence (USI), cystometric capacity, maximum flow rate, volume voided, detrusor pressure at maximum flow, opening detrusor pressure and post-void residual volume were recorded for each patient. All post-operative cystometry studies were carried out by the author in a research clinic setting.

The data were entered into a Microsoft Excel database, and separated into those who experienced resolution of OAB, as reflected in the relevant domains of the KHQ and the PGI-I (Group 1) and those who had worsening or no change in OAB symptoms (Group 2). A Wilcoxon Matched Pairs Signed Rank test was used to look for a significant change in flow rates following the anterior repair, and a student’s t-test was used to elicit any difference in maximum flow rate
at baseline and post-operatively. A similar analysis was used to evaluate changes in detrusor pressure at maximum flow and opening detrusor pressure. A Fisher’s exact test was used for discrete data. A p-value of less than 0.05 was considered significant. The Bladder Outlet Obstruction Index (BOO-I) was calculated for each group pre- and post-operatively using the formula below:

\[ \text{BOO-I} = P_{\text{det}}Q_{\text{max}} - 2(Q_{\text{max}}) \]

A Wilcoxon matched pairs signed rank test was used to assess for any significant change in BOO-I in each group post-operatively.

Ethical approval was obtained from West Kent Research Ethics Committee and each patient was asked to provide informed consent.

**Results**

A total of 67 women were identified for the study, of whom 49 were contacted and agreed to attend for follow-up, and 40 agreed to a repeat urodynamic evaluation. Patient demographics and the surgical procedure performed are described at table 6.1.

<table>
<thead>
<tr>
<th>Type of procedure</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior and posterior repairs</td>
<td>24</td>
</tr>
<tr>
<td>Vaginal hysterectomy + anterior and posterior repairs</td>
<td>19</td>
</tr>
<tr>
<td>Vaginal hysterectomy + anterior repair only</td>
<td>1</td>
</tr>
<tr>
<td>Vault suspension + anterior and posterior repairs</td>
<td>5</td>
</tr>
</tbody>
</table>

**Table 6.1. Age, time to follow up and procedure undertaken (n=49)**
DO was objectively cured in 25% of participants (10/40 women who underwent repeat urodynamics), 75% of participants (30/40 women) had persistent DO. 53% were subjectively cured of OAB (22/40 women). 13 women had DO on cystometry, but did not document OAB symptoms in the King’s Health Questionnaire and denied symptoms on direct questioning. There was a significant association between persistent OAB symptoms and persistent DO (17 of 18 patients with persisting symptoms had DO on cystometry, p=0.0003). The changes in flow rate are described in table 6.2.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=22)</th>
<th>Group 2 (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operative</td>
<td>12.8 (6.8)</td>
<td>14.5 (8.0)</td>
<td>0.44</td>
</tr>
<tr>
<td>Post-operative</td>
<td>17.3 (8.7)</td>
<td>11.9 (7.3)</td>
<td>0.047*</td>
</tr>
<tr>
<td>P</td>
<td>0.049*</td>
<td>0.02*</td>
<td></td>
</tr>
</tbody>
</table>

Table 6.2. Mean pre- and post-operative values for maximum flow rate in ml/sec, p<0.05 taken as significant (standard deviation in brackets). Group 1= resolution of OAB symptoms, group 2= persistent OAB symptoms.

Two of the 49 women (2%) women had symptomatic recurrent Grade 2 cystoceles and were offered surgical management. These women were both in group 1. Two women in group 1 developed USI. Each was offered a TVT after conservative measures had failed to control their symptoms. Nine patients declined urodynamics and supplied subjective data only. Of these, five had overactive bladder symptoms and one had stress incontinence symptoms, as indicated by the relevant domains of the King’s Health Questionnaire.

18 patients did not respond to the invitation to take part in the study. On review of their notes, nine of these patients had no urinary symptoms at 2-3 months’ post-operatively. The other nine had persistent overactive bladder symptoms. 12 of these patients were able to be contacted by telephone, and were asked about any urinary symptoms. Five of the nine patients who had
been asymptomatic post-operatively were contacted and denied any recurrent urinary symptoms. Seven of the nine patients who had had persistent overactive symptoms were contacted. Of these patients, five remained on antimuscarinic medications and two described very mild symptoms which did not require treatment. There was no significant difference in the presence or absence of symptoms at the time of the study between those who consented to undergoing urodynamics and those who did not (Chi squared test, p= 0.67).

The pre- and post-operative values for voided volume, detrusor pressure at maximum flow and opening detrusor pressure are detailed in table 6.3. The mean values for post-void residual for groups 1 and 2 were similar (16.3 mls vs. 18.0mls, p=0.72) and did not change significantly following surgery. The pre- and post-operative values for BOO-I are detailed in table 6.4. In group 1, the BOO-I values universally decreased with the mean fall in value being 21.4. In group 2, the mean change in value was 0.67, with the value rising in 76.9% of the group. A Mann Whitney U test comparing the change in BOO-I between groups 1 and 2 showed a non-significant trend towards a larger magnitude of change in group 1 (p= 0.055).
Table 6.3. Mean pre- and post-operative values for voided volume and detrusor pressure at maximum flow and at opening, p<0.05 taken as significant.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=22)</th>
<th>Group 2 (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voided volume (mls)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-operative</td>
<td>301.4</td>
<td>314.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Post-operative</td>
<td>378.0</td>
<td>237.8</td>
<td>0.01*</td>
</tr>
<tr>
<td>P</td>
<td>0.11</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Pdet at maximum flow (cmH\textsubscript{2}O)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-operative</td>
<td>50.3</td>
<td>45.5</td>
<td>0.41</td>
</tr>
<tr>
<td>Post-operative</td>
<td>50.8</td>
<td>45.0</td>
<td>0.36</td>
</tr>
<tr>
<td>P</td>
<td>0.94</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Pdet at opening (cmH\textsubscript{2}O)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-operative</td>
<td>27.9</td>
<td>31.1</td>
<td>0.54</td>
</tr>
<tr>
<td>Post-operative</td>
<td>11.5</td>
<td>30.6</td>
<td>0.1</td>
</tr>
<tr>
<td>P</td>
<td>0.01*</td>
<td>0.74</td>
<td></td>
</tr>
</tbody>
</table>

Table 6.4. Mean pre- and post-operative values for Bladder Outlet Obstruction Index, p<0.05 taken as significant

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=22)</th>
<th>Group 2 (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operative</td>
<td>19.4</td>
<td>13.7</td>
<td>0.54</td>
</tr>
<tr>
<td>Post-operative</td>
<td>-1.6</td>
<td>13.5</td>
<td>0.11</td>
</tr>
<tr>
<td>P</td>
<td>0.04*</td>
<td>0.98</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

The results have shown that 53% of women having prolapse surgery are cured of OAB symptoms. Women in whom OAB symptoms resolve demonstrate a significant increase in maximum flow rate with a decrease in opening detrusor pressure after the repair. In women who
did not show an improvement in OAB symptoms the maximum flow rate fell. This finding suggests that changes in flow rates in the presence of a prolapse may be important in the aetiology of OAB and raises again the issue that resistance to flow may be important in the aetiology of OAB.

A recent Cochrane review of the surgical management of pelvic organ prolapse noted that level Ia evidence concerning anterior repair and urinary symptoms is limited and inconclusive (Maher et al, 2006). There have been several observational studies examining the effect of anterior repair on OAB symptoms using validated subjective outcome tools, which have shown a significant decrease in overactive bladder symptoms post-operatively (Digesu et al, 2007b; Foster et al, 2007; Fayyad et al, 2008; Ek et al, 2010). de Boer and colleagues calculated risk ratios for the resolution of overactive bladder symptoms following a prolapse repair. They included studies from 12 published articles and 6 conference abstracts, and found that all had a RR of over 1.0 for resolution of OAB symptoms following repair (de Boer et al, 2010). There is also evidence that nonsurgical correction of prolapse may lead to similar beneficial effects on OAB symptoms. Fernando et al reported a significant decrease in voiding difficulty, urinary urgency and urgency incontinence after 4 month usage of a vaginal pessary (Fernando et al, 2006). Clemons and colleagues found usage of a vaginal pessary to be associated with resolution of voiding difficulty in 53% of women, and of urgency incontinence in 46% of women (Clemons et al, 2004).

Further evidence to link OAB and DO aetiologically with prolapse is seen in women with prolapse and OAB treated with antimuscarinics. A study of 235 women with OAB symptoms and proven DO on cystometry reported that women with pure anterior wall prolapse are less likely to improve with antimuscarinic treatment when compared to women with no prolapse
(Salvatore et al, 2007). An explanation for this may be that the physical distortion caused by the anterior prolapse results in an anatomical basis for the OAB which is less likely to be addressed by muscarinic blockade.

The voiding mechanism in women is known to be complex. Ultrasound studies have attempted to describe an anatomical basis for dysfunctional voiding in women with prolapse of differing compartments. It has been shown that women with significant bladder neck descent on ultrasound have significantly reduced maximum flow rate centiles in the presence of a closed retrovesical angle (the angle between the proximal urethra and the trigonal surface of the bladder) (see Fig 6.1). This relationship does not hold for those with an open retrovesical angle (Dietz et al, 2002). The same study also found the presence of an enterocele on ultrasound to be associated with a significant reduction in maximum flow rate centile, which raises the possibility that the posterior compartment may also be implicated in the relationship between prolapse and OAB symptoms.

![Fig. 6.1 Illustration of retrovesical angle](image)

Attempting to translate these findings into a clinical context yields conflicting results. A study of the prevalence of OAB symptoms by compartment identified a significant relationship between anterior and posterior compartment prolapse and urgency incontinence, but no association with apical prolapse (Miedel et al, 2008). Other studies have identified no such
relationship (Ellerkmann et al, 2001; Bradley and Nygaard, 2005). Indeed an earlier paper by Dietz found a negative correlation between ultrasound features of anterior “vaginal wall relaxation” and the presence of OAB symptoms (Dietz et al, 2001). However, this paper described ultrasound features of anterior compartment prolapse including an open retrovesical angle which is an appearance seen with spontaneous voiding; this may be the reason for this finding.

The group with persistent OAB symptoms have a significant fall in maximum flow rate following repair. The significance of this fall in flow rate in Group 2 should be treated with caution since this is accompanied by a significant fall in volume voided. Flow rate is related to voided volume. Hence the lower voided volume may be responsible for the lower flow rate. These finding may be consistent with worsening DO although no severity scales were used to assess OAB severity pre and postoperatively. There was an increase in voided volume post-operatively in group 1, which did not reach statistical significance. It may be argued that the increase in flow rates in this group is simply a reflection of this factor. It should be noted however that the change in flow rates was significant, whilst the change in volume was not. Liverpool nomograms are not entirely appropriate to this situation since they relate to non-intubated flow studies, however if the changes in volume are plotted using the Liverpool nomograms, they indicate an expected increase in flow of only 2 ml/s, which is less than 50% of the actual change that was found. The change in flow rates in this group therefore is likely to reflect a true change in voiding function.

The results for detrusor pressure at maximum flow indicated that there was no change in this parameter post-operatively regardless of changes in flow rates or symptoms. This may support the concept that the improvement in voiding was purely due to a decrease in urethral
resistance caused by relief of the urethral kinking caused by a cystocele. It may be commented that the PdetQmax in these patients was higher than usual pre-operatively (again, perhaps to overcome anatomical distorsion caused by anterior wall prolapse) and in fact remained high, despite the improvement in flow rates and symptoms. This in itself is a factor which merits further investigation. The ultra-structural changes caused by outflow obstruction (as discussed in chapter 3) may not reverse with simple anatomical correction of prolapse, and it is feasible that the detrusor muscle function may not change either.

