## Committee 4

# Pathophysiology of Urinary Incontinence, Faecal Incontinence and Pelvic Organ Prolapse


**Chairman**

*H. Koelbl (Germany)*

*V. Nitti (USA)*

**Members**

*K. Baessler (Germany),*

*S. Salvatore (Italy),*

*A. Sultan (U.K),*

*O. Yamaguchi (Japan)*

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| ACS | American College of Surgeons |
| ANS | Autonomic Nervous System |
| ACh | Acetylcholine |
| AChE | Acetylcholinesterase |
| ASR | Anal Sphincter Rupture |
| ATP | Adenosine Triphosphate |
| BPH | Benign Prostatic Hyperplasia |
| BPO | Benign Prostatic Obstruction |
| CNS | Central Nervous System |
| CI | Confidence Interval |
| cAMP | Cyclic Adenosine Monophosphate |
| DO | Detrusor Overactivity |
| DM | Diabetes Mellitus |
| DSD | Detrusor Sphincter Dyssynergia |
| EMG | Electromyography |
| EAS | External Anal Sphincter |
| IBD | Inflammatory Bowel Disease |
| IBS | Irritable Bowel Syndrome |
| IAS | Internal Anal Sphincter |
| ICI | International Consultation on Incontinence |
| IPSS | International Prostate Symptom Score |
| ISD | Intrinsic Sphincter Deficiency |
| LUTS | Lower Urinary Tract Symptoms |
| MRI | Magnetic Resonance Imaging |
| MS | Multiple Sclerosis |
| NO | Nitric Oxide |
| NOS | Nitric Oxide Synthase |
| NGF | Nerve Growth Factor |
| OAB | Overactive Bladder |
| PMC | Pontine Micturition Center |
| PFD | Pelvic Floor Dysfunction |
| POP | Pelvic Organ Prolapse |
| POPQ | Pelvic Organ Prolapse Quantitation |
| PNTML | Pudendal Nerve Motor Terminal Motor Latency |
| RRP | Radical Retropubic Prostatectomy |
| RCOG | Royal College of Obstetricians and Gynaecologists |
| SSRI | Selective Serotonin Re-uptake Inhibitor |
| STRESS URINARY INCONTINENCE | Stress Urinary Incontinence |
| TURP | Transurethral Prostatectomy |
| TUIP | Transurethral Incision of the Prostate |
| TTX | Tetrodotoxin |
| VLPP | Valsalva Leak Point Pressure |
| USI | Urodynamic Stress Incontinence |

# Pathophysiology of Urinary Incontinence, Faecal Incontinence and Pelvic Organ Prolapse

*H. Koelbl, V. Nitti,*
*K. Baessler, S. Salvatore, A. Sultan, O. Yamaguchi*

## PREFACE

For this fourth International Consultation on Incontinence, the Committee on Pathophysiology is organized to consider causes of pelvic prolapse and faecal, as well as urinary incontinence. For any woman, childbirth and pregnancy contribute to the development of urinary as well as faecal incontinence; therefore these two conditions have been naturally integrated into a single chapter. Special problems of the elderly have also been included for this ICI. We have also been asked to consider pathophysiological mechanisms underlying pelvic organ prolapse. These three areas urinary incontinence, pelvic organ prolapse and faecal incontinence, are closely interconnected by virtue of similar location within the body. In the case of women, childbirth and pregnancy may contribute to one or all of these conditions. Yet there are also neurological factors, and gender specific factors which must be considered in the evaluation of any given patient. Thus, we have tried to provide a balanced overview of the subject, keeping in mind both the common and the distinct qualities of the various conditions, while organizing them in a logical, narrative manner that make any one section of the chapter easy to read.

In the area of women's stress incontinence, intrinsic urethral function continues to receive increased attention. As newer pharmacological agents to provide neural stimulation of the striated sphincter appear, and the limits of vaginal suspensory operations for correction of urethral dysfunction are reported, considerations of pathophysiology have shifted from the 50 year old paradigm regarding urethral mobility associated with vaginal prolapse in the genesis of incontinence. However, these newer directions should be considered against the background of half a century of observation and practical clinical experience. We therefore continue to recommend a balanced approach.

In the area of men's incontinence, the greatest concern remains the problem of sphincter injury following radical pelvic surgery and brachytherapy. While many thousands of procedures are performed annually, our knowledge about sphincter anatomy and function has progressed little. Instead, empirical methods of treatment and hopefully prevention have been advanced to treat affected individuals, and insofar as prosthetic implants remain an effective method of treatment, enthusiasm for further basic research into male sphincter function remains limited. In contrast to this kind of sphincter injury, the causes of incontinence associated with bladder outlet obstruction and prostatic enlargement have been well characterized, and little new knowledge has appeared in recent years. Finally, with respect to faecal incontinence and pelvic organ prolapse, two areas for this Committee's concern, the sections addressing them may appear to provide some overlap and possible redundancy.

# A. THE OVERACTIVE BLADDER

## I. INTRODUCTION

The most common problem with urine storage arises when the bladder fails to remain relaxed until an appropriate time for micturition. The symptom syndrome is called "overactive bladder"(OAB), which refers to the symptoms of urgency, with or without urge incontinence, usually with frequency and nocturia [1]. According to the ICS terminology of 2002 [1], OAB symptoms are suggestive, but not diagnostic, of urodynamically demonstrable detrusor overactivity (involuntary detrusor contraction) during the filling phase which may be spontaneous or provoked. This may be further characterized as neurogenic when there is a relevant neurological condition. Common neurogenic causes include stroke, Parkinson's disease, multiple sclerosis and spinal injury. Non-neurogenic etiologies may be related to outflow obstruction, aging estrogen deficiency, female anatomical incontinence, but most cases are idiopathic. This section focuses on pathophysiology of the overactive bladder and reviews studies that have provided insight into the mechanisms underlying bladder overactivity and OAB symptoms.

## II. NEUROGENIC DETRUSOR OVERACTIVITY

### 1. SUPRAPONTINE LESIONS (Figure1)

It is generally accepted that suprapontine lesions such as cerebrovascular disease and Parkinson's disease produce detrusor overactivity. The patient with a suprapontine lesion loses voluntary inhibition of micturition, which corresponds to uninhibited overactive bladder according to a classification by Fall et al [2, 3].

Brain transaction studies in animals with an intact neuroaxis showed that suprapontine areas generally exert a tonic inhibitory influence on the pontine micturition center (PMC) [4, 5]. In humans, the cerebral cortex (medial frontal lobes) and the basal ganglia are thought to suppress the micturition reflex. Thus, damage to the brain induces bladder overactivity by reducing suprapontine inhibition.

The mechanism of overactive bladder induced by cerebral infarction or Parkinson's disease has been further studied using animal models [6-8]. In the central nervous system, a glutamatergic pathway is known to play a role in both excitatory and inhibitory regulation of micturition [6, 9, 10]. Central dopaminergic pathways also have dual excitatory and inhibitory influences on reflex bladder activity [11]. It has been demonstrated that in the rat cerebral infarction model, bladder overactivity is mediated by NMDA glutamatergic and D2 dopaminergic excitatory mechanisms [8], suggesting that cerebral infarction may alter a balance between the facilitatory and inhibitory mechanism that results in up regulation of an excitatory pathway and downregulation of a tonic inhibitory pathway. Similarly, neuropharmacological studies in a monkey model for Parkinson's disease have shown that detrusor overactivity may result from a loss of dopaminergic inhibition mediated by D1 receptors [4, 7].

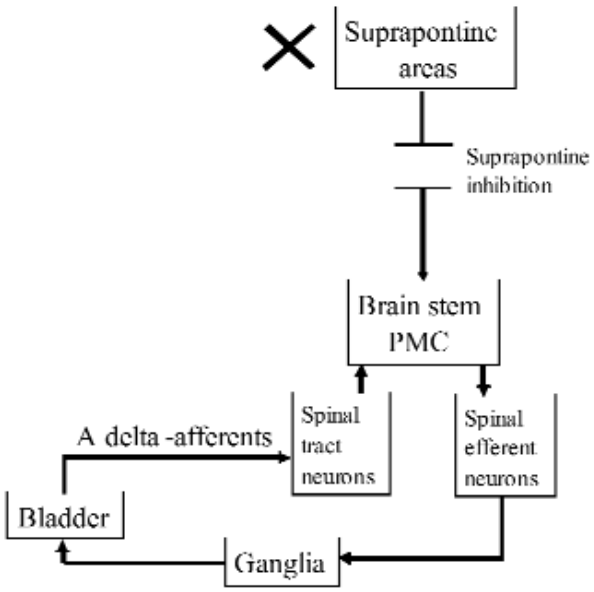


***Figure 1: Suprapontine lesions causing detrusor overactivity***

### 2. SPINAL CORD LESIONS (Figure 2)

A spinal cord lesion above the lumbosacral level eliminates voluntary and supraspinal control of micturition, leading to bladder overactivity mediated by spinal reflex pathways [4, 12]. Disruption below the level of the pons leads to unsustained and uncoordinated detrusor contractions often associated with uncoordinated sphincter overactivity (detrusor-sphincter dyssynergia, DSD). Impairment or loss of bladder sensation is a typical feature.

Electrophysiologic studies of the effect of capsaicin on voiding reflexes have shown that the afferent limb of the micturition reflex in chronic spinal cats, consists of unmyelinated C-fibre afferents, whereas in normal cats it consists of myelinated A-delta afferents [4, 13, 14]. Since C-fibre bladder afferents in the cat do not usually respond to bladder distension [15], a considerable reorganization of reflex connections takes place in the spinal cord following the interruption of descending pathways from the brain. In humans with spinal cord lesions, neurogenic detrusor overactivity

is likely to be mediated by capsaicin-sensitive C-fibre afferents. Clinical experience with capsaicin supports the role of these C-fibre afferents in the pathophysiology of neurogenic bladder overactivity. Capsaicin has been used for the treatment of neurogenic bladder overactivity in patients with spinal cord injury or multiple sclerosis. When administered intravesically, capsaicin increases bladder capacity, reduces micturition contraction pressure, decreases autonomic dysreflexia and reduces the frequency of incontinence [16-18]. More recently, resineferatoxin, an ultra-potent analogue of capsaicin, has been also used [19, 20].

In addition to changes in reflex pathways (i.e., C-fibre afferent-mediated micturition reflex), it has been demonstrated that a functional outlet obstruction resulting from DSD may alter the properties of bladder afferent neurons. For example, in chronic spinal animals, afferent neurons innervating the bladder increase in size, a change prevented by urinary diversion [21]. These observations suggest that some factors released in the obstructed bladder may be responsible for the neural change. Subsequently, the factors have been identified as nerve growth factor (NGF) [22].

Another type of plasticity in C-fibre bladder afferent neurons is evident as a change in excitability. Whole cell-patch clamp recordings have shown that hypertrophied bladder afferent neurons exhibit increased excitability due to a shift in expression of sodium channels from high-threshold Tetrodotoxin (TTX) resistant to low-threshold TTX-sensitive channels [23, 24]. In normal animals, TTX-resistant sodium channels are mainly expressed in C-fibre afferent neurons [25, 26].

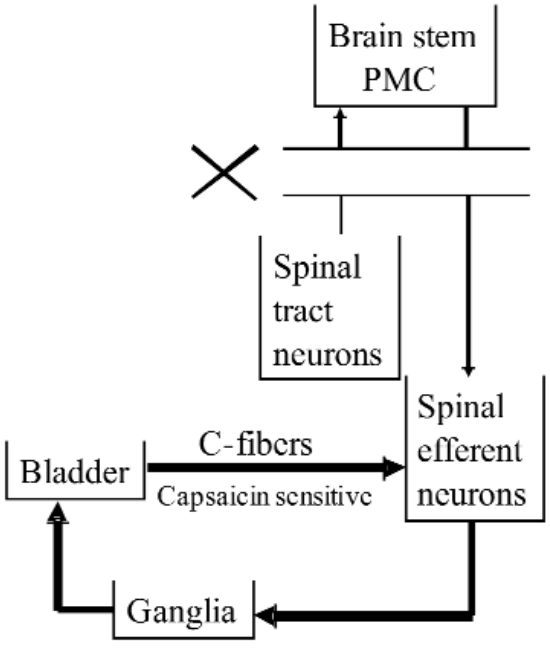


*Figure 2: Spinal cord lesions causing detrusor overactivity*

## III. NON-NEUROGENIC DETRUSOR OVERACTIVITY

### 1. OUTFLOW OBSTRUCTION (Figure 3)

Detrusor overactivity associated with outflow obstruction has long been recognized [27]. A recent study shows that approximately 50% of patients with symptomatic benign prostatic enlargement exhibit bladder outlet obstruction [28]. However, detrusor overactivity and OAB symptoms often occur independently of bladder outlet obstruction. Thus, detrusor overactivity and OAB symptoms in the male patients may result from outflow obstruction or a primary bladder abnormality [29]. The following review focuses on studies supporting outflow obstruction as the causative factor for detrusor overactivity.

#### *a) Partial denervation*

The hypothesis that denervation underlies obstructed non-neurogenic detrusor overactivity comes from the morphological studies of Gosling et al [30]. They demonstrated a reduction in acetylcholine esterase (AChe) staining nerves in obstructed human bladder muscle. Pharmacological studies performed on detrusor biopsies from patients with bladder outlet obstruction [31] have shown that muscle strips from patients with detrusor overactivity exhibit denervation supersensitivity to acetylcholine (the main excitatory neurotransmitter to the human bladder) and a reduction in nerve-mediated responses, as compared with strips from normal, stable bladder. Similar pharmacological and morphological evidences of denervation have been shown in studies using animal models of detrusor overactivity caused by urethral obstruction [32-34], demonstrating that there were significant increases in sensitivity to acetylcholine and other agonists such as high potassium, and the response to intramural nerve stimulation was significantly reduced (despite increased responsiveness of the muscle to exogenous acetylcholine), with both cholinergic and non-cho-

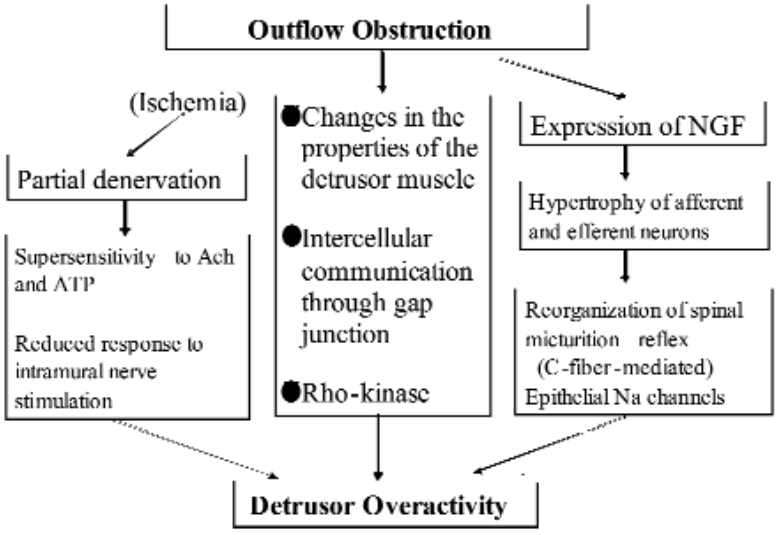


*Figure 3: Outflow obstruction causing detrusor overactivity*

linergic (purinergic) neurotransmission being affected. These changes suggest a post-functional supersensitivity secondary to partial denervation of the obstructed detrusor muscle, and may be the basis of unstable bladder behaviour.

However, it is not clear how denervation develops in outflow obstruction. One possibility is that there is a reduction of blood flow due to the effect of raised intravesical pressure during voiding or the increased tissue pressure of hypertrophied bladder wall during filling. Such haemodynamic change has been demonstrated in a canine model of outlet obstruction [35]. Greenland and Brading also showed that bladder outflow obstruction is associated with repeated episodes of prolonged detrusor ischemia in pigs [36]. Thus, the role of ischemia in changes in bladder function and structure following outlet obstruction has been well characterized. A more recent study using iNOS knockout mice [37] suggests that generation of NO soon after obstruction is necessary to prevent detrusor dysfunction, since NO produces vasodilatation and decreases platelet aggregation.

### *b) Changes in detrusor muscle contractility*

Obstruction can alter the properties of the detrusor muscle. In the obstructed guinea pig bladder, the detrusor muscle shows a decrease in force development, suggesting a deterioration in detrusor contractility [38]. The cable properties of detrusor cells are also changed [39]. The length constant is reduced, suggesting a decrease in cell to cell propagation of electrical activity. The time constant of the cell membrane is prolonged, leading to greater instability of membrane potential. This may facilitate depolarization of the cell and activate L-type calcium channels. Such a mechanism could be further amplified by depolarizing currents supplied by a purinergic system, which has been shown to emerge in human obstructed bladder [40]. These findings suggest that, in general, individual cells are more irritable while synchronous activation is damaged, findings that are consistent with the abnormal bladder behaviour of obstructed bladder, i.e., the decreased contractility coexisting with bladder overactivity. In this respect, the changes in intercellular communication through gap junction have been evaluated. Gap junction protein, connexin 43(C?43) was shown to decrease in rat detrusor muscle with chronic partial bladder outlet obstruction [41]. However, other studies indicate that connexin mRNA and C?43 protein are increased in a rat model of bladder overactivity induced by outflow obstruction [42, 43].

Recently, a role of Rho-kinase in obstruction-induced changes in detrusor muscle contractility has received attention. One main pathway for inhibition of myosin light chain phosphatase and indication of $Ca^{2+}$ sensitization involves a specific kinase(Rho-kinase), which is activated by RhoA via G-protein coupled receptors [44-46]. $Ca^{2+}$ sensitization, mediated by the Rho A/Rho-kinase pathway, enables the detrusor muscle to contract at low intracellular $Ca^{2+}$ concentration. It has been demonstrated that partial bladder outlet obstruction increased the expression of RhoA and Rho-kinase in rabbits [47, 48]. This upregulation of Rho-kinase may contribute to increased detrusor muscle tone or sustained contraction induced by the different contractile transmitter/mediators in the obstructed bladder [47, 49, 50].

### *c) C-fibre-mediated micturition reflex*

A different interpretation for the mechanism underlying the development of detrusor overactivity is a possible reorganization of spinal micturition reflexes following outlet obstruction. Partial urethral ligation in a rat model results in hypertrophy of bladder afferent as well as efferent neurons [22, 51]. This hypertrophy of bladder neurons is accompanied by increased expression of NGF in the bladder as well as in sacral autonomic centres [52], leading to facilitation of the spinal micturition reflex [22, 52]. Similarly, in patients with outflow obstruction, a spinal reflex may be responsible for the development of detrusor overactivity. This reflex is thought to be mediated by C-fibres and clinically detected as a positive response to the ice water test. C-fibre neurons are also known to contain tachykinin and other peptides as neurotransmitters. It has been suggested that in rats with bladder outlet obstruction, tachykinins can influence via NK receptors both the spinal and supraspinal control of the bladder [53, 54].

With regard to the possible mechanisms for activation of afferent C-fibre nerves, Araki et al suggest a role for the epithelial sodium channel(ENaC) expressed in human urinary bladder urothelium [55]. They found that the expression levels of alpha-ENaC, beta-ENaC and gamma-ENaC were significantly greater in the obstructed bladders than those in controls. In addition, the quantified ENaC expression was shown to correlate significantly with the storage symptom score. Thus, the ENaC expressed in the bladder urothelium might be implicated in the mechanosensory transduction in the bladder afferent pathway, thereby inducing detrusor overactivity by outflow obstruction [55].

## 2. AGING

Major epidemiologic studies [56-58] indicate that the prevalence of OAB in both men and women increases with age. A study of men and women without underlying disease causing micturition disorder shows that storage symptom scores also increase with age, suggesting that bladder function in both sexes is subject to common age related alterations [59]. However, in the elderly, the boundaries between neurogenic and non-neurogenic are uncertain, since age associated neurogenic diseases such as subclinical cerebrovascular disorders, autonomic neuropathy and chronic brain failure commonly occur.

Computerized tomography, magnetic resonance imaging or functional brain imaging sometimes can detect the presence of cerebral lesions in elderly patients with detrusor overactivity [60, 61]. This may distinguish neurogenic from idiopathic detrusor overactivity in a considerable number of older patients.

With regard to aging-related detrusor overactivity, Elbadawi et al. have proposed a possible explanation based on detailed ultrastructural study [62-64]. Electron microscopic findings of detrusor biopsies have revealed a characteristic structural pattern in specimens from the elderly with detrusor overactivity. The main ultrastructural features of this dysfunctional pattern were abundant distinctive protrusion junctions and abutments which it was proposed mediated electrical coupling between the muscle cells and were involved in generation of myogenic contraction in the overactive bladder. In addition, if the patients had impaired detrusor contractility, there was superimposed widespread degeneration of muscle cells and nerve axons, which matched the special group of elderly patients with DO (Detrusor Overactivity) [65].

Age-dependent alterations in detrusor function have also been evaluated. Cystometry in conscious rats shows that bladder compliance decreases with aging [66]. In the rat detrusor muscle, the relaxant response to noradrenalin or isoproterenol has been shown to decrease with age, a change which may be related to decreased density of beta-adrenoceptors and decreased cyclic adenosine Monophosphate (cAMP) production [67]. In addition, age-related changes in cholinergic and purinergic neurotransmission have been studied recently in human detrusor muscle, showing that during electrical nerve stimulation, acetylcholine (Ach) release is decreased while ATP release is increased with aging [68, 69]. These changes in neurotransmission may contribute to the changes in bladder function in the elderly.

## 3. ESTROGEN DEFICIENCY

Lower urinary tract symptoms (LUTS) are common in elderly women. Menopause and subsequent estrogen deficiency have been implicated in the etiology of LUTS such as OAB symptoms. There have been few controlled trials to confirm the impact of -estradiol $\alpha$estrogen therapy on OAB. However, in a placebo-controlled trial of 17 vaginal tablets, the LUTS of frequency, urgency and urge incontinence significantly improved in the estradiol-treated group [70]. A meta-analysis of the effects of estrogen therapy on symptoms suggestive of OAB in postmenopausal women also showed that estrogen therapy was associated with significant improvements in all symptoms of OAB [71]. These studies suggest that the menopause at least has a significant role in the development of bladder overactivity and OAB symptoms.

Estrogen receptors (ERs) have been identified in the bladder and urethra [72, 73]. The mechanisms producing the effects of estrogen on bladder function have yet to be elucidated, but estrogen can influence bladder contractility in animals [74]. Particularly, bladder compliance has been to decrease with estrogen deprivation [75-77]. The effects of oophorectomy and estrogen replacement on the function of Rho-kinase in rat bladder smooth muscle have been investigated, demonstrating that estrogen might inhibit the function of Rho-kinase in bladder smooth muscle [78]. Since Rho-kinase plays an important role in the regulation of detrusor muscle tone [49, 50], this finding suggests that if estrogen deficiency results in increased Rho-kinase activity, detrusor muscle tone increases, thereby decreasing bladder compliance: features suggestive of bladder overactivity. In addition, a recent study [79] of the female rat bladder showed that as a result of estrogen deficiency, stretch-induced acetylcholine(Ach) release possibly from the urothelium increased, which may be a contributing factor to the development of detrusor overactivity(described later). It was also demonstrated that Ach release from cholinergic nerves was decreased by ovariectomy [79], suggesting that reduced Ach release from cholinergic nerves may cause the decrease in detrusor contractility. This may explain an abnormal bladder behaviour in elderly women that shows a coexistence of detrusor overactivity and impaired contractility [65].

## 4. PELVIC FLOOR DISORDERS

Detrusor overactivity is known to be associated with female stress urinary incontinence as a result of pelvic floor relaxation. This condition is called “mixed incontinence” which is defined as the combination of stress and urgency incontinence. Mixed incontinence accounts for approximately 33% of all cases of incontinence in women [80]. Successful surgical repair of stress incontinence (Burch colposuspension, TVT, etc) is associated with the cure of the urgency incontinence in 50% to 85% of patients [80-84].