The results for the BOO-I in these women indicate that neither group was clinically obstructed prior to surgery. There was no significant difference between groups in this parameter at baseline. The women who experienced resolution of OAB symptoms post-operatively showed a significant decrease in BOO-I values, indicating an improvement in voiding. There was a trend towards women who experienced resolution of urgency having a significantly higher change in BOO-I post-operatively. Thus it may be postulated that it is the magnitude of change in voiding function associated with surgery for prolapse that is of importance in symptom resolution in women with prolapse and overactive bladder symptoms, rather than baseline voiding function. This may be related to the ultrasound findings described by Dietz, whereby the women who experience resolution of urgency are those in whom surgery has converted an intact, closed retrovesical angle into an open retrovesical angle.

There was a significant fall in ODP in women who experienced resolution of OAB symptoms. Those with persistent symptoms post-operatively showed no significant change in ODP. ODP has been suggested as being a surrogate marker for urethral resistance (Digesu et al, 2004). It has also been demonstrated that women with DO have higher ODP than those with normal detrusor function (Digesu et al, 2004). The significant fall in ODP in women with
resolution of symptoms is in keeping with a decrease in urethral resistance secondary to the prolapse repair, which may support decreasing urethral resistance as a mechanism by which prolapse repair is associated with relief of urgency in certain women.

There are certain limitations relating to the above study. This is a very select population and it is possible that the results are not generalisable to all women with OAB and DO. The retrospective nature of the study may lead to bias although there did not seem to be any difference between those women who came back for review and those who did not. There was also no difference between those women who underwent postoperative cystometry and those who did not. The study is limited by the fact that anterior repair was carried out in conjunction with other prolapse procedures; this may be a potential source of bias. In practical terms, the majority of women undergoing prolapse surgery will have multicompartamental prolapse requiring repair of more than one compartment. It would therefore be difficult and impractical to identify a population undergoing anterior repair alone. However, voiding dysfunction is not only related to anterior compartment prolapse and therefore including repairs of other compartments may be an advantage and result in a higher resolution of voiding dysfunction. The time to follow up varied between patients, which does potentially introduce a source of bias, although none had undergone subsequent continence or prolapse procedures in the interval between the anterior repair and follow up. Studies of the natural history of OAB have shown it to be a dynamic chronic condition, characterised by periods of stability, remission and progression (Heidler et al, 2011), and it is possible that changes in the rate of OAB over the study period reflect this natural history. All pre-operative cystometry studies were carried out by a urogynaecology nurse practitioner (as this was a follow up study of a retrospective group), and all post-operative studies were carried out by the author. There is therefore a theoretical possibility of operator
dependent differences in cystometry results. This possibility was minimised by the fact that all cystometry studies within the department are carried out within a strictly observed protocol.

The findings of this study suggest that improvement in voiding parameters caused by prolapse repair may be of importance in symptom resolution in women with overactive bladder symptoms, thus establishing the feasibility of studying this further within a standardised protocol. This study is limited however by relatively small numbers, varying times to follow up and the fact that it is retrospective in nature. The next chapter therefore describes a prospective study which attempts to confirm the association of changes in voiding parameters with symptom resolution in a larger population of women.
Chapter Seven

A prospective study to assess the effect of prolapse repair on voiding and overactive bladder symptoms
Introduction

The results from the previous chapter have indicated that repair of pelvic organ prolapse leads to resolution of urgency in approximately 50% of women, and that resolution of urgency in women with symptomatic anterior compartment prolapse is associated with a significant increase in maximum flow rate, and a significant decrease in opening detrusor pressure and BOO-I. This has the implication that a possible mechanism of symptom relief in this particular cohort was related to decreasing urethral resistance. The validity of these findings is limited by small numbers and a varying time to follow up. This retrospective study was also not powered to evaluate changes in voiding parameters, indicating a need for the findings to be confirmed in a prospective study powered to evaluate changes in voiding with a standardised protocol.

The aim of this study was therefore to prospectively assess whether relief of OAB symptoms in women undergoing prolapse repair is associated with any measurable change in voiding parameters.

Null hypothesis

Relief of overactive bladder symptoms following pelvic organ prolapse is not associated with any significant change in voiding parameters.

Methods

This was a prospective observational study. Eligible women were newly referred patients recruited from the Urogynaecology clinics at 2 large district general hospitals. Patients were
recruited between October 2008 and May 2010. The primary outcome measures were change in maximum flow rate and presence of OAB symptoms as determined by the Urgency Perception Scale (Cardozo et al, 2005) at 10 weeks post-operative. Secondary outcome measures were the change in POP-Q stage at 10 weeks’ post-operative and the change in quality of life at 10 weeks’ post-operative as determined by the KHQ (Kelleher et al, 1997b).

The inclusion and exclusion criteria for the study are listed below:

**Inclusion Criteria**

1. Symptomatic primary prolapse of stage 2 or above requiring surgery
2. Presence of overactive bladder symptoms on symptom questionnaire
3. Patients must be able to provide informed consent to participate in the study

**Exclusion Criteria**

1. Presence of concurrent urodynamic stress incontinence (since this would require a suburethral sling, which would affect voiding and thus be a confounder)
2. Patients with persistent POP of stage 2 or above at follow up (because this would not permit analysis of changes in voiding after anatomical correction of prolapse)
3. Patients who are medically unfit to undergo surgical intervention
4. Patients who have had previous continence or prolapse surgery (as this may affect voiding function at baseline)
5. Patients with haematuria of unknown origin or known bladder pathology
6. Patients with neurological disorders (as these may affect voiding)
7. Patients who do not have adequate contraception or who wish to become pregnant
Objective and subjective outcomes were evaluated at 10 weeks’ post-operatively. Entry was offered to all women with symptomatic pelvic organ prolapse requiring surgical repair, who had OAB symptoms based on scoring 1 or 2 on the UPS (Cardozo et al, 2005). The UPS is a 3 point scale that was developed for use in assessing urgency in antimuscarinic drug trials. An improvement in UPS following drug treatment was found to correlate well with improvements in urodynamic parameters. The UPS correlated well with the patients' perception of bladder condition (correlation coefficients - 0.29 to - 0.46; all P < 0.001) and with the voiding diary variables, especially incontinence episodes (-0.30 to - 0.41) and pad usage (-0.25 to - 0.38; all P < 0.001)

Based on the results of the previous retrospective study, a minimum increase of 5 ml/s in the maximum flow rate would be clinically significant (actual mean increase in previous study was 4.5ml/s). This, together with a cure rate after prolapse repair for OAB of approximately 50% was used in a power calculation. Assuming the factors above and an 80% power, the minimum total number of subjects needed to detect the minimum increase in flow rate was 144. It was aimed to recruit 160, to account for women not completing the follow-up visit.

Potential patients were referred into the Urogynaecology clinics either via their General Practitioners or from other consultants within the Gynaecology department. All women underwent an initial assessment with a full urogynaecological history and examination, UPS and KHQ and a free flow rate and post void residual measurement. In the retrospective study, there was found to be no change in detrusor pressure at maximum flow post-operatively in both the group of women who experienced resolution of urgency and in those who had persistent urgency, as well as no significant difference between the two groups of women at baseline. For this reason, full pressure flow studies were not undertaken in this larger group of women, and
non-intubated flow rates were chosen as a primary outcome measure. This was also felt to be more acceptable to the study population, and aided the feasibility of the study. Antimuscarinic medication or topical oestrogens were not commenced pre-operatively since these had the potential to confound the results.

A treatment delay arm was used as a control for the free flow rate measurements. Women underwent uroflowmetry on entry to the study and subsequently at the pre-operative pre-assessment visit (approximately 3 months later). These repeat measurements functioned as a check that there was no significant natural variation in flow rates over a 3 month period, which could confound the results.

Each patient underwent a standard anterior repair, i.e. fascial plication, either alone, or in combination with other prolapse procedures. The method of prolapse repair was standardised prospectively between the two recruiting units by discussion between the two lead surgeons and review of surgical videos. All procedures were done in an operating theatre environment under general or spinal anaesthesia. A single dose of antibiotic prophylaxis was given intra-operatively. An in-dwelling catheter was left in until the first post-operative day. Voided volumes and residuals were checked after removal of the catheter. Voiding was considered satisfactory once volumes of 200mls or more were passed with a post-void residual of less than 100mls. Patients were discharged home once voiding was satisfactory.

All subjects were seen at 10 weeks’ post-operatively in the urogynaecology clinic and assessed with an UPS, POP-Q and repeat free flow measurement and post-void residual. Women were considered to be cured of their OAB symptoms if they marked option 3 on the UPS (“I am usually able to finish what I am doing before going to the toilet”). Based upon this, subjects
were divided into those who are cured of OAB symptoms (Group 1) and those with persistent symptoms (Group 2).

The data were entered into a Microsoft Excel database for analysis. The Acceleration of Flow Rate (AFR) was calculated from the uroflowmetry data using the formula maximum flow rate/flow time. Statistical analysis was undertaken using Fisher’s Exact test for categorical values, student’s t-test for continuous parametric variables (paired and non-paired), and the Mann Whitney U test for continuous non-parametric variables. The Kolmogorov Smirnov test was used to evaluate continuous data for normality prior to significance testing.

Results

Between October 2008 and May 2010, 168 women were indentified and entered into the study. Of these 168 women, 11 did not undergo surgery, either due to personal or anaesthetic concerns, 16 were lost to follow up, leaving an eligible population of 140 women. The mean age of this group was 61.3 years (range 25-83), the mean parity was 1.7 and 32% were post-menopausal. There were no significant differences in clinical or demographic factors between the two hospitals. All had significant OAB symptoms (response 1 or 2 on the UPS), and none had stress urinary incontinence on direct questioning. There was no significant change in maximum flow rate between recruitment and the 3 month control flow rate measurement (p=0.87). The combinations of procedure carried out are detailed in table 7.1.
Anterior and posterior repair 50
Anterior repair 35
Anterior and posterior repair + vaginal hysterectomy 33
Anterior repair + vaginal hysterectomy 15
Anterior and posterior repair + vault suspension 7

Table 7.1 Types of prolapse procedure undertaken (n=140)

At the 10 week follow up visit, 82 women reported resolution of OAB symptoms, i.e. marking themselves at point 3 on the UPS, and 58 women reported persistent OAB symptoms. No patients had been discharged post-operatively with a catheter in situ. This gives a cure rate of 58.6% for OAB in this cohort. The types of prolapse repair undertaken within each patient group are detailed in table 7.2.

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Cured, % (n=82)</th>
<th>Not cured, % (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior+Posterior</td>
<td>29 (24)</td>
<td>47 (27)</td>
</tr>
<tr>
<td>Anterior</td>
<td>29 (24)</td>
<td>12 (7)</td>
</tr>
<tr>
<td>Posterior</td>
<td>4 (3)</td>
<td>15.5 (9)</td>
</tr>
<tr>
<td>Anterior+posterior+apical</td>
<td>21 (17)</td>
<td>15.5 (9)</td>
</tr>
<tr>
<td>Anterior+apical</td>
<td>17 (14)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>100 (82)</td>
<td>100 (58)</td>
</tr>
</tbody>
</table>

Table 7.2. Compartments repaired in Groups 1 and 2
18/140 participants voided less than 100mls at either the pre-operative or post-operative uroflowmetry measurement. Since flow is dependent on volume voided, and it has not been established whether centile calculations are valid at low volumes, the voiding data for these women was excluded from the analysis. The following voiding data is therefore based upon a group of 122 women. The mean values for maximum flow rates for the women who were cured of urgency (group 1) versus those with persistent urgency (group 2), together with 95% confidence intervals for the mean are given in table 7.2.