This clinical experience suggests a connection between urethral afferents and the micturition reflex. Barrington reported that running water through the urethra or distension of the proximal urethra caused contraction of the detrusor in the cat [85]. Jung et al. also showed that in the rats urethral perfusion facilitated detrusor activity, and that intraurethral lidocaine(1%) caused a significant decrease in bladder contraction frequency [86]. These studies suggest that mechanosensitive afferent nerves activated by fluid entering the urethra can increase the excitability of the micturition reflex. In patients with stress incontinence, urine easily enters the posterior urethra, which may induce involuntary detrusor contraction and urgency to void. This mechanism is assumed to involve the pathophysiology of mixed incontinence.

## 5. IDIOPATHIC DETRUSOR OVERACTIVITY (Figure 4)

The diagnosis of idiopathic detrusor overactivity requires the exclusion of all known causes, but this should include all situations where etiology is unknown. Thus, the term is used to apply to a wide range of different conditions that may have a common final pathophysiologic pathway [87]. The following mechanisms are considered to be involved in the pathophysiology of idiopathic detrusor overactivity.

### *a) Myogenic basis*

Brading and Turner [88, 89] have emphasized that myogenic changes (regardless of etiology) may contribute to the pathophysiology of idiopathic detrusor overactivity. On the basis of observation that denervation is consistently found in detrusor biopsy specimen from patients with various forms of non-neurogenic detrusor overactivity [90], they have proposed that partial denervation of the detrusor may alter the properties of smooth muscle, leading to increased excitability and increased coupling between cells. Thus, local contraction (activity) that occurs somewhere in the detrusor will spread throughout the bladder wall, resulting in coordinated myogenic contraction of the whole bladder. However, electrophysiological studies [91] have shown that gap junction coupling is reduced rather than increased in detrusor muscle from patients with detrusor overactivity, suggesting the opposite effect on intercellular communication. Thus, it remains to be elucidated whether local activity spreads throughout the bladder wall.

In addition, this local contraction in the bladder wall has been shown to generate afferent discharge [92]. Recently, localized bladder activity was assessed by the micromotion detection method, demonstrating that women with increased bladder sensation on filling cystometry had a significantly higher prevalence of localized activity than the control group [93]. This observation suggests that localized distortion of the bladder wall simulates afferent activity, which would precipitate a feeling of urgency and detrusor overactivity [93-95].

Thus, as Brading has stated [88], the changes in smooth muscle properties seem to be a necessary prerequisite for the production of detrusor overactivity.

### *b) Urothelial afferent function*

Recently, the roles of the urothelium and suburothelial myofibroblasts in afferent activation have become the focus of intense interest. The C-fibre afferents generally have endings in the suburothelial layer of the bladder wall, but in some cases, they also penetrate the urothelium [96, 97]. Ferguson et al [98] demonstrated that ATP was released from the urothelium by bladder distension. In addition, ATP receptors(P2X3) are expressed on sensory afferent nerves [99, 100]. Thus, bladder filling causes a release of ATP from the urothelium, and ATP, in turn, can activate P2X3 receptors on afferent nerve terminals to evoke a neural discharge. Supporting this view, P2X3-deficient mice exhibit marked bladder hyporeflexia, associated with decreased voiding frequency and increased bladder capacity [101, 102].

In addition to ATP, prostanoids and nitric oxide(NO) are synthesized locally in both mucosa and muscle, and they are also released by bladder distension [103-106]. It is most likely that a cascade of stimulatory (eg.ATP, prostanoids, tachykinins) and inhibitory (eg.NO) mediators are involved in the transduction mechanisms underlying the activation of sensory afferent fibres during bladder filling [107].

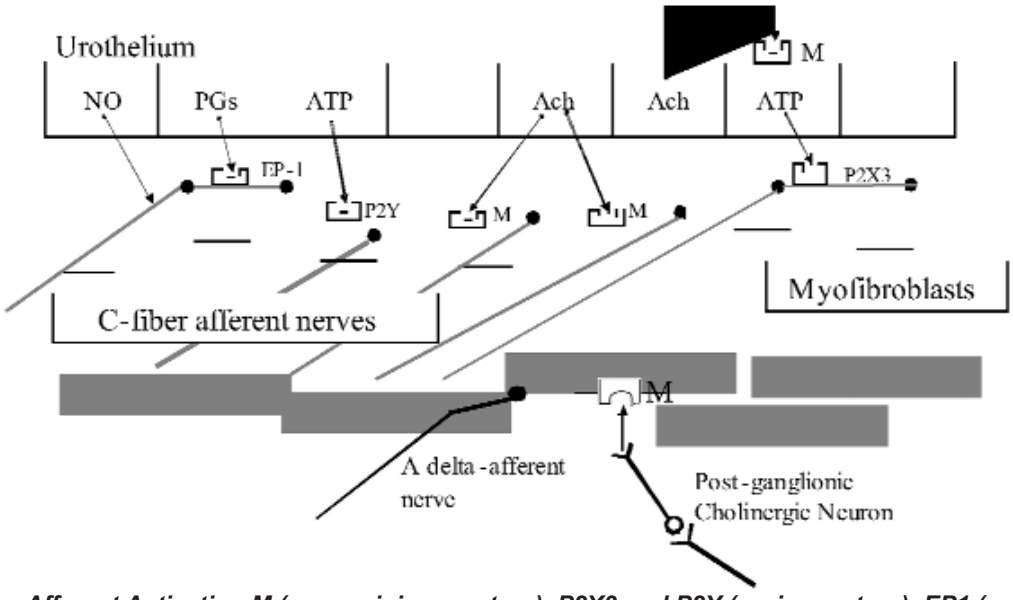


***Figure 4 : Afferent Activation M (muscarinic receptors), P2X3 and P2Y (purinoceptors), EP1 (prostaglandin receptors)***

This urothelial afferent transduction process suggests that up-regulation of the afferent activation mechanisms(eg. an increased generation/release of ATP, increased sensitivity of afferent nerves to mediators, increased number of afferent nerves) can induce detrusor overactivity, causing the symptoms of OAB. Smet et al [108] have shown that the density of nerve fibres immunoactive for substance P and CGRP was significantly higher in women with idiopathic detrusor overactivity than in normal age-matched women.

Furthermore, intravesical vanilloids (capsaicin and resineferatoxin) have been shown to improve OAB symptoms in patients with idiopathic detrusor overactivity as well as with hypersensitivity disorders [109-111]. These studies suggest that C-fibres play an important role in idiopathic detrusor overactivity.

This sensory process is more complex than originally thought. A suburothelial layer of myofibroblasts (interstitial cells) that from a functional syncitium through C?43 gap junction can be identified in the bladder wall [112, 113]. These myofibroblasts make close appositions to unmyelinated nerves(afferent C-fibre nerves) [112]. The studies investigating human myofibroblasts show that the cells can respond to ATP by generating an intracellular $Ca^{2+}$ transient, which is mediated by a P2Y receptor, most likely including a P2Y6 [114, 115]. On the basis of these observations, it has been hypothesized that the close relation between nerves and myofibroblasts allows for an amplification of the afferent system in its response to stimulatory mediators such as ATP.

### *c) Muscarinic mechanisms*

Recent evidence supports a role for muscarinic mechanisms in urothelial sensory function. As mentioned previously, the bladder urothelium releases signalling molecules (ATP, prostaglandin, etc) that are considered to act on underling afferent nerve fibres. Acetylcholine (Ach) is one of these urothelial signalling molecules [116, 117]. Recently, several studies [116-118] have shown the presence of Ach-synthesizing enzymes (ChAT, CarAT) in the bladder urothelium. Yoshida et al. [116] found by microdialysis technique that there is a basal Ach release in human bladder, and that the released Ach was of non-neuronal origin, at least partly, generated by the urothelium. This non-neuronal release of Ach was shown to increase when bladder strips with intact urothelium were stretched [116], implying that the shear stress of the urothelium during distension of the bladder may be one of the releasing mechanisms.

Muscarinic receptors (mRNA and protein levels) are found in the urothelium [119-122]. The receptor subtypes identified by radioligand binding have been demonstrated to be predominant M2 receptors with a minor population of M3 and M1 receptors [120]. Furthermore, one study [122] showed M2 and M3 receptor immunoreactivity on suburothelial myofibroblast-like cells in the human bladder.

Thus, Ach released from the urothelium can activate muscarinic receptors in the urothelium in an autocrine fashion. Activation of muscarinic receptors in the urothelium releases substances (eg., ATP) that modulate afferent nerves [123].

Ach and ATP released from the urothelium can activate muscarinic receptors and P2Y receptors, respectively on myofibroblasts that may be involved in the transfer of information between the urothelium and suburothelial afferent nerves [115]. In addition, Ach could be expected to enhance the myogenic localized activity which may increase firing of afferent nerves [92].

Based on this evidence, it can be assumed that an increase in Ach release from the urothelium and/or upregulation of muscarinic receptors in the urothelium as well as in suburothelial myofibroblasts may increase afferent nerve activity and contribute to the development of detrusor overactivity.

Supporting this view, Yoshida et al [116] showed that in isolated human detrusor, the non-neuronal Ach release was age-dependent and significantly higher in bladders from old(>65 years) than from young(<65 years) patients. These age-related changes in Ach release may contribute to the increased prevalence of OAB in the elderly. Mukerji et al. [122] also showed a significantly increased M2 and M3 muscarinic receptor immunoreactivity in myofibroblasts-like cells in bladder specimens from patients with idiopathic detrusor overactivity as compared with that in controls. Furthermore, the increase in M2 and M3 immunostaining in myofibroblasts significantly correlated with the urgency score.

## 6. PATHOPHYSIOLOGY OF NOCTURIA

Nocturia is now recognised as a clinical entity in its own right [124], and is highly prevalent and bothersome condition [125]. Whilst it may often co-exist with other LUTS, its pathophysiology is complex and multi-factorial. Patients may experience nocturia for a wide variety of reasons [124], and it is crucial that the physician accurately identify the pathophysiology of the condition in each individual. This may include such diverse causes as endocrine disorders, sleep problems, OAB, BPO and so on, However, there is an increasing body of literature indicating that the most prevalent cause of nocturia is nocturnal polyuria (overproduction of urine at night). Half of all adults experience nocturia [125], and studies show that as many as 84% of these have nocturnal polyuria, either alone or in combination with other conditions [126-129]. Amongst women with a diagnosis of OAB, around 62% have nocturnal polyuria [129] amongst men with a diagnosis of BPO, up to 95% have nocturnal polyuria [130]. However, if patients have a diagnosis of BPO

or OAB, the additional – or in some cases, only – true causal factor, nocturnal polyuria, can be overlooked.

This lack of awareness amongst physicians of the need to check for, and treat, nocturnal polyuria, can mean that for many patients, prescribed therapies (eg $\alpha_1$-blockers and anticholinergics) do not meaningfully improve theirs nocturia. Brubaker & Fitzgerald (2007) [129] report that, in the 62% of their OAB patients who had a nocturnal polyuria, solifenacin monotherapy led to no significant improvement in nocturia compared with placebo. Furthermore, discontinuation and non-adherence rates on OAB therapy are notably high, with only 32% on oxybutinin IR therapy adhering past 30 days [131]. Whilst poor adherence is a challenge that exists throughout the medical field, 68% discontinuation within a month is an unacceptably high rate, and may reflect the fact that patients do not perceive their medication as useful. The case is similar in BPO, with failure of traditional therapies often being attributable to the presence of underlying nocturnal polyuria: Yoong et al (2005) [132] report that 85% of BPO patients with nocturia unresponsive to $\alpha_1$-blocker treatment have nocturnal polyuria. Surgery (TURP) and traditional pharmacological therapies for BPO therefore frequently fail to provide a significant reduction in night-time voiding [133, 134].

Since nocturia is reported to be one of the most bothersome of LUTS [135, 136], it is crucial that patients are adequately treated. However, confusion or lack of awareness amongst physicians regarding the likely pathophysiology of nocturia means that many patients are not prescribed therapy that can improve their condition, and that they continue to experience night-time voiding to the detriment of their daytime quality of life. Patients may then assume that their nocturia cannot be treated, rather than continuing to seek help by requesting that their doctor reassess their condition. Steps to raise physicians' awareness of the pathophysiology of nocturia should therefore be taken in order to improve the standard of care provided to patients.