<table>
<thead>
<tr>
<th></th>
<th>Cured (n=72)</th>
<th>Not cured (n=50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Operative</td>
<td>11.8 (3.4-20.1)</td>
<td>15.6 (13.0-18.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>Post-Operative</td>
<td>26.2 (17.1-35.2)</td>
<td>12.2 (8.3-16.1)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Table 7.3 Mean pre- and post-operative values for maximum flow rate (ml/sec), p<0.05 taken as significant (95% confidence interval for mean in brackets).

The pre- and post-operative voided volume and AFR data for both groups is given in table 7.4, together with 95% confidence intervals for the mean.
In this cohort of women, resolution of OAB symptoms was associated with a significant increase in maximum flow rate, with no significant change in volume voided or acceleration of flow rate. As previously mentioned, flow may be depended on volume voided. To account for this, centile values were calculated for the maximum flow rate values using the Liverpool Nomogram as previously described (Dietz and Haylen, 2005). This confirmed a significant increase in maximum flow rate centile post-operatively in those in whom urgency resolved (mean centile value 12.7 versus 27.2, p= 0.03). In the group with persistent urgency, there was a fall in the maximum flow rate centile post-operatively but it did not reach statistical significance (mean centile value 21.5 versus 7.19, p= 0.06).
Discussion

The findings of this study indicate that 56% of women with overactive bladder symptoms and pelvic organ prolapse experience resolution of OAB symptoms following surgical repair. Women who reported resolution of OAB in the post-operative period were found to have a significantly increased maximum flow rate on uroflowmetry, with no corresponding change in volume voided or acceleration of flow. This finding of an association between symptom resolution and an increase in flow rate is in agreement with the findings of the pilot and feasibility study.

Much of the background literature on the association between OAB symptoms and prolapse has been discussed in the previous chapter. The finding of an association between symptom resolution and a significant increase in maximum flow rate again suggests a role for urethral resistance in the aetiology of OAB symptoms in women with co-existing prolapse. Other authors have examined pre-operative predictive factors for symptom resolution. Fletcher et al studied pre-operative demographic and urodynamic parameters in women undergoing surgery for prolapse and identified a higher pre-operative $P_{\text{det}}Q_{\text{max}}$ to be an independent risk factor for persistent urgency incontinence post-operatively (Fletcher et al, 2010), which may imply an element of increased urethral resistance in women with persistent symptoms. Other urodynamic variables or demographic factors were not found to be significant risk factors. De Boer and colleagues examined demographic variables, stage of prolapse, type of surgery and symptom severity in a population of women with pelvic organ prolapse undergoing surgery (i.e. a non-selected group), and found the absence of bothersome OAB symptoms to be the best predictor for the absence of post-operative symptoms (de Boer and Vierhout, 2011). There are
no published data in the literature (other than the published pilot data from this study) examining changes in voiding parameters after surgery. The ultrasound studies of Dietz and colleagues have been discussed in the previous chapter, with a closed retrovesical angle (i.e. urethral kinking) being associated with reduced maximum flow rate centiles in women with bladder neck descent (Dietz et al, 2002). This is not found with an open retrovesical angle. A more recent study of 222 women with anterior compartment prolapse also showed an association between a closed retrovesical angle and objective evidence of voiding dysfunction (Eisenberg et al, 2010). In the present study, there was no difference between the 2 groups at baseline, meaning that the degree of urethral resistance at baseline was not a predictor for symptom resolution or persistence. Both these data and the pilot data seem to indicate that it is the change in voiding parameters that is the predictor for symptom resolution- perhaps because those in whom symptoms resolve are those in whom surgery converts a closed retrovesical angle into an open retrovesical angle. It has been reported that anterior vaginal prolapse leading to anatomic compression of the urethra causes a progressive decline in flow rate with increasing stage of prolapse, with straining to void and poor emptying being the urinary symptoms which are most highly correlated with increasing stage of prolapse (Bradley and Nygaard, 2005; Ghetti et al, 2005). However, evidence on the association between the severity of prolapse and the presence or severity of OAB symptoms is conflicting with no firm relationship being established (Digesu et al, 2005; Gutman et al, 2008). It may be speculated therefore that changes in voiding associated with resolution of OAB symptoms is an “all or nothing” phenomenon, in that surgical repair of prolapse does not lead to a progressive improvement in voiding and urgency, but rather will be associated with relief of urgency if it successfully unkinks the urethra, i.e. opens a closed retrovesical angle. Whilst ultrasound studies have shown a correlation between hiatal
dimensions and severity of prolapse symptoms (Dietz et al, 2008), there is a paucity of direct data to prove that clinical prolapse stage is well correlated with ultrasound stage, particularly the retrovesical angle. Eisenberg and colleagues classified women with cystocele according to bladder neck position, urethral rotation and retrovesical angle, and found that women with intact (i.e. closed) retrovesical angles had more severe prolapse, as well as a higher incidence of voiding dysfunction (Eisenberg et al, 2010). In women who experience persistent overactive bladder symptoms post-operatively, it may be that surgical repair has not opened the retrovesical angle, or alternatively that these women did not have a closed retrovesical angle pre-operatively. In this latter group, an alternative explanation is that the presence of pelvic organ prolapse and overactive bladder symptoms are aetio logically unrelated. Both conditions increase in incidence with increasing age, and their coexistence in the same individual may simply be a reflection of this.

The proportion of women who underwent surgical repair of isolated posterior compartment prolapse was almost four times higher in Group 2 than Group 1 (15.5% versus 4%). This may imply that correction of a posterior compartment prolapse is less likely to be associated with symptom resolution, either because a posterior compartment prolapse is less likely to be aetio logically connected with overactive bladder symptoms or because effecting anatomical changes associated with overactive bladder symptoms is less likely to be successful with repair of the posterior compartment. Studies looking at the prevalence of OAB symptoms by compartment show conflicting results. A study of 282 women with urgency incontinence found an obvious relationship with anterior and posterior compartment prolapse, but not apical prolapse (Miedel et al, 2008). Other authors have identified no consistent relationship between
compartment and the presence of symptoms (Bradley and Nygaard, 2005; Sobhgol and Charandabee, 2008).

The aim of this study was to build on the pilot data outlined in the previous chapter in order to more firmly establish the association of changes in voiding with changes in OAB symptoms. In this aim it has been successful, in that the finding of an increase in flow rate being associated with symptom resolution has been confirmed prospectively in a larger cohort of women (with the study size being powered to look for changes in voiding) with a standardised follow up. The methodological problems of the pilot study related to a varying time to follow up meaning that a true association between surgical repair of prolapse and changes in symptoms or voiding parameters could not be established. The protocol in the present study overcame this problem, and the inclusion of a control flow measurement 3 months after recruitment allowed a check for any natural variation in flow rates over this relatively short period.

This study suggests that a change in voiding is associated with an improvement or persistence of urgency. An improved flow rate results in resolution of urgency, whilst there is a trend suggesting that a fall in flow rate results in persistent urgency. The baseline maximum flow rate may also be important. In the present study although a statistically significant difference between the preoperative flow rates in the cured and non-cured groups was not demonstrated, the p value was only marginally non significant (p=0.06). The a priori power calculation was for a study population of 140 and the study was powered to identify a change in flow rates after surgery of 5ml/sec. The eventual study group of 122 may leave the study underpowered to achieve a difference in the baseline means of 3.8 (15.6-11.8). Therefore, to identify if a difference in preoperative flow rate is a relevant factor, a larger population would be required. It
could be argued that these flow rate changes are small and clinically insignificant. However, in terms of biological models a change in a flow rate from 11.8ml/sec to 26.2 is very large.

As discussed in the methodology, unintubated free flow measurements were used as an outcome measure. Clearly pressure flow studies would have yielded more information for study, but the feasibility of doing full urodynamics both pre- and post-operatively for all women in this study was questioned, particularly in light of the fact that pressures were not a primary outcome measure. Also, since no change in pressures was identified in the pilot study, the ethics of asking a large group of participants to undergo two sets of intubated flow studies as part of the protocol was questioned.

In conclusion, in this large prospectively recruited cohort of women, relief of OAB symptoms following prolapse repair is associated with a significant increase in maximum flow rate. This may imply an aetiological role for increased urethral resistance in OAB symptoms, with surgery to correct this being associated with anatomical changes in the relationship between the urethra and the bladder leading to changes in voiding. As discussed previously, ultrasound studies to investigate the relationship between changes in anatomy, flow and symptoms would be of great benefit.

The next two chapters will describe investigations to establish whether measures to directly alter urethral resistance using mechanical means are effective at altering voiding parameters, and whether this translates into a clinical benefit in terms of OAB symptoms.
Chapter Eight

The effect of urethral dilatation on pressure flow studies in women with voiding dysfunction and overactive bladder- pilot data
Introduction

Previous chapters have focused on whether voiding at baseline can predict treatment outcomes with antimuscarinics, and also whether attempting to improve voiding indirectly, i.e. by restoration of anatomy in patients with pelvic organ prolapse, leads to any improvement in OAB symptoms. Voiding in women is multifactorial with the interaction between the detrusor muscle contractility, urethral resistance and pelvic floor culminating in the rate and pressure of flow. As discussed in previous chapters, the pattern seen in the subset of women with overactive bladder under investigation in this thesis is of relatively low flow rates in combination with high or normal detrusor pressures during flow. Strategies to change this pattern would therefore need to focus on urethral resistance. There are relatively few treatment modalities which can be used to manipulate this axis directly. One such option would be urethral dilatation, aiming to increase the calibre of the urethra, leading to a reduction in its resistance to flow.

The next two chapters describe studies undertaken to assess whether urethral dilatation does lead to any measurable improvement in urgency, and whether this is associated with any changes in voiding function.

Voiding dysfunction in women is a poorly understood condition and suffers from a lack of standard definitions for guidelines for treatment. Aetiological factors include poor or absent detrusor contraction, or bladder outlet obstruction caused by urethral overactivity or anatomical obstruction, e.g. gross pelvic organ prolapse, previous continence surgery (Groutz and Blaivas, 2002). Treatment options for women with troublesome voiding dysfunction are limited. Repair of genital prolapse or urethrolysis of continence procedures may provide relief of symptoms secondary to outlet obstruction, however many patients are left with catheterisation (suprapubic,
urethral or self) as treatment. Urethral dilatation (UD) has been used by urologists and urogynaecologists for many years to manage a variety of different symptom complexes. It was first described in 1923, and gained in popularity in the 1960s for the treatment of recurrent urinary tract infections and urethritis; it has since also been used for complaints such as urgency, frequency and bladder pain. The basis for its use was the presumption that these symptoms were due to voiding dysfunction secondary to increased urethral outlet resistance. Despite this, there is a stark lack of evidence in the literature regarding the efficacy of this procedure.

True urethral stricture is rare in women. A recent study of 587 women referred to a tertiary centre with voiding symptoms revealed only 7 cases of proven urethral stricture (Groutz et al, 2000). In spite of this lack of prevalence, and usually in the absence of objective evidence of stricture, UD has been used as a treatment for various lower urinary tract disorders for several decades.

Reports of medical insurance claims and hospital episode statistics do seem to indicate that UD is performed by clinicians with some regularity. A 1999 questionnaire based survey of Texan urologists revealed that almost 50% overall used UD six or fewer times per year, with 23.7% using it over 30 times (Lemack et al, 1999). The use of UD for urethral syndrome or any other urinary complaints tended to be less common amongst urologists trained during the decade before the study was carried out, and more recently trained urologists also perceived it to be a less efficacious treatment. The reason for this disparity in use and perceptions of UD is unclear. Differences in training and experience may be one explanation; however it may also reflect the fact that the aetiology of female voiding disorders is poorly understood, making any consensus on the effect of altering outlet resistance difficult to reach. A national US study of the frequency
of office UD in women which was published 10 years later showed it to still be a common procedure (929 per 100000 patients), with overall costs of $61 million per year (Santucci et al, 2008).

A search of the literature reveals few studies reporting outcomes for UD in women with urinary symptoms. In 1988, Rutherford and colleagues reported on a randomised trial of urethral dilatation compared with cystoscopy alone in women with recurrent frequency and dysuria (Rutherford et al, 1988). Women with urgency, frequency and urgency incontinence without dysuria were excluded. Although cystometry and pressure flow studies were undertaken prior to the procedure, they did not form part of the inclusion criteria, meaning that the study group was heterogenous in terms of urodynamic diagnosis. The urethras of the women in the UD arm of this trial were dilated to between 36 and 42F, and care was taken to avoid overdistension of the bladder at cystoscopy and over-dilatation in all patients. The results showed significant improvements in overall symptom score and in dysuria specifically in both groups. There were however no differences in symptom improvement between the two groups (32% “success” in cystoscopy group, versus 30% in UD group), indicating that dilating the urethra following a cystoscopy conferred no significant additional benefit in these patients. The authors also reported a 14% incidence of temporary SUI in the UD arm of the trial, raising the concern that dilating the urethra may impair urethral function. The authors report using a cystoscope sheath that dilated the urethra to at least 32F, meaning that even women in the cystoscopy alone group will have undergone some degree of urethral dilatation. This may explain the lack of difference between the two groups, and does raise some concerns about the external validity of this study. The only other report on outcomes that could be identified on a thorough search of the literature described the effect of urethral calibration on voiding parameters in 20 women with bladder
outlet obstruction (Yee et al, 2012). The authors found no significant difference in pre- and post-calibration Qmax and post-void residual volume, and a significant decrease in PdetQmax. This study did not attempt to correlate changes in symptoms to changes in urodynamic parameters.

The primary aim of this study was to evaluate whether UD leads to any objective change in pressure flow study parameters and whether this was associated with improvement of symptoms. The secondary aim was to obtain outcome data for women undergoing UD, in order to carry out a power calculation for a randomised trial of cystoscopy and urethral dilatation versus urethral dilatation alone in women with voiding dysfunction and overactive bladder.

Null Hypothesis

UD does not lead to any change in pressure flow parameters, or improvement in OAB symptoms.

Methods

This was a retrospective observational study. The study population consisted of 43 women who underwent cystoscopy and UD between 2006 and 2008. Women with OAB symptoms resistant to conservative therapies (bladder drill and antimuscarinics) were offered filling and voiding cystometry. The cohort comprised consecutive women with OAB identified as having co-existent voiding dysfunction. The diagnosis of OAB was made clinically by direct questioning and by the patient indicating moderate or severe urgency or urgency incontinence in the symptom domains of the King’s Health Questionnaire. Voiding dysfunction was defined as a maximum flow rate of less than 15 ml/s with a voided volume of 200mls or above and/or post-void residual over 200mls. Exclusion criteria were women with USI and/or pelvic organ
prolapse undergoing concurrent surgery since continence surgery and prolapse surgery may alter voiding parameters. Women with neurological disorders or bladder pathology on cystoscopy were also excluded.

Twin-channel subtraction normal saline cystometry was undertaken as per International Continence Society guidance as described in Chapter 4. Provocative manoeuvres were undertaken during filling and a pressure flow study was carried out at cystometric capacity.

All women underwent cystoscopy and UD under general anaesthesia. Saline cystoscopy was undertaken with a 5mm rigid 70 degree cystoscope. The urethra was not dilated prior to cystoscopy. The bladder was systematically inspected and any epithelial abnormalities were noted. A second fill was carried out and any petechial haemorrhages noted. UD was undertaken after cystourethroscopy using Hegar dilators. Dilatation started with the largest calibre dilator that could be passed without resistance (this was taken to be the initial urethral calibre), and went to a maximum of 10 Hegar. Each patient was given a single dose of intravenous gentamicin at induction of anaesthesia. All women were treated as day case procedures.

Participants were reassessed with a King’s Health Questionnaire, PGI-I and repeat filling and voiding cystometry 6 weeks following the urethral dilatation. Patients were defined as improved if they described themselves as “moderately improved” or “greatly improved” on the PGI-I, and if they failed to document moderate or severe urgency or urgency incontinence in the symptom domain of the KHQ. Since voiding is not part of the symptom domain of the KHQ, patients were asked directly about their flow symptoms. Their symptoms were reviewed again 6 months after the urethral dilatation. Patients with persistent OAB symptoms at 6 weeks were offered alternative anticholinergic treatments at this point. Patients who had a transient
improvement in OAB symptoms but were found to have persistent OAB symptoms at 6 months were offered anticholinergics at this point. Patients who had persistent symptoms requiring anticholinergic treatment were classified as failing to improve with UD (at either 6 weeks or 6 months). Since flow is volume dependent, maximum flow rate centiles were calculated as previously described (Dietz and Haylen, 2005).

A Wilcoxon Matched Pairs Signed Rank test was used to evaluate any difference in maximum flow rate, voided volume, flow rate centiles, voiding time, detrusor pressure at maximum flow and post void residual. A Mann Whitney test was used to evaluate any baseline differences in pressure flow parameters between women who experienced an improvement in symptoms and those who did not. A p-value of less than 0.05 was taken as significant. SPSS version 15 was used for all statistical calculations.

The primary outcome measure was change in flow rate centile, detrusor pressure at maximum flow and post-void residual following UD. Secondary outcome measures were improvement in symptoms as judged by the PGI-I, severity of OAB symptoms (based on KHQ) and improvement in urinary flow (based on direct questioning).

**Results**

The mean patient age was 59 years. All the women complained of OAB and impaired voiding (poor flow, incomplete emptying) at initial assessment. On urodynamic assessment all 43 women demonstrated voiding dysfunction (as defined in the Methods section). 10 women were found to have co-existent detrusor overactivity (DO) of whom 2 also demonstrated USI (although neither of these women complained of stress urinary incontinence). All women
emptied their bladders by generating a detrusor contraction. The initial urethral calibre in this cohort was in the range 3 to 8 mm (Hegar). Mean pre- and post-procedure values for maximum flow rate, voided volume, detrusor pressure at maximum flow, voiding time and post-void residual, together with p-values are shown in table 8.1.

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>P</th>
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<tbody>
<tr>
<td><strong>Qmax (ml/s)</strong></td>
<td>10.3(3.3)</td>
<td>13.0(7.9)</td>
<td>0.02*</td>
</tr>
<tr>
<td><strong>Volume (ml)</strong></td>
<td>307(138.1)</td>
<td>328.3(148.2)</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Qmax Centile</strong></td>
<td>0.8 (1.79)</td>
<td>4.2(13.1)</td>
<td>0.07</td>
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<tr>
<td><strong>PdetQmax (cmH2O)</strong></td>
<td>55.8(36.1)</td>
<td>45.1(28.1)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Voiding time (secs)</strong></td>
<td>96.0(62.5)</td>
<td>70.2(26.8)</td>
<td>0.03*</td>
</tr>
<tr>
<td><strong>PVR (ml)</strong></td>
<td>133.1(116.5)</td>
<td>133.4(129.1)</td>
<td>0.77</td>
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</table>

Table 8.1. Mean pre- and post- UD pressure flow parameters and maximum flow rate centiles for whole cohort (n= 43), p values from wilcoxon matched pairs signed rank test, standard deviations in brackets.

At the 6 week assessment, 22/43 (51%) patients had no improvement in either voiding or OAB symptoms. 7/43 (16%) patients had a subjective improvement in their flow rate on direct questioning but complained of persistent OAB symptoms which were not relieved (or worsened). 14/43 (33%) had a subjective improvement in OAB (as defined by the PGI-I and KHQ) and reported an increased flow rate. This improvement was maintained at 6 months in 8 of these 14 patients (19%)- these patients had undergone UD alone and had received no other treatments. Overall 21/43 (49%) reported some improvement in either flow rate or OAB at 6 weeks.
At 6 months, 28 women were on antimuscarinic medications, 5 were being taught clean intermittent self-catheterisation and in 2 the decision was made to undertake a repeat UD (requested by patients due to an initial improvement in symptoms).

At cystometry, 2 patients with pre-procedure DO had no evidence of DO on post-procedure urodynamics; one of these reported no improvement, one reported a transient improvement with later deterioration. 5/39 (13%) had de novo USI, with one later requiring a tension free vaginal tape (4 women had pre-existing USI). Four of these five women with de novo USI were in the group with an improvement in OAB and flow rate symptoms at 6 weeks. Mean pre- and post-procedure pressure flow parameters for patients with an improvement in OAB and voiding symptoms at 6 weeks are shown in table 8.2. There was no significant difference in pressure flow parameters and post-void residual measurement at baseline between women who had no response to the UD and women who did.

<table>
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<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
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<tbody>
<tr>
<td>Qmax (ml/s)</td>
<td>9.69(3.5)</td>
<td>15.14(9.3)</td>
<td>0.1</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>330.9(155.7)</td>
<td>422.3(106.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>Qmax Centile</td>
<td>0.83(2.1)</td>
<td>4.93(15.6)</td>
<td>0.02*</td>
</tr>
<tr>
<td>PdetQmax (cmH2O)</td>
<td>66.0(41.1)</td>
<td>54.4(28.8)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Voiding time (secs)</td>
<td>97.6(65.7)</td>
<td>70.9(14.1)</td>
<td>0.3</td>
</tr>
<tr>
<td>PVR (ml)</td>
<td>129.6(125.5)</td>
<td>60.1(63.6)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Table 8.2. Mean pre- and post-UD pressure flow parameters and maximum flow rate centiles, p values from wilcoxon matched pairs signed rank test for patients with symptomatic improvement (n=21). Standard deviations in brackets.
Discussion

These results suggest that 49% of patients have a short term subjective improvement in their flow rates after UD. 33% had improvement in their OAB symptoms. Relief of OAB symptoms is associated with a significant improvement in both maximum flow rate centile values and detrusor pressure at maximum flow. However, only 19% experience persistence of this improvement beyond 6 months. 5 women (13%) developed USI although only one became symptomatic and needed further surgery to correct stress incontinence.

The combined change in PFS is towards a less obstructed picture than at baseline. It can be speculated that a lesser degree of obstruction leads to improvement in OAB. It may be that the urethral dilatation opens up the bladder outflow, meaning that the detrusor contraction necessary for voiding is lower. The relief of obstruction in women could be compared to the effect of a TURP in men, which relieves OAB in two thirds of cases. However, in men there is ongoing debate whether obstruction is an important aetiological factor (Thomas and Abrams, 2000). Previous work has suggested a place for dysfunctional voiding in the aetiology of DO and OAB in women with mixed incontinence undergoing tension free vaginal tape (Duckett and Basu, 2007). A recent controlled study of women with idiopathic DO found there to be a significantly lower maximum flow rate and higher detrusor pressure at maximum flow in the DO group when compared to a control group (Kayigil et al, 2007).