## B. PREGNANCY, CHILDBIRTH AND THE PELVIC FLOOR

Reduction in both perinatal and maternal mortality rates in recent decades has focused increasing attention on maternal morbidity and the long-term sequelae of childbirth. Antenatal education encourages expectant mothers to anticipate normal vaginal delivery, leading to an early restoration of normal pelvic floor function after the performance of routine pelvic floor exercises. Not least because of improved investigative techniques available during the past decade, the incidence and mechanisms of obstetric injury to the pelvic floor have come under scrutiny. A survey of female British obstetricians [137] revealed that one third indicated a personal preference for elective caesarean delivery of their own hypothetical uncomplicated singleton pregnancy; a general fear of pelvic floor trauma was cited as the most common reason for this choice. Despite being based on incomplete prognostic data, this sentiment may be echoed increasingly among obstetric patients and may lead to an unselective, and even misguided, increase in caesarean delivery rates.

Epidemiological studies have reported prevalence of stress incontinence ranging from 23 to 67 percent during pregnancy and 6 to 29 percent after childbirth, but little is known about how the condition affects women at this time. However, the prevalence of urinary incontinence may be nearly the same 8 weeks postpartum as during pregnancy.

About half of all women develop transient urinary incontinence during pregnancy. Three months postpartum, the prevalence and incidence rates of urinary incontinence are 9% to 31% and 7% to 15%, respectively. Antenatal incontinence increases the risk of postpartum incontinence, which in turn increases the risk of long-term persistent incontinence. After the first delivery, women delivered vaginally have two-fold more incontinence than those delivered by caesarean. The protective effect of caesarean on urinary incontinence may dissipate after further deliveries, decreases with age, and is not present in older women. Data are mixed about whether caesarean done before labour confers greater protection than caesarean done after labour. To understand the true impact of caesarean delivery on urinary incontinence, future studies must compare incontinence by planned (not actual) delivery modes, consider a woman's entire reproductive career, focus on leakage severe enough to be problematic, consider other bladder symptoms as well as incontinence, and take into account other risk factors, particularly ante partum urinary incontinence. [138]

Caesarean section rates are progressively rising in many parts of the world. One suggested reason is increasing requests by women for caesarean section in the absence of clear medical indications, such as placenta praevia, HIV infection, contracted pelvis and, arguably, breech presentation or previous caesarean section. The reported benefits of planned caesarean section include greater safety for the baby, less pelvic floor trauma for the mother, avoidance of labour pain and convenience. The potential disadvantages, from observational studies, include increased risk of major morbidity or mortality for the mother, adverse psychological sequelae, and problems in subsequent pregnancies, including uterine scar rupture and greater risk of stillbirth and neonatal morbidity. An unbiased assessment of advantages and disadvantages would assist discussion of what has become a contentious issue in modern obstetrics.

Lavender et al. assessed, from randomised trials, the effects on perinatal and maternal morbidity and mortality, and on maternal psychological morbidity, of planned caesarean delivery versus planned vaginal birth in women with no clear clinical indication for caesarean section. A search of the Cochrane Pregnancy and Childbirth Group's Trials Register (December 2005), MEDLINE (1974 to April 2005), EMBASE (1974 to April 2005), CINAHL (1982 to April 2005) and PsycINFO (1887 to April 2005) was carried out. Studies were selected for comparisons of intention to perform caesarean section and intention for women to give birth vaginally; random allocation to treatment and control groups; adequate allocation concealment; women at term with single fetuses with cephalic presentations and no clear medical indication for caesarean section. No studies were identified that met the inclusion criteria. Thus, there is no evidence from randomised controlled trials, upon which to base any practice recommendations regarding planned caesarean section for non-medical reasons at term. In the absence of trial data, there is an urgent need for a systematic review of observational studies and a synthesis of qualitative data to better assess the short- and long-term effects of caesarean section and vaginal birth. [139]

Lal et al. compared the incidence and severity of anal incontinence in primiparas after caesarean delivery versus spontaneous vaginal delivery. The trial comprised 184 primiparas who delivered by caesarean (104 emergency, 80 elective) and 100 who delivered vaginally were interviewed 10 +/- 2 months postpartum. Anal incontinence assessed by a comprehensive bowel function questionnaire was first present in nine (5%) mothers after caesarean delivery and eight (8%) after vaginal delivery (relative risk 0.611, 95% confidence interval 0.25, 1.53). Severe symptoms necessitating pad use affected two (3%) mothers after elective caesarean and one (1%) after vaginal delivery. Two (3%) mothers after elective caesarean, one (1%) after emergency caesarean, and two (2%) after vaginal delivery had at least two symptoms. Anal incontinence followed prelabor emergency caesarean in two mothers. Of the 22 mothers who sustained a second-degree tear, five (23%) had new anal incontinence compared with only one (3%) of 40 mothers with an intact perineum (Fisher exact test value = 9.697, P =.014).

Because severe anal incontinence followed elective and prelabor emergency caesarean, it seems that pregnancy itself can lead to pelvic floor disorders. A high incidence of anal incontinence is associated with a second-degree tear. Measures to detect and reduce postpartum anal incontinence should target all pregnant women and mothers, even after prelabor caesarean delivery. [140]

It is important that contributory obstetric factors are identified and their occurrence minimized. Vaginal birth has been recognized as being potentially traumatic to the pelvic floor. Women who have sustained significant anal sphincter injury are at greater risk of further damage of faecal incontinence with subsequent deliveries.

## I. EFFECTS OF PREGNANCY ON PELVIC FLOOR FUNCTION

In spite of the great advances that have been made in many areas of obstetric care, ignorance still persists regarding the fundamental physiological facts about the impact of pregnancy and delivery on lower urinary tract function. There is a striking dearth of prospective studies regarding the relationship of pregnancy and delivery to the problem of urinary incontinence among women. Further research may reveal that stress incontinence in women is related, at least in part, to the pregnant state itself, rather than to trauma sustained at delivery. If true, this has significant implications for subsequent research efforts investigating the etiology of female urinary incontinence. Cutner and Cardozo have summarized the few papers that do exist as follows [141]:

"Lower urinary tract symptoms are so common in early pregnancy that they are considered normal. Their progression throughout the ante partum period and their resolution postpartum has been documented by several authors. However, the data are confusing and the underlying causes remain uncertain. The effects of normal pregnancy on the physiology of the lower urinary tract remain largely uninvestigated, in spite of the common pronouncements on this subject in the obstetrical literature [142-145]".

"It is commonly assumed that stress incontinence develops (at least in part) as the result of delivery trauma to the pelvic floor. However, several researchers have documented that many young nulliparous women suffer from occasional stress incontinence which is a significant clinical problem in as many as 5 % [146-148]".

In a study of the relationship of pregnancy to stress incontinence, Francis [142] found that 40 % of primigravid women had a history of occasional stress incontinence before becoming pregnant, and that if such a history was present their stress incontinence invariably became worse during pregnancy. If incontinence developed during pregnancy, it tended to disappear after the puerperium, but recurred with subsequent pregnancies and became progressively worse, eventually becoming a clinical problem when these women were no longer pregnant. Francis concluded that in women who develop stress incontinence in middle life, pregnancy itself, rather than parturition, revealed the defect and made it worse. Similar conclusions have been reached by other researchers [149-151].

The prevalence of persistent stress urinary incontinence is reported to be significantly higher in grand multiparae compared with nulliparae [152].

Moreover, Buchsbaum et al. investigated the role of vaginal delivery and familial factors in the development of urinary incontinence by comparing the prevalence of this condition in nulliparous women and their parous sisters. Among this sample of biological sisters, urinary incontinence was reported by 47.6% of nulliparous women and by 49.7% of parous women (P = .782). Considering the high concordance in continence status between sister pairs, and considering that the majority of parous women are continent, an underlying familial predisposition toward the development of urinary incontinence may be present [153].

## II. PATHOPHYSIOLOGIC MECHANISMS OF BIRTH INJURY TO THE PELVIC FLOOR

Vaginal delivery, notably the first, is strongly associated with later surgery for stress incontinence, but the association is modified by maternal conditions and interventions during delivery. Vaginal delivery may initiate damage to the continence mechanism by direct injury to the pelvic floor muscles, damage to their motor innervations, or both. Additional denervation may occur with aging, resulting in a functional disability many years after the initial trauma. Physical and emotional health problems are common after childbirth, and are in frequently reported to health professionals despite the fact that many women would like more advice and assistance in dealing with them. There would seem to exist four major mechanisms by which childbirth (vaginal delivery) might contribute to the increased risk of urinary incontinence among women:

1. Injury to connective tissue supports by the mechanical process of vaginal delivery, especially instrumental vaginal delivery (forceps > ventouse delivery)
2. Vascular damage to the pelvic structures as the result of compression by the presenting part of the fetus during labour
3. Damage to the pelvic nerves and/or muscles as the result of trauma during parturition
4. Direct injury to the urinary tract during labour and delivery. The physiologic changes produced by pregnancy may make pregnant women more susceptible to injury from these pathophysiological processes

In a three-dimensional computer model Lien et al. predicted levator ani muscle stretch during vaginal birth. Serial magnetic resonance images from a healthy nulliparous 34-year-old woman, published anatomic data, and engineering graphics software were used to construct a structural model of the levator ani muscles along with related passive tissues. The model was used to quantify pelvic floor muscle stretch induced during the second stage of labour as a model the fetal head progressively engaged and then stretched the iliococcygeus, pubococcygeus, and puborectalis muscles. The medial pubococcygeus muscles undergo the largest stretch of any levator ani muscles during vaginal birth. They are therefore at the greatest risk for stretch-related injury [154].

Furthermore, in a prospective observational study Dietz et al. investigated 61 nulliparous women at 36-40 weeks of gestation and 2-6 months post partum. The assessment included an interview and 3-dimensional translabial ultrasound and was repeated 2-6 months postpartum. Fifty women (82%) were seen postpartum. Of the 39 women delivered vaginally, levator avulsion was diagnosed in 14 (36%, 95% confidence interval 21-51%). Among those delivered vaginally, there were associations with higher maternal age (P = .10), vaginal operative delivery (P = .07), and worsened stress incontinence postpartum (P = .02). Avulsion of the inferomedial aspects of the levator ani from the pelvic sidewall occurred in approximately one third of all women delivered vaginally and was associated with stress incontinence 3 months after childbirth [155].

Boreham et al described levator ani (LA) anatomy in postterm nulliparas using 3-dimensional (3-D) magnetic resonance (MR). LA insertion into the symphysis was visible in 93%, and the iliococcygeus muscle assumed a convex shape (arch) in 92% of the 84 women. The LA shape was characterized as “U” in 53% and “V” in 47%. Mean LA volume was 13.5 (3.7) $cm^3$. There was a positive association between LA volume and higher fetal station (P = .02) and increasing BMI (P < .001). However, no relationship between LA volume and station was found after adjusting for BMI. BMI was correlated with LA volume in postterm nulliparas. LA insertion into the symphysis and the iliococcygeus arch were well-preserved overall and morphometry was variable [156].

Vaginal delivery causes partial denervation of the pelvic floor (with consequent re-innervations) in most women having their first baby. Pelvic floor muscle strength is impaired shortly after vaginal birth, but for most women returns within two months. In a few this condition is severe and is associated with urinary and faecal incontinence. For some it is likely to be the first step along a path leading to prolapse and/or stress incontinence [157].

There is a growing body of evidence that multiparity, forceps delivery, increased duration of the second stage of labour, partially due to epidural anaesthesia, third degree perineal tear and high birth weight (> 4000 g) are important factors leading to pudendal nerve damage [158-161].

Peschers et al showed that pelvic floor muscle strength is significantly reduced three to eight days postpartum in women following vaginal birth but not in women after caesarean delivery. Six to ten weeks later palpation and vesical neck elevation on perineal ultrasound do not show any significant differences to ante partum values, while intravaginal pressure on perineometry remains significantly lower in primiparae, but not in multiparae. Pelvic floor muscle strength is impaired shortly after vaginal birth, but for most women returns within two months [162].

There is also EMG evidence of re-innervations in the pelvic floor muscles after vaginal delivery in 80%. Mainly women who have a long active second stage of labour and heavier babies show the most EMG evidence of nerve damage. An elevation in perineal body position as well as a decrease in the area of the urogenital hiatus and of the levator hiatus at two weeks postpartum suggests a return of normal levator ani geometry after vaginal delivery in most patients [163].

In a longitudinal study of a cohort of 96 primigravidae followed up 7 and 15 years pelvic floor neurophysiology was performed and questionnaires were administered to determine the natural history of stress incontinence and to establish whether pelvic floor denervation after the first delivery is associated with symptoms of stress urinary incontinence in the future. Urinary incontinence symptoms were recorded and pelvic floor neurophysiology was performed antenatally and postnatally. Repeat neurophysiological tests and questionnaires were completed by those relocated 7 and 15 years later. Prevalence of stress incontinence was highest during pregnancy and had increased seven years after the first postnatal period ($P = 0.0129$). Two-thirds of women with antenatal stress incontinence had stress incontinence 15 years later. One-third of women with stress incontinence at any time appear to undergo resolution of symptoms. Motor unit potential duration increased at seven years ($P = 0.036$). Vaginal squeeze pressure improved during the same period ($P = 0.0007$). When stress urinary incontinence arises during the first pregnancy, the risk of stress incontinence occurring 15 years later is doubled. Although pelvic floor reinnervation progressed after the postnatal period, the absence of an adequate marker for pelvic floor denervation makes it of uncertain clinical significance [164].

To identify obstetric factors associated with development of levator ani injury after vaginal birth magnetic resonance images were taken of the pelvic floor of 160 women 9 to 12 months after first term vaginal delivery. Half the women had de novo stress incontinence and half were continent controls. Abnormalities of the pubovisceral portion were identified on magnetic resonance as present or absent. Defect severity was further scored in each muscle from 0 (no defect) to 3 (complete muscle loss). A summed score for the 2 sides (0 to 6) was assigned and grouped as minor (0-3) or major (4-6). Obstetric details were collected. The following increased odds ratios for levator defect were found: forceps use 14.7 (95% confidence interval [CI] 4.9-44.3), anal sphincter rupture 8.1 (95% CI 3.3-19.5) and episiotomy 3.1 (95% CI 1.4-7.2) but not vacuum delivery 0.9 (95% CI 0.19-4.3), epidural use 0.9 (95% CI 0.4-2.0), or oxytocin use 0.8 (95% CI 0.3-1.8). Women with levator injury were 3.5 years older and had a 78-minute longer second stage of labour. Injuries to the levator ani muscles in women after their first vaginal delivery are associated with several obstetric factors indicating difficult vaginal birth and with older age. LEVEL OF EVIDENCE: II-3. [165]

Baytur investigated the respective roles of the mode of delivery and strength of pelvic floor muscles in the sexual function of women. Pelvic floor muscle strength was significantly lower in the group vaginally delivered compared with the group delivered by caesarean section and the nulliparous group ($P<0.05$). There was no difference between the groups regarding sexual function ($P>0.05$), and there was also no correlation between sexual function and pelvic muscle strength [166].

To compare pelvic floor symptoms at three years following instrumental delivery and caesarean section in the second stage of labour and to assess the impact of a subsequent delivery Bahl et al. conducted a prospective cohort study of 393 women with term, singleton, cephalic pregnancies who required instrumental vaginal delivery in theatre or caesarean section at full dilatation between. 283 women (72%) returned postal questionnaires at three years. Urinary incontinence at three years post delivery was greater in the instrumental delivery group as compared to the caesarean section group (10.5% vs 2.0%), OR 5.37 (95% CI, 1.7, 27.9). There were no significant differences in ano-rectal or sexual symptoms between the two groups. Pelvic floor symptoms were similar for women delivered by caesarean section after a failed trial of instrumental delivery compared to immediate caesarean section. A subsequent delivery did not increase the risk of pelvic floor symptoms at three years in either group. An increased risk of urinary incontinence persists up to three years following instrumental vaginal delivery compared to caesarean section in the second stage of labour. However, pelvic floor symptoms are not exacerbated by a subsequent delivery [167].

Female pelvic floor dysfunction is integral to the woman's role in the reproductive process, largely because of the unique anatomic features that facilitate vaginal birth and also because of the trauma that can occur during that event. Interventions such as primary elective caesarean delivery have been discussed for the primary prevention of pelvic floor dysfunction; however, existing data about potentially causal factors limit our ability to evaluate such strategies critically.

The risk of pelvic floor disorders is independently associated with vaginal delivery but not with parity alone. Caesarean delivery has a protective effect, similar to nulliparity, on the development of pelvic floor disorders when compared with vaginal delivery. LEVEL OF EVIDENCE: II-2. [168, 169]

Younger white primiparous women had a better recovery at 6 months than older white women [170].

The pudendal nerve terminal motor latency (PNTML) measured 48-72 h after delivery is increased in women delivered vaginally compared to nulliparous control subjects.

Multiparity, forceps delivery, increased duration of the second stage of labour, third degree perineal tear and high birth weight are important factors leading to pudendal nerve damage [158].

Compared with spontaneous vaginal births, women having forceps or ventouse extraction have increased odds for perineal pain, sexual problems, and urinary incontinence [159].

Vaginal delivery, notably the first, is strongly associated with later surgery for stress incontinence, but the association is modified by maternal conditions and inter- ventions during delivery [171].

Women with three or more deliveries were more likely to have incontinence and excessive pelvic floor descent [171].

There is no evidence to suggest that at five years after delivery use of the ventouse or forceps has specific maternal benefits or side effects [172].

Meyer et al. found that, after spontaneous and instrumental deliveries, 21% and 34% of women complained of stress urinary incontinence and 5.5% and 4% reported faecal incontinence, respectively. Substantial bladder neck hypermobility was present together with diminished functional urethral length and intravaginal and intra-anal pressures. Only 22% of patients with stress urinary incontinence during pregnancy had such incontinence after delivery [173].

Women with postpartum urinary stress incontinence have significantly greater antenatal bladder neck mobility than those women who were continent post partum [174].

To investigate and compare the effects of different modes of delivery on urethral sphincter volume, bladder neck mobility, and changes to levator hiatus distensibility using ultrasound imaging, 156 women underwent antenatal ultrasound pelvic floor assessment. One hundred and ten (71%) completed the 6-month follow-up. There were no differences in the urethral sphincter volume between the different modes of delivery. Overall, the urethral sphincter was smaller after delivery compared to the third trimester. Vaginal delivery was associated with a significantly larger levator hiatus area on valsalva antenatally and at rest, squeeze, and valsalva postnatally compared to caesarean section. Antenatal and postpartum bladder neck mobility was also significantly greater in the women who delivered vaginally. Urethral sphincter changes postpartum are independent of mode of delivery. Vaginal delivery is strongly associated with a larger, more distensible levator hiatus and a greater degree of bladder neck mobility both antenatally and postpartum [175].

Displacement and recovery of the vesical neck position during pregnancy and after childbirth and to discriminate between compliance of the vesical neck supporting structures with and without pelvic floor contraction. Compliance of the supporting structures remains relatively constant during pregnancy and returns to normal values 6 months after childbirth. Hysteresis**,** however, showed an increase after childbirth, persisting at least until 6 months post partum [176].

## III. EPIDURAL ANALGESIA DURING LABOUR

**Regional anaesthesia for the relief of labour** pain has become more popular during the past 20 years. Despite interest in its possible obstetric consequences, little attention has been paid to its potential effects on the pelvic floor and perineal injury. The available published data describe conflicting results. Some studies suggest that epidural analgesia, by enabling relaxation of the pelvic floor, leads to greater control of delivery of the fetal head and consequently fewer perineal lacerations [177] but prolongation of the second stage may also increase the incidence of pudendal nerve damage [161, 178].

Robinson et al. [179] recently examined the relationship between epidural analgesia and perineal damage, and found that the rate of significant perineal injury was higher with epidural analgesia (16,1 % compared with increased use of operative intervention). Episiotomy and instrumental delivery were responsible for this difference. Such an association may partly explain why institutions are reporting increased rates of significant perineal injury, paralleling local increases in epidural usage [171].

In a study of 82 women Meyer et al assessed the effects of epidural analgesia on pelvic floor function. Eighty-two primiparous women (group 1, consisting of 41 given an epidural, and group 2 of 41 not given an epidural) were investigated during pregnancy and at 2 and 10 months after delivery by a questionnaire, clinical examination, and assessment of bladder neck behaviour, urethral sphincter function and intravaginal/ intra-anal pressures. Ten months after spontaneous

delivery, there were no significant differences in the prevalence of stress urinary incontinence and decreased sexual vaginal response, or in bladder neck behaviour, urethral sphincter function and pelvic floor muscle strength between women who had or had not had epidural analgesia [180].

Comprising 70 matched pairs of primiparous mothers Sartore et al. found no significant difference in the incidence of stress urinary incontinence, anal incontinence and vaginal prolapse in the two study groups. No significant differences were found between the study groups with regard to the digital test, vaginal manometry and urine stream interruption test. The use of epidural analgesia is not associated with symptoms related to perineal trauma and pelvic floor muscle weakness [181].

## 1. ROLE OF EPISIOTOMY (Figure 5)

Episiotomy is a widely performed intervention in child birth, despite equivocal scientific evidence regarding its benefit. Practice patterns vary widely, as do professional opinions about maternal risks and benefits associated with routine use. It is one of the few surgical procedures performed without the patients consent and is the most commonly performed surgical procedure in the United States. There is a widespread assumption that it may do more harm than good [171, 179]

Restrictive episiotomy policies appear to have a number of benefits compared to routine episiotomy policies. Proponents of routine episiotomy claim that it avoids spontaneous uncontrolled tears and long-term relaxation of the pelvic floor, but these advantages are difficult to substantiate. There is no evidence that either first or second-degree perineal tears cause long-term consequences [143].

So any argument that episiotomy prevents such spontaneous tears is inconsequential. A growing body of evidence suggests that episiotomy offers no protection against third and forth-degree tears, which are associated with adverse sequelae. A recent overview by Myers-Helfgott and Helfgott emphasized the absence of scientific evidence to support a role for liberal elective episiotomy in the reduction of third-degree lacerations during childbirth [144].

Indeed, several reports have implicated routine episiotomy in the genesis of major perineal and anal sphincter tears, even after controlling for confounding variables [145-147, 182].

In particular, midline episiotomy is associated with significantly higher rates of third and fourth-degree perineal tears than are mediolateral episiotomies [149-151].

Midline episiotomy is not effective in protecting the perineum and sphincters during childbirth and may impair anal continence [183].

Coats et al., in a randomized controlled trial of 407 women, found that with midline episiotomy, 11, 6 % of patients experienced lacerations of the anal canal versus 2 % who experienced these complications in association with mediolateral episiotomies. This association is compounded when instrumental delivery is employed, with anal sphincter injury rates of 50 % reported with the use of midline episiotomy and forceps [184].

In spite of these data, midline episiotomy is still bewilderingly widespread, presumably because it is perceived to heal better and cause less postnatal discomfort.

Restrictive episiotomy policies appear to have a number of benefits compared to routine episiotomy policies. There is less posterior perineal trauma, less suturing and fewer complications, no difference for most pain measures and severe vaginal or perineal trauma, although there was an increased risk of anterior perineal trauma with restrictive episiotomy [185, 186].