The percentage of patients with a symptomatic benefit of 6 months or above was only 19%. This possibly reflects the nature of the urethral tissue, with the increased calibre only being a temporary effect caused by mechanical stretching, rather than a true increase. The nature of urethral tissue is such that in most women with functional obstruction, rather than a
mechanical obstruction such as a stricture, undergoing a single urethral dilatation will not lead to a permanent change. It would have been of interest to have examined pressure flow data in the women whose symptoms reverted to baseline at 6 months to assess whether the urodynamic changes were also reversible.

Other authors have focussed on using pharmacological agents to provide a sustained decrease in outlet resistance by causing relaxation of the urethral sphincter complex. Botulinum toxin injected directly into the urethral sphincter in men and women with voiding dysfunction has been shown to lead to a 67% subjective improvement in voiding (Phelan et al, 2001). Almost 100% of the cohort were able to void without catheterisation following the treatment. Pharmacological strategies have also been used to address outlet resistance. Alpha adrenoreceptor blockade with alfuzosin (Athanasopoulos et al, 2009), terazosin (Kessler et al, 2006) and tamsulosin (Pischedda et al, 2005) has been shown to lead to improvements in bladder emptying, quality of life and lower urinary tract symptoms in women with voiding dysfunction. Although alpha blockers have been used in men with bladder outlet obstruction for many years, use in women has excited interest only relatively recently; it remains to be seen whether these initial reports will translate into good longer term outcomes.

This evidence would seem to support the fact that reducing urethral resistance is an effective strategy in women with functional BOO, so it may indeed be that mechanical dilatation itself does not provide a sustained effect. One answer may be to carry out repeated dilations. Anecdotally, there are some women who request serial dilations due to a transient improvement in symptoms after an initial procedure. There is no evidence as to whether or not this improves outcomes. Given this, it is debatable whether subjecting a woman to general anaesthetics for
repeated procedures is ethical. Dilatation can be carried out as an office procedure under local anaesthesia. Indeed the majority of respondents in Lemack and colleagues’ survey of practice patterns report carrying out the procedure under local or no anaesthesia (Lemack et al, 1999). This raises the question of whether an effective dilatation can be carried out under local or no anaesthesia- it must be remembered however, that it is not known what constitutes an “effective dilatation”, particularly if one wishes to avoid de novo incontinence. It is also possible that a degree of fibrosis may be caused by urethral dilatation. Thus the need for repeated dilatations could be self-perpetuating, i.e. bladder outlet obstruction secondary to fibrosis caused by the dilatation itself.

A 13% incidence of new onset USI with dilatation up to 10mm was identified, which would presumably increase with greater degrees of dilatation. Only one of these patients eventually required a continence procedure, indicating that the stress urinary incontinence may have been caused by mechanical stretching of the urethra, which later resolved. All of the patients with this complication were in the group with an improvement in OAB and voiding symptoms at 6 weeks, which would agree with this explanation. When the overall poor success rate of urethral dilatation is considered, it may be argued that a 13% incontinence risk, even short term, is prohibitively high. This would be a subject for further study.

The idea of decreasing outlet resistance mechanically and causing an increase in flow together with lower voiding pressures is an attractive and deceptively simple one. The voiding mechanism in female subjects is being increasingly recognised as more complex than in men. The pelvic floor seems to be an important factor in voiding in incontinent women. The conventional idea of a detrusor contraction being the main force behind micturition has now been
overtaken by various studies showing women to void via a variety of mechanisms including abdominal straining plus pelvic floor relaxation, pelvic floor relaxation alone or either of these in combination with a detrusor contraction (Chassagne et al, 1998; Dietz and Haylen, 2005). Clearly if a woman voids by pelvic floor relaxation without generating a detrusor contraction, dilating the urethra may have a different impact when compared to a woman generating a detrusor contraction to void. Absence of a detrusor contraction in combination with a poor flow rate would imply non-obstructive voiding dysfunction- such patients may not be expected to benefit from UD. There were no such patients in this cohort, meaning that pelvic floor function in terms of voiding was a constant factor in the pre- and post-operative evaluation.

There are a number of limitations to the study, most of which are attributable to the lack of standardisation in definitions and treatments of voiding dysfunction in women. There is no clear consensus on the definition of non-neurogenic voiding dysfunction in women. A flow rate less than 15 ml/sec with a minimum voided volume (to ensure that the low flow was not due to a low volume) as described by Stanton was used in this study (Stanton et al, 1983). However other authors have used lower flow rates, or incorporated detrusor pressure at maximum flow into the definition (Chassagne et al, 1998). Pressure flow studies have the benefit over free flow studies of giving useful information on the detrusor pressure. A combination of free flow and pressure flow studies is likely to be the most comprehensive way of diagnosing voiding dysfunction (Dietz and Haylen, 2005) but free flow data was not available for all women. Defining voiding dysfunction on the basis of pressure flow and free flow data may merely introduce more confusion. There is increasing evidence that the presence of a urethral catheter during pressure flow studies lowers maximum flow rates, by causing a degree of functional obstruction (Blaivas and Groutz, 2000). It is therefore possible that voiding dysfunction was
over-diagnosed. The mean detrusor pressure at maximum flow was higher than expected and is probably due to an effect of the dual lumen filling catheter. Until some degree of standardisation is reached with regards to this, interpreting and comparing different studies will be difficult. The most recent joint International Continence Society and International Urogynaecological Association report on terminology for female pelvic floor dysfunction does not give any further guidance on the urodynamic definition for female voiding dysfunction.

An issue with this, and any other study of UD, is that the normal calibre of the female urethra is unknown. It is difficult to know whether the initial urethral calibre in this cohort of patients was normal or abnormal. The calibre of the urethra in this cohort was assessed by noting the largest sized dilator that could be passed into the urethra with no resistance. This is an inherently subjective measurement. A 1978 study of 250 women with no lower urinary tract symptoms showed the mean urethral calibre to be 22F (7.3mm) (Uehling, 1978); there have been no confirmatory studies or studies in women with OAB and DO. In addition, there is little information in the literature on what constitutes an effective urethral dilatation. The patients in this study were dilated up to 10mm using Hagar dilators (30F) as this is the practice of the senior clinician involved in the study. A study of practice patterns amongst American urologists revealed that 45% dilated to 32F (10.7mm) and 37% dilated to 26F (8.7mm) (Lemack et al, 1999). Thus it can be seen that the degree of dilatation in the subjects in this cohort was comparable to the published literature. With dilatation to 10mm, 5 patients developed de novo USI. Whilst dilating to a higher degree may increase efficacy, there is a danger that this would be at the expense of more de novo USI.
The results from this study suggest that relief of OAB after UD in women with VD is associated with a less obstructive picture on PFS. This is the first study to have documented objective outcomes after UD and to equate them to subjective outcome. Whilst these data give us valuable insight into possible links between voiding, outflow obstruction and OAB, one must remember that the long term efficacy of UD in this cohort was poor, and it would therefore be difficult to justify it as an effective treatment. However a third of patients did get a transient benefit as a minimum, so one may be able to justify carrying out UD at the time of cystoscopic investigation, rather than as a primary treatment. Patients should however be warned of the risk of new onset stress urinary incontinence. In the absence of pelvic organ prolapse or previous continence surgery causing voiding dysfunction, treatment will often centre around permanent or intermittent self catheterisation. It is known that the majority of women find catheterisation as a treatment unacceptable (Robinson et al, 2003), so many may be keen to try UD prior to this, despite the relatively poor success rates. A further challenge is to identify whether there are certain patient groups that are more likely to benefit from UD than others and to define the diagnosis of urethral stricture in women.

Although the results of this study have provided some insight into outcomes after urethral dilatation, there are limitations to observational retrospective data, as outlined above. In order to provide a higher level of evidence, the data from this study were used to generate a protocol and sample size calculation for a prospective randomised trial of cystoscopy and urethral dilatation versus cystoscopy alone. The methodology and results of this study will be described in the next chapter.
Chapter Nine

A randomised trial of cystoscopy and urethral dilatation versus cystoscopy alone in women with overactive bladder symptoms and voiding dysfunction
Introduction

In the last chapter, an association between relief of OAB symptoms in women undergoing urethral dilatation and an increase in maximum flow rate and decrease in detrusor pressure at maximum flow was described. Thus it can be postulated that the mechanism of action of any improvement in urgency associated with urethral dilatation in women with OAB symptoms may involve an improvement in voiding parameters via a decrease in urethral resistance. The overall long term efficacy of the procedure in the cohort studied was poor however, which may be due to the soft tissue nature of the urethral tissue, and the fact that any pre-existing outflow resistance was functional rather than mechanical. The work detailed in the previous chapter was a retrospective analysis which leads to the potential for selection bias. The lack of a comparator group also makes the place of urethral dilatation in clinical practice difficult to define, since this procedure is generally carried out in conjunction with a cystoscopy. Whilst the retrospective study did offer insight into the existence of a possible association between carrying out an intervention to decrease urethral resistance and resolution of OAB symptoms, the findings did not evaluate whether the intervention in question was of any therapeutic value to women with OAB above cystoscopy alone. This chapter describes a randomised study which aimed to overcome these issues and to establish whether urethral dilatation as a strategy to decrease urethral resistance is a useful adjunct to treatment for overactive bladder symptoms.

The primary aim of the study detailed in this chapter was to assess whether performing a urethral dilatation in addition to cystoscopy leads to any increase in symptom relief compared to performing a cystoscopy alone. The secondary aim was to assess whether urethral dilatation
leads to any objective change in voiding parameters or in symptom related quality of life versus cystoscopy alone.

**Null Hypothesis**

Urethral dilatation does not lead to any additional improvement in OAB symptoms when compared to cystoscopy alone.

**Methods**

This was a parallel randomised trial with an allocation ratio of 1:1. All women with significant OAB symptoms and objective evidence of voiding dysfunction were eligible to enter the trial. This was a single centre trial. All subjects were recruited from the urogynaecology clinic at Medway Maritime Hospital. The inclusion and exclusion criteria are detailed below:

**Inclusion Criteria**

1. Significant overactive bladder symptoms
   a. based on scoring 1 or 2 on the UPS
   b. on the symptom domain of the KHQ
   c. More than 8 voids per day on frequency volume chart\(+/-\) 2+ episodes of nocturia
2. Maximum flow rate of less than 15ml/sec on a voided volume of more than 200 mls, with a high or normal detrusor pressure at maximum flow or post-void residual of 200mls or over (based on one measurement of residual).
**Exclusion Criteria**

1. Presence of concurrent USI
2. Symptomatic pelvic organ prolapse requiring intervention
3. Patients with bladder pathology (including urinary tract infection) or haematuria of unknown origin
4. Patients with neurological disorders (as these may affect voiding)
5. Patients unfit or unwilling to undergo a general anaesthetic

The pre-operative protocol included an initial assessment consisting of a full urogynaecological history and examination, 3 day bladder diary, KHQ and UPS, together with twin channel subtraction filling cystometry and pressure flow studies. Filling and voiding cystometry were performed according to International Continence Society standards (see chapter 4). Those deemed eligible and who consented to enter the trial were randomised on the day of surgery to undergo cystoscopy plus urethral dilatation or cystoscopy alone. Subjects were randomised using a block randomisation sequence with allocation to each group being assigned via a series of sequentially numbered opaque envelopes. Due to the sample size, random allocation using the population as a single block was undertaken.

All procedures were carried out under general anaesthesia with a single dose of intravenous gentamicin being given at induction of anaesthesia. The bladder was emptied prior to cystoscopy using a rigid metal catheter. Saline cystoscopy was undertaken with a rigid 5mm 70 degree cystoscope. The urethra was not dilated prior to introduction of the cystoscope. A systematic inspection of the bladder epithelium was undertaken and a second fill was carried out to look for any petechial haemorrhages, ulceration or glomerulations. The bladder was emptied
following this. In subjects randomised to undergo urethral dilatation, this was done using Hegar dilators to a maximum of 10mm. The rationale for this has been discussed in the previous chapter. Women were discharged on the same day if voiding adequately. Any intra- or post-operative complications were noted, however all data were analysed on an intention to treat basis.

Post-operative outcomes were assessed at an outpatient appointment at 6 weeks, and by postal questionnaire at 6 months. The primary outcome measure for this trial was cure of urgency at 6 weeks and 6 months, defined as a score of 3 on the UPS. Secondary outcome measures were changes in pressure flow parameters at 6 weeks and in quality of life at 6 weeks and 6 months as measured by the KHQ. Any late adverse events, e.g. the development of stress urinary incontinence, were also noted at the 6 week consultation.

A priori power calculation was carried out to determine the required sample size, based on a cure rate for urgency of 0.4 for the urethral dilatation arm (from pilot data) and 0.1 for the cystoscopy alone arm. For a power of 80% and a significance level of 0.05, it was calculated that a total of 50 women would need to be randomised. Due to the relatively small sample size, it was not planned to carry out any form of interim analysis.

Enrolling and randomisation of participants was carried out by a member of the research team. Participants were blinded as to which of the treatment groups they had been allocated to. Due to obvious differences between the procedures, the members of the team carrying out the procedure could not be blinded to the group allocation.

Statistical analysis was undertaken using Fisher’s Exact test for categorical values, student’s t-test for continuous parametric variables, and the Mann Whitney U test for continuous
non-parametric variables. The Kolmogorov Smirnov test was used to evaluate continuous data for normality prior to significance testing.

All participants were given written information on the study and procedures, and gave informed consent. Approval for the study was granted by West Kent Research Ethics Committee and the trial protocol was registered on Clinicaltrials.gov.

**Results**

Between November 2008 and March 2011, 50 women with overactive bladder symptoms meeting the eligibility criteria were enrolled into the trial. The final 6 week follow up visit was conducted in May 2011, and the final 6 month postal questionnaire was received in December 2011. The flow of participants through the trial is detailed in figure 9.1.

After randomisation, 22 participants underwent cystoscopy and urethral dilatation and 28 participants underwent cystoscopy alone. All participants returned for urodynamic studies and provided subjective outcome data at 6 weeks. Questionnaires were received at 6 months from 16/22 in the urethral dilatation group and 21/28 in the cystoscopy alone group. Data were analysed on an intention to treat basis. The baseline demographic and clinical characteristics of each group are detailed in table 9.1.
Table 9.1 Baseline demographic and clinical characteristics in each group

<table>
<thead>
<tr>
<th></th>
<th>Urethral dilatation (n=22)</th>
<th>Cystoscopy alone (n=28)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55</td>
<td>55.5</td>
<td>NS</td>
</tr>
<tr>
<td>Parity</td>
<td>1.8</td>
<td>2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Post-menopausal, %</td>
<td>52.6</td>
<td>50</td>
<td>NS</td>
</tr>
<tr>
<td>Proven DO, %</td>
<td>90.9</td>
<td>89.3</td>
<td>NS</td>
</tr>
<tr>
<td>POP &gt; stage 2, %</td>
<td>18.1</td>
<td>17.9</td>
<td>NS</td>
</tr>
<tr>
<td>Prior treatment with antimuscarinics, %</td>
<td>33.1</td>
<td>29.8</td>
<td>NS</td>
</tr>
<tr>
<td>Total KHQ score</td>
<td>229.1</td>
<td>441.7</td>
<td>0.03</td>
</tr>
<tr>
<td>UPS 1, %</td>
<td>67</td>
<td>71</td>
<td>NS</td>
</tr>
<tr>
<td>Qmax (ml/sec)</td>
<td>12.1</td>
<td>12.5</td>
<td>NS</td>
</tr>
<tr>
<td>PdetQmax</td>
<td>52.7</td>
<td>39.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

The primary outcomes for each group at 6 weeks and 6 months, with p values calculated using a one-tailed Fisher’s Exact test, are detailed in table 9.2.

<table>
<thead>
<tr>
<th></th>
<th>UD (n=22)</th>
<th>non-UD (n=28)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No urgency</td>
<td>10</td>
<td>5</td>
<td>0.03*</td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No urgency</td>
<td>4</td>
<td>4</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Table 9.2 Primary outcome measure at 6 weeks and 6 months (“no urgency” taken as response 3 on the UPS), *= p < 0.05

Outcome data were available for all patients at 6 weeks, however 5 patients in the UD group and 6 patients in the non-UD group failed to contribute to the postal follow up despite
several requests. Non-responders were included in the analysis as treatment failures such that all participants were included in the final 6 month analysis.

One patient in the cystoscopy alone group experienced a bladder rupture at a volume of 800mls. This was sutured laparoscopically and an in-dwelling catheter left in situ for 10 days. Of note, the histopathological analysis on a bladder biopsy for the subject reported changes consistent with chronic cystitis. This patient was analysed within the group she had originally been allocated to. There were no other cases of patients requiring an in-dwelling catheter post-operatively. 6 patients in total (2 in the UD group, 4 in the non-UD group) developed de novo USI although none have required a continence procedure to date.

Pre and post-operative voiding data were available for all randomised participants and are presented in table 9.3. Because flow rates may be volume dependent, maximum flow rate centiles were calculated and are also presented below. Kolmogorov- Smirnov testing of the voiding data revealed all parameters apart from the maximum flow rate centiles to be consistent with a normal distribution, hence a paired student’s t test was used for evaluation of the pre- and post-operative values for voided volume, maximum flow rate, detrusor pressure at maximum flow and post-void residual, and a Mann Whitney U test was used for evaluation of maximum flow rate centiles. There were no baseline differences in voiding parameters.
<table>
<thead>
<tr>
<th></th>
<th>Pre-operative</th>
<th>Post-operative</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urethral dilatation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voided volume (ml)</td>
<td>318 (240.6-394.9)</td>
<td>324 (264.0-384.6)</td>
<td>0.89</td>
</tr>
<tr>
<td>Qmax (ml/sec)</td>
<td>12.1 (8.2-16.0)</td>
<td>16.0 (12.7-19.3)</td>
<td>0.13</td>
</tr>
<tr>
<td>Qmax centile</td>
<td>0.60 (0.20-0.94)</td>
<td>9.17 (0.12-18.2)</td>
<td>0.008*</td>
</tr>
<tr>
<td>P_{det}Q_{max} (cmH_2O)</td>
<td>52.7 (32.2-73.2)</td>
<td>45.5 (31.0-60.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>Residual (mls)</td>
<td>80.9 (-5.4-156.2)</td>
<td>50.1 (-7.5-107.7)</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Non-urethral dilatation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voided volume (ml)</td>
<td>306 (233.8-377.9)</td>
<td>333 (262.4-402.7)</td>
<td>0.59</td>
</tr>
<tr>
<td>Qmax (ml/sec)</td>
<td>12.5 (10.3-14.7)</td>
<td>12.8 (10.7-14.9)</td>
<td>0.87</td>
</tr>
<tr>
<td>Qmax centile</td>
<td>6.32 (-3.1-15.7)</td>
<td>4.97 (-0.64-10.6)</td>
<td>0.51</td>
</tr>
<tr>
<td>P_{det}Q_{max} (cmH_2O)</td>
<td>39.5 (23.5-55.6)</td>
<td>41.8 (25.7-57.8)</td>
<td>0.84</td>
</tr>
<tr>
<td>Residual (mls)</td>
<td>65.6 (27.8-154)</td>
<td>39.4 (-47.1-125.8)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

Table 9.3. Pre- and post-operative mean voiding parameters for each study group with 95% confidence intervals (*, statistically significant, p < 0.05)

Results from the incontinence related quality of life domains of the King’s Health Questionnaire at 6 weeks are given in table 9.4. The mean change in domain scores was significantly higher in the non-urethral dilatation group (p= 0.004), and was in a negative direction (i.e. decrease in domain scores post-operatively). There were no significant changes in KHQ domain scores at 6 months.
<table>
<thead>
<tr>
<th>Domain</th>
<th>Urethral dilatation (n=22)</th>
<th>Non-urethral dilatation (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Role limitations</td>
<td>16.67</td>
<td>30</td>
</tr>
<tr>
<td>Physical</td>
<td>33.4</td>
<td>38.3</td>
</tr>
<tr>
<td>Social</td>
<td>14.8</td>
<td>27.8</td>
</tr>
<tr>
<td>Personal</td>
<td>16.1</td>
<td>19</td>
</tr>
<tr>
<td>Emotional</td>
<td>25.9</td>
<td>47.2</td>
</tr>
<tr>
<td>Sleep/energy</td>
<td>66.7</td>
<td>51.7</td>
</tr>
<tr>
<td>Severity measures</td>
<td>55.5</td>
<td>53.3</td>
</tr>
</tbody>
</table>

Table 9.4 Mean scores from the domains of the King’s Health Questionnaire pre and 6 weeks post-procedure, with p values taken from Mann Whitney U test

Discussion

The results from this randomised trial indicate that urethral dilatation in women with OAB symptoms and voiding dysfunction is associated with a significantly higher subjective cure rate for urgency, together with an increased flow rate centile at 6 weeks. This is poorly sustained however and not maintained at 6 months. There were no significant changes overall in quality of life in either group.

This study is the first reported randomised trial to evaluate outcomes of UD in women with OAB. The main strength of these data is the attainment of subjective outcome and quality of life data, plus voiding data, for all participants at 6 weeks’ follow up. 5/22 participants in the UD group and 6/28 participants in the non-UD group failed to respond to the postal follow up at 6 months. This does have the potential to render the 6 month follow-up underpowered to evaluate the primary outcome. The decision was taken to include non-responders as treatment failures in the statistical analysis, in order to adopt a “worst case scenario” approach so as to
avoid a type 2 error. Rerunning the analysis with the opposite assumption, i.e. that all non-responders were treatment successes, did not lead to a significant difference in outcome between the 2 treatment groups. One can therefore be confident that the treatment benefit is actually lost at 6 months. As can be seen from table 9.1, there was a significant difference in baseline KHQ scores between the two groups. There were no deviations from the protocol in terms of randomisation, and no significant differences between the groups in any other clinical or demographic parameters (including baseline UPS). This difference is therefore unexplained. This does mean that any interpretation of the quality of life data is unreliable, although post-operative changes in the KHQ domain scores within the two groups may still be reliable. The use of the UPS to assess the primary outcome measure is another potential criticism. The UPS is a 3 point scale which assesses for the presence or absence of pathological urgency or urgency incontinence. It is therefore not able to assess the severity of urgency. However, since the primary aim of this trial was to assess whether UD had any role in relieving urgency or urgency incontinence, it was felt that the use of such a tool was appropriate. Whilst severity scales would have picked up on more subtle improvements in symptoms, it was felt that the UPS would detect cure versus non-cure, thus enabling a good evaluation of UD as a treatment modality. This is a single centre trial, meaning that results should be viewed with caution in terms of generalisability. The latest ICS/IUGA terminology report still does not include a urodynamic definition of voiding dysfunction (Haylen et al, 2010), meaning that other units with differing methods of defining voiding dysfunction may obtain differing results.