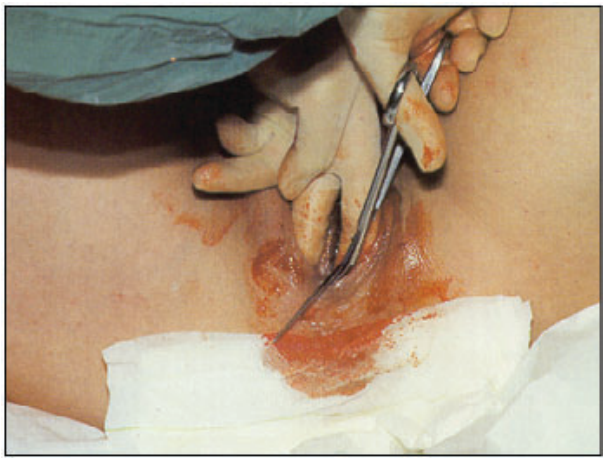

***Figure 5: Mediolateral episiotomy***

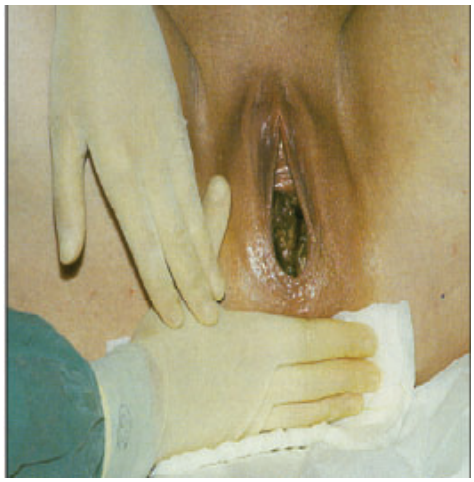

***Figure 6 : Vaginal delivery showing passage of the fetal head through the outer part of the birth channel compressing the perineum.***

Women who have episiotomies have a higher risk of faecal incontinence at three and six months postpartum compared with women with an intact perineum. Compared with women with a spontaneous laceration, episiotomy triples the risk of faecal incontinence at three months and six months postpartum, and doubles the risk of flatus incontinence at three months and six months postpartum. A non-extending episiotomy (that is, second degree surgical incision) triples the risk of faecal incontinence and doubles the risk of flatus incontinence post partum compared with women who have a second degree spontaneous tear. The effect of episiotomy is independent of maternal age, infant birth weight, and duration of second stage of labour, use of obstetric instrumentation during delivery, and complications of labour. Therefore**,** midline episiotomy is not effective in protecting the perineum and sphincters during childbirth and may impair anal continence and should be restricted to specified fetal-maternal indications [183, 187-190].

Routine midline episiotomy increases the risk of third- and fourth-degree perineal lacerations, which may lead to faecal incontinence. Routine use of mediolateral episiotomy does not prevent urinary incontinence (UI) or severe perineal tears. It is possible to reduce the rate of mediolateral episiotomy to as low as 20% in primiparas without increasing the risk of anal sphincter damage.

Control of obesity before delivery, as well as pelvic floor exercises and regular physical exercise both before and after delivery, seem to reduce the risk of postpartum UI [191, 192].

In a systematic review Hartmann et al. looked for the best evidence available about maternal outcomes of routine vs restrictive use of episiotomy. Immediate maternal outcomes of routine episiotomy, including severity of perineal laceration, pain, and analgesia use, are not better than those with restrictive use. Evidence is insufficient to provide guidance on choice of midline vs mediolateral episiotomy.

Evidence regarding long-term sequelae is fair to poor. Incontinence and pelvic floor outcomes have not been followed up into the age range in which women are most likely to have sequelae. With this caveat, relevant studies are consistent in demonstrating no benefit from episiotomy for prevention of faecal and urinary incontinence or pelvic floor relaxation. Likewise, no evidence suggests that episiotomy reduces impaired sexual function—pain with intercourse was more common among women with episiotomy. Evidence does not support maternal benefits traditionally ascribed to routine episiotomy. In fact, outcomes with episiotomy can be considered worse since some proportion of women who would have had lesser injury instead had a surgical incision.

Another systematic review using the Medline Database set was performed with the key words: episiotomy, dyspareunia, faecal incontinence, urinary incontinence, maternal morbidity, pelvic floor defects and sexual function. When performed liberally, episiotomy appears to increase the risk of post partum bleeding. More restrictive use does not appear to increase the risk of serious perineal injury.

In the event of instrumental extraction, use of episiotomy appears to be associated with more severe damage. Medial episiotomy does not appear to be associated with third or fourth degree tears. Episiotomy appears to be the cause of more perineal pain and dyspareunia during the early post partum weeks [193].

## 2. PERINEAL TRAUMA (Figure 6)

Awareness of perineal damage after vaginal delivery has increased in recent years, due in part to better understanding of its consequences, improved methods of accurate neurophysiological evaluation and accumulation of data on prognosis. Faecal incontinence represents a distressing social handicap, and vaginal delivery is now recognized as its principal cause [194].

Obstetricians should have an awareness of the causes, symptoms, appropriate investigation and treatment options available for this complication of childbirth. Limiting episiotomy can be strongly recommended. In the absence of strong data to the contrary, women should be encouraged to engage in perineal massage if they wish and to adopt the birth positions of their choice. Factors shown to increase perineal integrity include avoiding episiotomy, spontaneous or vacuum-assisted rather than forceps birth, and in nulliparas, perineal massage during the weeks before childbirth. Second stage position has little effect [195].

Further information on techniques to protect the perineum during spontaneous delivery is badly needed. Wherever possible, women with post partum faecal incontinence should be assessed in a specialized clinic, which has developed a close liaison with physiotherapy, dietetic and colorectal surgical advisers.

Episiotomy, forceps use, and birth weight are important predictors of third and fourth-degree tears. However, determinants of sulcus tears appear to be present before pregnancy. Third and fourth-degree tears are related to physician management. Exercise mitigates the potential for severe trauma induced by episiotomy [196].

Eason et al. have systematically reviewed techniques proposed to prevent perineal trauma during childbirth and performed a meta-analysis of the evidence gathered from randomized controlled trials regarding their efficacy. The conclusion was that avoiding episiotomy decreased perineal trauma (absolute risk difference 0.23, 95% confidence interval (CI] -0.35, 0.11). In nulliparas, perineal massage during the weeks before giving birth also protected against

perineal trauma (risk difference -0.08, CI -0.12, -0.04). Vacuum extraction (risk difference -0.06, CI -0.10, 0.02) and spontaneous birth (-0.11, 95% CI -0.18, 0.04) caused less anal sphincter trauma than forceps delivery. The mothers' position during the second stage had little influence on perineal trauma (supported upright versus recumbent: risk difference 0.02, 95% CI -0.05, 0.09).

Factors shown to increase perineal integrity include avoiding episiotomy, spontaneous or vacuum-assisted rather than forceps birth, and in nulliparas, perineal massage during the weeks before childbirth. Second-stage position has little effect. Further information on techniques to protect the perineum during spontaneous delivery is needed [197].

Reduction in both perinatal and maternal mortality rates in recent decades has focused increasing attention on maternal morbidity and the long-term sequelae of childbirth. Antenatal education encourages expectant mothers to anticipate normal vaginal delivery, leading to an early restoration of normal pelvic function after the performance of routine pelvic floor exercises. Not least because of improved investigative techniques available during the past decade, the incidence and mechanisms of obstetric injury to the pelvic floor have come under scrutiny. A survey of female British obstetricians [137] revealed that one third indicated a personal preference for elective caesarean delivery of their own hypothetical uncomplicated singleton pregnancy; a general fear of pelvic floor trauma was cited as the most common reason for this choice.

Despite being based on incomplete prognostic data, this sentiment may be echoed increasingly among obstetric patients and may lead to an unselective, and even misguided, increase in caesarean delivery rates. Epidemiological studies have reported prevalence of stress incontinence ranging from 23 to 67 percent during pregnancy and 6 to 29 percent after childbirth, but little is known about how the condition affects women at this time. However, the prevalence of urinary incontinence may be nearly the same 8 weeks postpartum as during pregnancy. It is important that contributory obstetric factors are identified and their occurrence minimized. Vaginal birth has been recognized as being potentially traumatic to the pelvic floor. Women who have sustained significant anal sphincter injury are at greater risk of further damage of faecal incontinence with subsequent deliveries.

# C. PATHOPHYSIOLOGY OF STRESS INCONTINENCE IN WOMEN: URETHRAL STRUCTURE, SUPPORT AND FUNCTION

The factors necessary for the urethra to remain closed at rest and during increased abdominal pressure have been well characterized, but their functional inter-relationships are still not fully understood. These factors include: 1) healthy, functioning striated sphincter controlled by pudendal innervation, 2) well vascularised urethral mucosa and sub- mucosa, 3) properly aligned and functioning intrinsic urethral smooth muscle, and 4) intact vaginal wall support.

## I. THE FEMALE UROGENITAL DIAPHRAGM: URETHRAL SPHINCTER LOCATION

Detailed descriptions of the urogenital diaphragm have been made by Max Brodel working with Howard Kelly [198], Oelrich [199] and further expanded by DeLancey [200]. These reports have provided clear descriptions of the urethral rhabdosphincter. The proximal one-third of the urethra is shown surrounded by a sleeve of striated muscle continuous with a longer ascending cone which extends to the vaginal introitus. Manometric and electrophysiological recordings from this proximal one-third of the urethra have shown that it generates the highest level of resting pressure and electromyographic activity.

This portion of the urethra is an intra-pelvic structure located immediately posterior to the pubic bone. In the past, much has been made of the loss of this intra-pelvic position in stress incontinence. It had been suggested that when the urethra descended away from its intra-abdominal position, intra-abdominal forces no longer constricted it during straining. This concept has survived and been modified into the "hammock hypothesis" [201] which suggests that the posterior position of the vagina provides a backboard against which increasing intra-abdominal forces compress the urethra. Data supporting this hypothesis are drawn from urethral pressure transmission studies showing that continent patients experience an increase in intra-urethral pressures during coughing. This pressure increase is lost in stress incontinence and may be restored following successful operations designed to stabilize or elevate the sub-urethral vaginal wall [202-211].

The urethra is supported posteriorly and inferiorly by the anterior vaginal wall. The superior vaginal sulcus, most clearly found in nullipara, exists at this junction

of the lower and middle third of the vaginal wall. This point represents the two lateral insertion points of the vaginal "hammock ". Portions of the pubococcygeus muscle attach to these to sulci within the pelvis and can produce elevation during voluntary contraction.

Immediately anterior to the proximal urethra are found the reflections of the endopelvic fascia. The most prominent of these, the pubo-urethral ligaments, are sufficiently condensed to form distinct and recognizable ligaments on either side of the pubis. Although these structures form one continuous complex, they are distinguished by their names, as posterior and anterior pubo-urethral ligaments. The posterior pubo-urethral ligaments, which can be seen at the time of retropubic surgery, are the more familiar of these. These are strong fascial condensations which most likely maintain their characteristics throughout life. Previous investigators, however, have suggested that elongation of these structures may be responsible for the loss of urethral support seen in stress incontinence.

While the lower one-third of the vagina is oriented more vertically in the nullipara, the upper two-thirds of the vagina deviate horizontally. This orientation is due:

1) to the posterior attachments of the cervix by the cardinal and utero-sacral ligaments and 2) to the anterior position of the levator hiatus. Barium vaginograms have demonstrated this horizontal angulation of the upper two-thirds of the vagina, and show that during coughing and stressful manoeuvres, the levator hiatus is shortened in an anterior direction by the contraction of the pubococcygeus muscles. Thus, the pelvic organs receive support from the shape and active contraction of the levator muscles.

Modifications of the genital hiatus determining an increase in the genitohiatal distance can be associated with urodynamic stress incontinence. In a retrospective study of 396 women with urodynamic stress incontinence [212], pelvic floor ultrasound revealed a negative association of the genitohiatal distance to urodynamic functional urethral parameters such as the functional profile length, the maximum urethral closure pressure and a low Valsalva leak-point pressure ($r = -0.148$, $P = 0.018$ and $r = -0.227$, $P = 0.009$, $r = -0.199$, $P = 0.02$ respectively).

## II. EFFECT OF CHILDBIRTH, VAGINAL PROLAPSE AND URETHRAL POSITION ON URINARY CONTINENCE

Labour and delivery alter vaginal and pelvic anatomy and innervation in several ways as has been discussed in other sections of this chapter. Each of these may contribute to the eventual development of urinary incontinence (**Figure 7**):

1 Direct crushing or traction on the pudendal nerve has been discussed above and has previously been suggested as a primary cause of sphincter incompetence in stress incontinence.

2 Cardinal and utero-sacral ligaments may be stretched or torn, resulting in anterior displacement of the uterus during straining or under the influence of gravity.

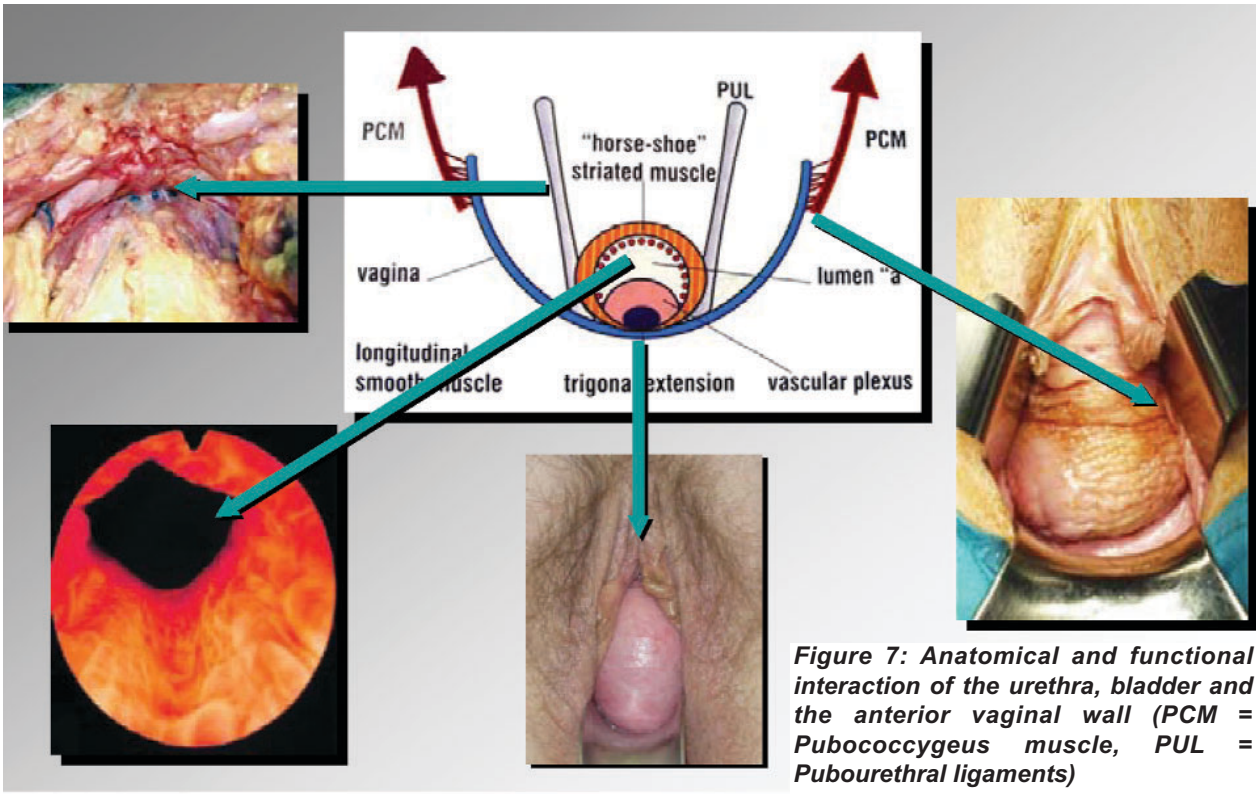


***Figure 7: Anatomical and functional interaction of the urethra, bladder and the anterior vaginal wall (PCM = Pubococcygeus muscle, PUL = Pubourethral ligaments)***

3 The vagina itself may be torn away from its intrapelvic attachments with subsequent loss of the superior vaginal sulcus. There may be direct attenuation of the vaginal wall itself, manifested by loss of vaginal rugae and a thin appearance. Cullen Richardson has suggested four distinct kinds of vaginal injuries: paravaginal, central, distal, and cervical, the first two being the most commonly seen in women with stress incontinence. These defects have been identified by sonographic examination [213].

4 Finally, stretching, tearing and avulsion of the levator muscles result in a longer and wider levator hiatus. Consequently, the perineum is displaced anteriorly and posteriorly under stress and temporarily fails to support the pelvic organs. These changes in the levator hiatus with or without associated relaxation of cervical support result in chronic anterior displacement of pelvic organs with a loss of both active and passive organ support during rest and especially during straining.

In the patient with stress urinary incontinence these changes typically give rise to a rotational descent of the proximal urethra away from its retropubic position. Radiographic images of stress urinary incontinence in women have noted this and generated our earliest concepts of this condition. Jeffcoate and Roberts [214], using lateral cystourethrograms, concluded:

"…the most common characteristic anatomical change, present in four out of five cases of incontinence, is loss of the posterior urethro-vesical angle so that the urethra and trigone tend to come into line."

In 2002, fifty years later, perineal sonographic studies of urethrovesical angle differences in incontinent and normal patients have found excellent correlation identified between angle and degree of incontinence, supporting these original observations [215].

Hodgkinson, using a suspension of barium paste placed in the bladder and a small bead chain in the urethra, produced images of the urethra at rest and during maximum straining in women with stress urinary incontinence [216, 217]. He concluded:

"…it is clear that the distinguishing topographic pathological feature is depression of the urethrovesical junction to the lowest level of the bladder during the peak of the straining effort. It is also clear that the spatial relationships of the bladder and urethra to the symphysis make no difference in either the incidence or severity of stress incontinence."

These kinds of radiographic studies, however, cannot distinguish between lateral or central defects in vaginal wall support. Therefore, while urethral movement can be identified as an important finding in stress incontinence, one cannot determine the exact location of the vaginal defect. Because the proximal urethra rotates out of the focal plane of ultrasonograhic probes or MRI, coronal images of vaginal relaxation have not yet shown anatomical detail at the moment of incontinence. They cannot distinguish central from paravaginal defects. For this, an examination of the patient is required.

Although we have considerable knowledge about anatomical defects in the majority of patients with urodynamic stress incontinence (USI), less is understood about the exact effect of these defects, and indeed, vaginal position itself, on urethral closure. Early experience with operations for stress incontinence showed that not all women with stress urinary incontinence had vaginal prolapse, that correction of vaginal relaxation did not always correct stress incontinence, and that women who redeveloped stress incontinence symptoms after apparently successful surgery did not necessarily show a recurrence of their prolapse [218].

The effect on the urethral mechanism of anatomical defects induced by vaginal delivery has been recently investigated. In a rat model a birth trauma has been simulated inducing vaginal distension by balloon catheter inflation [219]. Sneeze induced stress urinary incontinence was caused by decreased active closure mechanisms at the mid urethra without affecting the passive transmission of abdominal pressure in the proximal urethra.

The greater involvement of the urethral mechanism in the occurrence of post-partum stress incontinence was confirmed in a case control study evaluating urethral closure pressure and bladder neck movement assessed with ultrasound [220]. Eighty primiparous women complaining of de-novo stress incontinence 9-12 months after delivery were compared with 80 primiparous continent and 80 nulliparous continent women. Lower maximal urethral closure pressure was most associated with de novo stress incontinence after first vaginal birth followed by vesical neck mobility.

## III. EMERGING CONCEPTS OF URETHRAL WEAKNESS AND ISD

The idea that primary urethral weakness could cause urinary incontinence independent of vaginal weakness appeared in a proposed classification by Blaivas et al [221]. In their classification, they named this Type III incontinence to distinguish it from Types I and II, each of which showed movement, while Type III did not. This term still remains in the contemporary literature, although it has now been largely replaced by the term intrinsic sphincter deficiency (ISD), focusing attention on urethral elements which appear to be independent of vaginal position and mobility. These elements include pudendal innervation, striated sphincter mass and function, and urethral smooth muscle, mucosa and submucosal cushions.

When ISD was first introduced as a concept to explain surgical failures and the presence of stress incontinence in the absence of vaginal mobility, the diagnostic tendency was to consider the cause of stress incontinence as a dichotomy, due either to hypermobility (displacement, or prolapse of the vaginal wall) or ISD. The typical patient with ISD was described as having low urethral closure pressures, a "stovepipe" appearance on cystoscopy, and opening or funnelling of the urethra under resting or minimal increases in intra-abdominal pressures on radiographic images. The common causes were thought to be surgical injury, ischemia following previous pelvic or vaginal surgery or radiation damage.

It appears now, that these examples of ISD may have represented the most advanced or extreme forms.

## IV. HYPERMOBILITY VS. ISD: FROM DICHOTOMY TO CONTINUUM

Currently, there appears to be a shift away from this simple categorization of stress incontinence as being due either to hypermobility or ISD. This has arisen in part because of the development of the concept of Valsalva Leak Point Pressure (VLPP) [222, 223] and more recent analyses of long term results of stress incontinence surgery [224].

VLPP emerged as an alternative method to study urethral closure during stress for studies of urethral bulking with collagen. Investigators recognized that improvements in continence following urethral bulking did not correlate with urethral closure pressures, but did correlate with the amount of pressure required to produce leakage in the absence of intrinsic detrusor contraction. Although VLPP still lacks specific anatomic or theoretical grounding and many uncertainties related to standardization of recording methods and associated prolapse remain, low VLPP (without specified or established values) has been widely embraced as an indicator of ISD.

Just as the concept of VLPP blurred the previous distinction between simple ISD and simple hypermobility, long term outcome studies of correction of hypermobility have suggested that there may be more urethral weakness among patients with hypermobility than had been previously considered. Long term outcome studies of stress incontinence surgery have shown that there is a much greater failure rate of many of the commonly performed stress incontinence operations than had been generally appreciated, and that slings providing direct sub-urethral support seemed to give the greatest long term protection against recurrence of incontinence [224]. Since slings had traditionally been the procedure of choice for recurrent incontinence or "Type III" (now ISD) incontinence, the possibility that ISD was more common than previously thought was more widely considered. Recently, Horbach and Ostergaard have found that age is a significant, independent predictor of ISD in the setting of urodynamic stress incontinence [225], suggesting that age-related reduction in muscle mass, slowed reflexes or repeated episodes of prolapse may all contribute to the condition.

In two interesting studies Perucchini et al [226, 227] showed that aging can cause a decrease in the number and density of urethral striated muscle fibres at the bladder neck and along the ventral wall of the urethra. (**Figure 8 and 9** [226])

These two developments have led to a growing clinical impression that some degree of ISD may exist in many patients who, until recently, were thought to have only hypermobility as a cause of their incontinence. A typical expression of this approach can be found in the conclusion of Kayigil et al. [228]

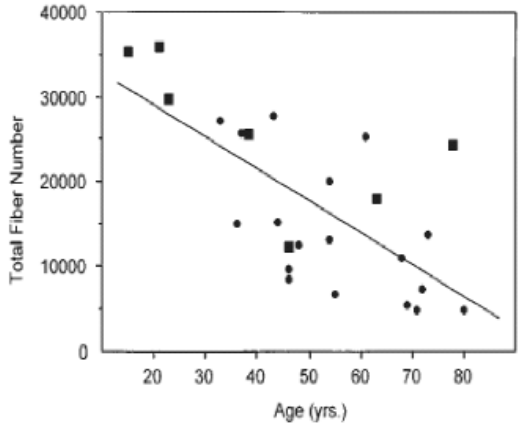


***Figure 8: Graph shows the decrease of the total fibre number in the ventral urethral wall with age. The squares highlight the fibre number of nulliparous individuals.***

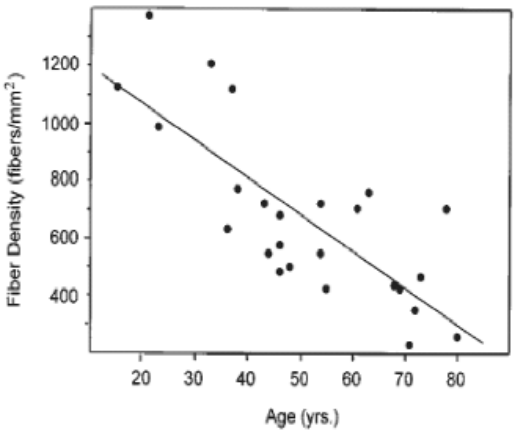


***Figure 9: Graph illustrates the influence of age on density of fibre in the ventral urethral wall***

following examination of 50 patients; “The high rate of intrinsic sphincter deficiency in patients with urethral hypermobility indicates that the incidence with stress incontinence may be greater than previously believed, and may influence the apparently higher failure rates after bladder neck suspension.” In contemporary clinical practice, this impression has given rise to a growing tendency to recommend suburethral sling surgery as a form of primary surgical treatment for all women with stress incontinence, where as formerly this approach was reserved almost exclusively for patients with recurrent stress incontinence or significant ISD [229, 230].

## 1. DIRECT STUDIES OF URETHRAL FUNCTION

As recognition of the importance of urethral function has increased, so too have the number of investigations of urethral position, urethral closure and transmission pressure profiles, Valsalva leak point pressure measurements and electromyographic examinations of the pudendal nerve and the striated sphincter.