Overall, the findings of this prospective, randomised trial are in agreement with the pilot data. Whilst UD does confer a short term benefit in terms of relief of urgency and/or urgency incontinence, this is poorly sustained. This does limit its usefulness as a treatment for women
with OAB symptoms. One may speculate that any beneficial effects seen in either treatment group may be due to distension caused by bladder filling, however the evidence in the literature suggests that even formal cysto-distension has poor efficacy for treating overactive bladder symptoms, making this unlikely (McCahy and Styles, 1995). The presence of a bladder rupture with even a short distension indicates that it is also not without risk. Bladder rupture during cystoscopy is an extremely rare event. This adverse event should be noted since it confirms that even “minor” procedures are not risk free and should be undertaken after careful decision making. This patient was not filled beyond cystoscopic capacity, but one may speculate that more caution with the degree to which a patient is filled at cystoscopy is warranted. The finding of chronic cystitis on a bladder biopsy from this patient may explain this event to some degree. There has been one case report in the literature detailing a bladder rupture during cystoscopy with hydrodistension in a woman with interstitial cystitis (Platte et al, 2011). The relapse in symptoms over longer follow up is in keeping with the soft tissue nature of the urethra, as suggested in the previous chapter. It can be thus postulated that any change in calibre of the urethra effected by UD is temporary, meaning that symptom relief will only be temporary. It is noteworthy that even at 6 weeks, there was no significant change in quality of life in either study group.

This study was not powered to evaluate changes in voiding parameters post-operatively, but the finding of a significant increase in maximum flow rate centile is consistent with the concept that UD does lead to some improvement in voiding parameters, albeit a probable short term improvement. There was no change in voiding pressures following UD; this may be because a change in detrusor muscle function and contractility may not be seen in the short term, whereas an increase in flow would be been as an immediate consequence of the increase in
urethral calibre. As the results from the last chapter suggest, it may be this change which is responsible for symptom improvement. Whilst the benefits of UD are not long term, similar mechanisms may be responsible for the effect of the alpha adrenoreceptor blocker tamsulosin in women. This has been shown to improve voiding and storage symptoms when used either in combination with tolterodine (Kim et al, 2011) or alone (Chang et al, 2008) in women with a flow rate of less than 12 mls/sec.

The rate of de novo USI in the UD group was 9.1%, which is comparable to the pilot data. It is of more interest that there was a 14% rate of de novo USI in the non-UD group. The mechanism of this is unclear. It may be that these cases represent a failure to demonstrate USI on pre-operative urodynamics, rather than true de novo USI.

Whilst the results of this trial fail to support the routine use of UD in the long term management of women with OAB and voiding dysfunction, they do support the concept that strategies to decrease urethral resistance do lead to symptom improvement. It has been reported that women with DO have higher urethral resistance pressures and detrusor opening pressures than women with other urodynamic diagnoses (Digesu et al, 2007). Whilst it is essentially unknown whether this is a cause or effect of underlying DO, the fact that symptoms improve with treatments which aim to decrease urethral resistance suggests that there may be an aetiological basis to the relationship.
Figure 9.1 Flow of participants through the trial

- **Enrollment**
  - Assessed for eligibility n=59
    - Excluded n=9
      - Not meeting inclusion criteria n=6
      - Declined to participate n=3
      - Other reasons n=0

- **Randomized** n=50

  - **Allocation**
    - Allocated to urethral dilatation n=22
      - Received allocated intervention n=22
      - Did not receive allocated intervention n=0
    - Allocated to cystoscopy alone n=28
      - Received allocated intervention n=28
      - Did not receive allocated intervention, n=0

  - **Follow-Up (6 weeks)**
    - Lost to follow-up n=0

  - **Analysis**
    - Analysed n=22
      - Excluded from analysis n=0
    - Analysed n=28
      - Excluded from analysis n=0
Chapter Ten

Conclusions and suggestions for future research
Conclusions

The overall null hypothesis of this thesis was “routine evaluation of the voiding phase of urodynamics is of no value in women with overactive bladder symptoms”. Over the course of the experiments conducted and described in this thesis, evidence has been collected which allows rejection of the null hypothesis, since voiding parameters have been found to be associated with the outcome of the various treatment models studied. Therefore evaluation of voiding parameters in women with OAB symptoms may be of benefit in clinical decision making. These data also suggest that there is an association between voiding and OAB in selected women, although the exact link is uncertain.

The initial study focused on women with OAB undergoing drug treatment with the antimuscarinic solifenacin. Treatment with solifenacin lead to resolution or significant improvement in OAB symptoms in 49% of women with DO only on pre-treatment urodynamics. The response rate was lower in women with mixed DO and USI. In women with isolated DO, non-response to antimuscarinic treatment was found to be associated with a significantly lower pre-treatment Q_{max} than in responders. There was no significant difference in voided volume or P_{det}Q_{max} in responders versus non-responders. This association between Q_{max} and treatment response was not seen in women with mixed DO and USI, possibly because voiding parameters in women with mixed incontinence are intermediate between those with DO and those with USI. The actual difference in flow rate values between responders and non-responders was small (18.7 versus 14.2 ml/sec), which makes clinical relevance less certain. This association does however suggest a possible role for increased urethral resistance in the pathophysiology of OAB, and may explain why certain women do not respond to antimuscarinic therapy as one would expect.
The next two chapters used women with pelvic organ prolapse as a model for increased urethral resistance in order to study the effect of attempting to improve voiding on OAB symptoms. Chapter six detailed a retrospective cohort study of women with anterior compartment prolapse and OAB, who had previously undergone an anterior repair. The women were followed up with a symptom assessment and cystometry, with a mean time to follow up of 30 months. The cure rate for OAB following anterior repair was 53%, with cure being associated with a significant increase in $Q_{\text{max}}$ and a significant decrease in opening detrusor pressure following surgery. There was also a significant fall in BOO-I post-operatively in women cured of OAB, although neither responders nor non-responders were clinically obstructed at baseline. This, together with the fact that there were no significant baseline differences in voiding parameters, suggests that it is the change in voiding effected by an anterior repair which is a marker of importance in symptom resolution. This retrospective study was followed up by a larger, prospective study which was powered to evaluate changes in voiding following a prolapse repair. Symptom relief was again found to be associated with a significant improvement in $Q_{\text{max}}$ (from 11.8 to 26.2 ml/sec), supporting the concept that restoration of anatomy in prolapse repair leads to an improvement in voiding which is in turn associated with relief of OAB symptoms.

Repair of prolapse cannot be said to effect a “direct” change on urethral resistance. One can evaluate voiding parameters as surrogate markers of alterations in voiding following a repair, but intra-operatively, it is not possible to assess whether the repair itself will lead to a decrease in urethral resistance. Chapter eight evaluated outcomes in women with OAB and voiding dysfunction (i.e. a selected group with pre-existing difficulties emptying) undergoing urethral dilatation, which is an intervention designed to cause a “direct” effect on urethral resistance.
Evaluation of this cohort identified a 33% improvement in OAB symptoms at 6 weeks, which fell to 19% at 6 months, and was associated with a 13% risk of de novo USI at 6 weeks. Symptomatic improvement was associated with a significant increase in maximum flow rate centile and a significant decrease in $P_{\text{det}}Q_{\text{max}}$, with persistence of symptoms being associated with no significant change in voiding parameters. It would appear in this cohort that successful attempts to reduce urethral resistance are associated with improvement in OAB symptoms. The value of urethral dilatation as an intervention for women with OAB and voiding dysfunction was subsequently explored in chapter nine, which detailed a randomised controlled trial of urethral dilatation and cystoscopy versus cystoscopy alone in such women. This trial identified a significantly higher cure rate for OAB in women undergoing urethral dilatation in the short term, but no significant long term benefits. These results are of interest in terms of possible aetiological associations between OAB and voiding, since they suggest that strategies to decrease urethral resistance will lead to an improvement in OAB symptoms. However the clinical relevance of this is limited as there is no evidence for a long term effect, which is likely to be due to the soft tissue nature of the urethra, with any increase in urethral calibre being transient.

Overall, the evidence presented in this thesis does suggest an association between voiding parameters and OAB, with lower Qmax being associated with non-response to drug treatments and strategies aiming to improve voiding and achieving an increase in flow rates with or without a reduction in voiding pressures (reflecting a possible decrease in urethral resistance) being associated with symptomatic improvement.

This association does not prove causation however, and the possible aetiological relationship between voiding and OAB is worthy of further study. There may be multiple pathophysiology implicated in the development of OAB symptoms. Because of this fact, the
evidence presented in this thesis cannot be used to endorse strategies to decrease urethral resistance as a treatment for OAB. From an academic viewpoint however, the associations presented here are worthy of further investigation. The concept of an improvement in voiding leading to an improvement in OAB symptoms requires a mechanism via which symptom improvement is effected. Until this pathway is investigated, any associations between voiding and OAB will remain just associations. It is possible that voiding is a surrogate biomarker for some other underlying process which is more directly linked with OAB, and the future challenge is to identify this underlying process.

Overall however, the finding of these associations does imply that routine evaluation of the voiding phase of urodynamics is of value in women with overactive bladder symptoms.

**Suggestions for future research**

Evaluation of voiding parameters in much larger populations of women with OAB being treated with antimuscarinics may allow the modelling of threshold values below which treatment failure is more likely.

- Complete voiding data for populations of over 1000 women
- Model with Receiver Operating Characteristic curves to identify if there is a threshold for treatment failure

3D ultrasound imaging of the urethra could be used to assess whether any relationship between urethral morphology, voiding parameters and response to drug treatment exists, with the aim as before of assessing predictive factors for treatment response to antimuscarinics.
- Perineal ultrasound with rendered 3D and 4D images to evaluate factors such as urethral length, urethral width, longitudinal smooth muscle thickness, presence of urethral hypermobility, and retrovesical angle.

2D ultrasound imaging of bladder and urethral morphology pre- and post-prolapse repair could be evaluated with voiding parameters and symptoms to assess the actual changes in anatomy which are associated with relief of OAB symptoms in women undergoing prolapse repair, as well as to determine if the anatomical relationship between the bladder neck and urethra prior to surgery is predictive of an effect on OAB symptoms.

Evaluation of urothelial markers following prolapse repair in women with OAB, in order to assess whether resolution of symptoms is mediated eventually via an afferent pathway.

- Assay of candidate markers from urine/bladder wall biopsies (such as ATP, NO, NGF) before and after prolapse repair
- Symptom questionnaires to assess for improvement in OAB symptoms
- Evaluation of any differences in baseline urothelial markers or change in levels of markers post-operatively, between responders and non-responders.
- Association between urothelial markers and changes in voiding parameters

Evaluation of urethral function pre- and post-prolapse repair, in order to correlate possible changes in urethral function with subjective outcomes (i.e. using urethral pressure profilometry to assess urethral function)
References


Parsons M, Amundsen C, Cardozo L, Vella M, Webster G, Coats A; Bladder Diary Research Team. *Neurourol Urodyn** **26**: 800-806


Robinson D, Cardozo L, Terpstra G, Bolodeoku J; Tamsulosin Study Group (2007). A randomized, double-blind placebo controlled multicentre study to explore the efficacy and safety
of tamsulosin and tolterodine in women with overactive bladder syndrome. *BJU Int* 100: 840-845


phenylethyl)amino]ethyl}acetanilide (YM178), a novel selective beta 3-adrenoreceptor agonist, on bladder function. *J Pharmacol Exp Ther* **321**: 642-647


### Appendix I: Abbreviations Used In Text

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACh</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine Triphosphate</td>
</tr>
<tr>
<td>BOO</td>
<td>Bladder Outlet Obstruction</td>
</tr>
<tr>
<td>BOO-I</td>
<td>Bladder Outlet Obstruction Index</td>
</tr>
<tr>
<td>BoNT-A</td>
<td>Botulinum Neurotoxin Type A</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>cAMP</td>
<td>Cyclic Adenosine Monophosphate</td>
</tr>
<tr>
<td>DO</td>
<td>Detrusor overactivity</td>
</tr>
<tr>
<td>ER</td>
<td>Extended release</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>ICS</td>
<td>International Continence Society</td>
</tr>
<tr>
<td>IR</td>
<td>Immediate Release</td>
</tr>
<tr>
<td>ISC</td>
<td>Intermittent Self Catheterisation</td>
</tr>
<tr>
<td>IUGA</td>
<td>International Urogynecology Association</td>
</tr>
<tr>
<td>KHQ</td>
<td>King’s Health Questionnaire</td>
</tr>
<tr>
<td>NGF</td>
<td>Nerve Growth Factor</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric Oxide</td>
</tr>
<tr>
<td>OAB</td>
<td>Overactive Bladder (syndrome)</td>
</tr>
<tr>
<td>PDE</td>
<td>Phosphodiesterase</td>
</tr>
<tr>
<td>P_{det}Q_{max}</td>
<td>Detrusor Pressure at Maximum Flow</td>
</tr>
<tr>
<td>PFMT</td>
<td>Pelvic Floor Muscle Training</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PGE2</td>
<td>Prostaglandin E2</td>
</tr>
<tr>
<td>PGI-I</td>
<td>Patient Global Impression of Improvement</td>
</tr>
<tr>
<td>PTNS</td>
<td>Posterior tibial nerve stimulation</td>
</tr>
<tr>
<td>ODP</td>
<td>Opening Detrusor Pressure</td>
</tr>
<tr>
<td>Q_{max}</td>
<td>Maximum Flow Rate</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
</tr>
<tr>
<td>RTX</td>
<td>Resiniferatoxin</td>
</tr>
<tr>
<td>SNS</td>
<td>Sacral Nerve Stimulation</td>
</tr>
<tr>
<td>Acronym</td>
<td>Full Form</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single Photon Emission Computerised Tomography</td>
</tr>
<tr>
<td>TRPV1</td>
<td>Transient Receptor Potential Vanilloid 1</td>
</tr>
<tr>
<td>TURP</td>
<td>Transurethral Resection of the Prostate</td>
</tr>
<tr>
<td>TVT</td>
<td>Tension Free Vaginal Tape</td>
</tr>
<tr>
<td>SUI</td>
<td>Stress Urinary Incontinence</td>
</tr>
<tr>
<td>UPP</td>
<td>Urethral Pressure Profile</td>
</tr>
<tr>
<td>UPS</td>
<td>Urgency Perception Scale</td>
</tr>
<tr>
<td>URP</td>
<td>Urethral Resistance Pressure</td>
</tr>
<tr>
<td>USI</td>
<td>Urodynamic Stress Incontinence</td>
</tr>
</tbody>
</table>
Appendix II: Patient Global Impression of Improvement (PGI-I) and King’s Health Questionnaire

Patient Global Impression of Improvement

Circle the one number which best describes how your bladder condition is now, compared to how it was before you began treatment:

1. Very much better
2. Much better
3. A little better
4. No change
5. A little worse
6. Much worse
7. Very much worse

The Patient Global Impression scales were first developed to measure incontinence severity prior to treatment for stress urinary incontinence, as well as improvement after treatment. Two scales were originally developed: severity (PGI-S) and improvement (PGI-I). The PGI-I was shown to be a sensitive indicator of improvement in symptoms of stress incontinence, as judged by other markers (bladder diary parameters, pad test loss, quality of life instruments) (Yalcin and Bump, 2003). The simplicity of these scales has lead to them being widely adopted as outcome tools in clinical studies, and they have now been also validated for use in the context of pelvic organ prolapse (Srikrishna et al, 2010) as well as DO (Tincello et al, 2013).

In women with OAB, Tincello et al used 6 week follow-up data from 192 women being treated with onabotulinum toxin or placebo, to assess the validity of the PGI-I. Responses demonstrated significant associations with magnitude of change across a variety of instruments including bladder diary variables and disease-specific quality of life questionnaires, indicating good validity with improvement after treatment in women with DO (Tincello et al, 2013).
The King’s Health Questionnaire

1. How would you describe your health at the present?

Please tick one answer

- Very good
- Good
- Fair
- Poor
- Very poor

2. How much do you think your bladder problem affects your life?

Please tick one answer

- Not at all
- A little
- Moderately
- A lot

Please turn the page
Below are some daily activities that can be affected by bladder problems.
How much does your bladder problem affect you?

We would like you to answer every question. Simply tick the box that applies to you

### 3. ROLE LIMITATIONS

<table>
<thead>
<tr>
<th>Question</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Does your bladder problem affect your household tasks? (cleaning, shopping etc)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>B. Does your bladder problem affect your job, or your normal daily activities outside the home?</td>
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</tbody>
</table>

### 4. PHYSICAL/SOCIAL LIMITATION

<table>
<thead>
<tr>
<th>Question</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Does your bladder problem affect your physical activities (e.g. going for a walk, running, sport, gym etc)?</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>B. Does your bladder problem affect your ability to travel?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. Does your bladder problem limit your social life?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D. Does your bladder problem limit your ability to see and visit friends?</td>
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</tbody>
</table>

### 5. PERSONAL RELATIONSHIPS

<table>
<thead>
<tr>
<th>Question</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Does your bladder problem affect your relationship with</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
your partner?

B. Does your bladder problem affect your sex life?

C. Does your bladder problem affect your family life?

1                  2                    3                    4

6. EMOTIONS

Not at all      Slightly      Moderately    Very much

A. Does your bladder problem make you feel depressed?

B. Does your bladder problem make you feel anxious or nervous?

C. Does your bladder problem make you feel bad about yourself?

1                  2                  3                    4

7. SLEEP/ENERGY

Never      Sometimes      Often        All the time

A. Does your bladder problem affect your sleep?

B. Does your bladder problem make you feel worn out and tired?

1 2 3 4

8. Do you do any of the following?

If so how much?

1 Never

A. Wear pads to keep dry?
B. Be careful how much fluid you drink?

C. Change your underclothes because they get wet?

D. Worry in case you smell?

We would like to know what your bladder problems are and how much they affect you? From the list below choose only those problems that you **have at present**, Leave out those that don’t apply to you.

**How much do they affect you?**

**FREQUENCY**: going to the toilet very often

<table>
<thead>
<tr>
<th>1. A little</th>
<th>2. Moderately</th>
<th>3. A lot</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

**NOCTURIA**: getting up at night to pass urine

<table>
<thead>
<tr>
<th>1. A little</th>
<th>2. Moderately</th>
<th>3. A lot</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

**URGENCY**: a strong and difficult to control desire to pass urine

<table>
<thead>
<tr>
<th>1. A little</th>
<th>2. Moderately</th>
<th>3. A lot</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

**URGE INCONTINENCE**: urinary leakage associated with a strong desire to pass urine

<table>
<thead>
<tr>
<th>1. A little</th>
<th>2. Moderately</th>
<th>3. A lot</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>
**STRESS INCONTINENCE:** urinary leakage with physical activity eg. coughing, running

<table>
<thead>
<tr>
<th>1. A little</th>
<th>2. Moderately</th>
<th>3. A lot</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

**NOCTURNAL ENURESIS:** wetting the bed at night

<table>
<thead>
<tr>
<th>1. A little</th>
<th>2. Moderately</th>
<th>3. A lot</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**INTERCOURSE INCONTINENCE:** urinary leakage with sexual intercourse

<table>
<thead>
<tr>
<th>1. A little</th>
<th>2. Moderately</th>
<th>3. A lot</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**WATERWORKS INFECTIONS**

<table>
<thead>
<tr>
<th>1. A little</th>
<th>2. Moderately</th>
<th>3. A lot</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**BLADDER PAIN**

<table>
<thead>
<tr>
<th>1. A little</th>
<th>2. Moderately</th>
<th>3. A lot</th>
</tr>
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</table>

The King’s Health Questionnaire (KHQ) was developed with the aim of assessing disease specific quality of life in women with urinary incontinence (Kelleher et al, 1997). In a validation study using 293 consecutive women with urinary incontinence, the KHQ demonstrated good reliability and internal consistency, as well as a consistent correlation with scores obtained using generic quality of life instruments (Kelleher et al, 1997). Usage of a short form of the KHQ has also been described (Homma and Uemura, 2004), however all relevant studies in this thesis used the full version.

The scoring system is given below. Domain scores are calculated out of 100, with a higher score indicating a higher degree of quality of life impairment. A minimally important
difference of 10 to 15 points for a medium treatment effect and 5 to 6 points for a small effect has been calculated (Kelleher et al, 2004).

PART 1

1) General Health Perceptions

<table>
<thead>
<tr>
<th>Health Perception</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>1</td>
</tr>
<tr>
<td>Good</td>
<td>2</td>
</tr>
<tr>
<td>Fair</td>
<td>3</td>
</tr>
<tr>
<td>Poor</td>
<td>4</td>
</tr>
<tr>
<td>Very poor</td>
<td>5</td>
</tr>
</tbody>
</table>

Score = ((Score to Q1 – 1)/4) x 100

2) Incontinence Impact

<table>
<thead>
<tr>
<th>Impact Level</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>1</td>
</tr>
<tr>
<td>A little</td>
<td>2</td>
</tr>
<tr>
<td>Moderately</td>
<td>3</td>
</tr>
<tr>
<td>A lot</td>
<td>4</td>
</tr>
</tbody>
</table>

Score = (Score to Q2 – 1)/3) x 100

PART 2

Individual scores as recorded at the top of each column of possible responses

3) Role limitations

Score =(((Scores to Q 3A + 3B) – 2)/6) x 100

4) Physical limitations

Score =(((Scores to Q 4A + 4B) – 2)/6) x 100
5) Social limitations

[If 5C >= 1] Score =[((Score to Q 4C + 4D + 5C) − 3)/9] X 100
[If 5C = 0] Score =[((Score to Q 4C + 4D) − 2)/6] x 100

6) Personal relationships

[If 5A+5B >=2] Score =(((Scores to Q 5A + 5B) − 2)/6) x 100
[If 5A+5B =1] Score =(((Scores to Q 5A + 5B) − 1)/3) x 100
[If 5A+5B =0] Treat as missing value

7) Emotions

Score =(((Score to Q 6A + 6B + 6C) − 3)/9) X 100

8) Sleep / energy

Score =(((Scores to Q 7A + 7B) − 2)/6) x 100

9) Severity measures

Score =(((Scores to Q 8A + 8B + 8C + 8D) − 4)/12) x 100

PART 3

<table>
<thead>
<tr>
<th>Scale</th>
<th>score</th>
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</thead>
<tbody>
<tr>
<td>Omitted</td>
<td>0</td>
</tr>
<tr>
<td>A little</td>
<td>1</td>
</tr>
<tr>
<td>Moderately</td>
<td>2</td>
</tr>
<tr>
<td>A lot</td>
<td>3</td>
</tr>
</tbody>
</table>