### *a) Studies of urethral position*

Stress incontinence is frequently associated with loss of urethral position. This has been the primary pathophysiological paradigm since the observations of Hodgkinson and Jeffcoate and Roberts. Similar observations are still reported today [231, 232]. Even when some displacement is seen in continent nulliparous females, incontinent women show a greater degree of mobility [233].

Successful suspensory operations, whether by sling or paraurethral suspension stabilize urethral position [218] and, when studied, increase pressure transmission during stress. It is not clear if the active contraction of urethral support seen in the female is restored after surgery, nor is it known if it is necessary for continence. It has been suggested that passive support alone is what restores continence after suspension.

### *b) Studies of urethral pressure and resistance*

Stress incontinence is generally thought to be characterized by a decrease in urethral transmission profiles and resting closure pressure. The correlation between low resting pressures and low leak point pressures is still controversial. With a bladder filled up to 200ml Almeida et al [234] reported a significant correlation between MUCP and LPP. Patients with a LPP of 60 cm $H_2O$ or less also had shorter urethral functional length and lower sphincter activity. Moreover Sinha et al [235] showed that women with urodynamic stress incontinence were more likely to leak at cough leak point pressure than the Valsalva manoeuvre, with the opposite happening for women with detrusor overactivity. On the contrary Martan et al [236] could not find any significant correlation between MUCP and VLPP.

Different urodynamics parameters have also been considered to assess urethral function and to correlate with women with stress incontinence. Digesù et al [237] showed that urethral resistance pressure (URP) and pressure flow parameters were reduced in women with stress incontinence. Salvatore et al [238] found that the opening vesical pressure is significantly correlated to ISD.

Sonographic studies have recently shown a relationship between low urethral resistance and decreased urethral smooth and skeletal muscle layers [239].

Improvement in transmission pressures is associated with successful outcomes after suspensory operations for STRESS URINARY INCONTINENCE[202, 206, 209, 210, 240, 241]. The exact mechanism for this increase in transmission is not clear. Increased exposure to intra-abdominal forces has been suggested [211, 242, 243]. Compression against the pubis by the pelvic viscera has also been suggested [244]. The final position of the urethra, however, may not be the key variable [202].

### *c) Electrophysiological studies of urethral function*

Snooks and Swash [245, 246] first brought attention to the importance of urethral denervation after childbirth and its possible contribution to urinary and faecal incontinence. Stress incontinence is frequently associated with a decline in the electrophysiological function of the pudendal nerve [247], the striated urethral sphincter [248], and the pelvic floor muscles [249, 250]. Most recent studies continue to support the finding of prolonged pudendal nerve terminal motor latency in STRESS URINARY INCONTINENCE [251].

Electromyographic studies of normal sphincter function show that in continent women, pressures begin to rise in the urethra before rising in the bladder, suggesting an active muscular component [252]. Women with stress incontinence have an altered pattern of pelvic floor muscle response during successive coughing efforts [253] with a sharp decrease in MUCP after repeated coughs [254].EMG studies have also shown that women with persistent stress incontinence after previous surgery have poorer urethral neuromuscular function than naïve stress incontinent women [255]. Experimental studies of urethral function and the role of Onuf’s nucleus in the sacral spinal cord have led to recent practical innovations in the development of serotonin uptake inhibitor agents in the treatment of stress incontinence [256]. Most electrophysiological studies have concentrated on motor rather than sensory innervation, however, and the role of urethral sensation in urodynamic stress incontinence is unknown.

### *d) Genetic factors*

Recent research is now focusing on the identification

of factors related to stress incontinence which might be genetically determined. Chen et al [257] reported that genes involved in elastin metabolism were differentially expressed in vaginal tissue from women with stress incontinence, suggesting that elastin remodelling may be important in the molecular etiology of stress incontinence. Wen et al [258] recently reported a decreased expression of alpha2-M mRNA and protein and protease inhibitory activity in the vaginal wall tissues of women with stress incontinence.

There is a need for a hypothesis which would integrate these various observations regarding hypermobility, ISD and pudendal nerve function, place them within the context of an abnormal pelvic floor and provide a model to guide research and studies of the natural history of the condition.

## 2. ROLE OF ADVANCED IMAGING IN UNDERSTANDING PATHOPHYSIOLOGY

Radiographic imaging has provided considerable insight into pathophysiology of stress incontinence, ever since the advent of bead chain cystograms and simple static and straining lateral cystograms.

Magnetic resonance imaging (MRI) and real time ultrasonography, in addition to showing the events of stress incontinence on both a global pelvic and local urethral scale, have suggested a relationship of the proximal urethra to vaginal wall movement.

### *a) Magnetic resonance imaging*

Dynamic fastscan MRI can visualize all compartments of the female pelvis during increased intraabdominal straining [259]. MRI is comparable to standard cystography in demonstrating cystocele defects [260]. Using the pubococcygeal line as a reference marker, the normal displacement of bladder base, cervix or cervical cuff, and the rectum can be identified and compared to women with prolapse. The urethra is shown in the context of global pelvic relaxation [261]. Although most MRI studies have been descriptive rather than quantitative, they still show far more soft tissue detail than earlier radiographic studies and continue to offer promising research opportunities. Recent studies have utilized an endovaginal coil to obtain higher resolution images of the urethra [262].

Dynamic MRI with cine-loop reconstruction produces vivid, intuitively appealing images which can show movement of all compartments of the relaxed pelvis during straining [261]. Static MRI shows details of urethral and peri-urethral anatomy and the striated sphincter can be clearly seen [263] . Pending further improvements in resolution, MRI remains a most promising tool for studying details of urethral movement [264].

Ultrasonography, however, is simpler and less expensive, and, for now, provides better visualization of moving structures.

Functional MRI has recently been evaluated to assess the efficacy of pelvic floor muscle training with EMG-biofeedback in women with stress incontinence. After a 12-week training period a more focused activation in the primary motor and somatosensory cortical representation sites of the lower urogenital tract was found [265]. (**Figure 10**)

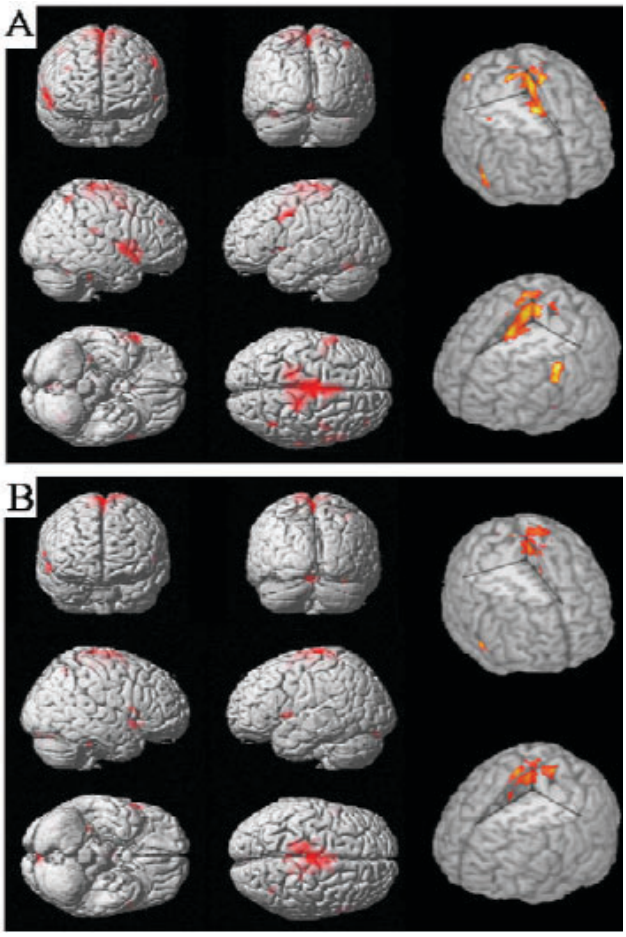


***Figure 10: Group activation maps in pre- (A) and post-test (B) rendered on a canonical single subject brain. Repetitive contraction of the pelvic floor induced significant activations in the precentral and postcentral gyrus in both conditions. The top view of the activated somatomotor and somatosensory areas before (A) and after (B) training showing a more focussed activation after the training. [265]***

### *b) Real time ultrasonography*

Several sonographic approaches have been used for the study of stress incontinence: suprapubic, translabial and transperineal. As resolution of sonographic probes has improved, the detail previously best seen with the transrectal approach may now be seen by a transperineal approach (**Figure 11**).

Earlier studies with a transrectal approach have shown that funnelling of the proximal urethra was the sonographic sign most-frequently associated with loss of urine [266]. In about half the patients with stress incontinence in this study, funnelling was seen

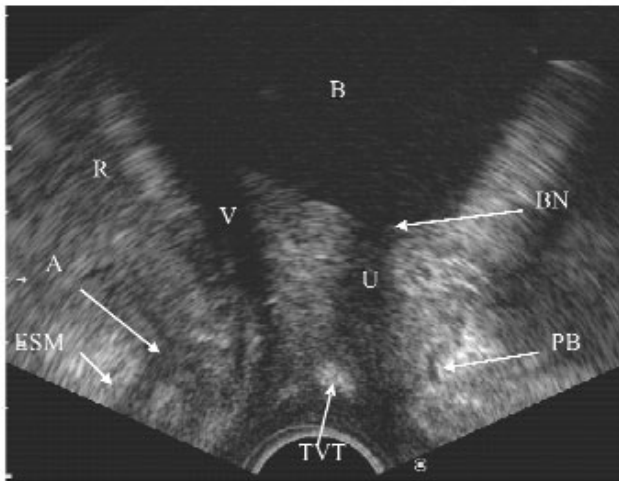


***Figure 11: Perineal ultrasound demonstrating the bladder (B), the bladder neck (BN), the urethra (U), the pubic bone (PB), the vagina (V), the rectum (R), the external sphincter (ESM), and the anus (A) after successful vaginal tape surgery.***

only with straining. In the other half, some degree of funnelling was already present at rest, increasing with straining and present with actual leakage. Enhanced views of the urethra are possible with sonographic contrast material [267]. Most recently, 3-D reconstruction from translabial views of the urethra has been used to compare findings in normal volunteers and those with ISD [268].

The most recent sonographic study of women with stress urinary incontinence found funnelling at rest in 109 of 330 patients, and found that the degree of vaginal relaxation as well as the parameters of intrinsic urethral function, including VLPP and urethral closure pressures, were worse in patients with funnelling than without. The authors of this study concluded that: “In primary genuine stress incontinence, bladder neck funnelling on ultrasound cystourethrography implies the potential coexistence of poor anatomic support and an intrinsic sphincter defect. [269].” Ghoniem et al [270] also found that urethral funnelling was more likely to be associated with low closure pressures, low VLPPs, and a higher incidence of ISD in patients with stress urinary incontinence. However, recently, Tunn et al [271] could not find an association between the ultrasound findings of urethral funnelling with stress incontinence using an introital approach, demonstrating it only in 59% of the patients with stress urinary incontinence.

Ultrasound has been used to identify paravaginal defects prior to Burch colposuspension to guide surgical modification, and then repeated after surgery to show correction of the defects [272].

Urethral movement and funnelling seen by ultrasound resemble the rotational descent previously described by Nichols and Randall [273]. It is also consistent with the previously cited descriptions of Jeffcoate and Roberts, and that of Hodgkinson. Improved soft tissue detail seen with ultrasound has permitted an extension of these original observations. The anterior and posterior walls of the proximal urethra appear to move differently during increases in intra-abdominal pressure. At first, they appear to move together: the urethra begins its descent as a single unit. At some point, however, the anterior urethra becomes arrested in its rotational movement and appears to move more slowly. The posterior portion of the urethra continues to descend along with the vaginal wall [266, 274]. This difference in movement suggests a shearing apart of the two walls, leading to the appearance of funnelling, which can be seen as urine leaks out of the urethra.

Anatomic correlation suggests that the pubourethral ligaments may restrict the movement of the anterior urethral wall, facilitating downward traction by the prolapsing vagina during stress, contributing to the shear. At the level of the pubis, the posterior portion of the pubourethral ligament travels beneath the pubis to form an anterior portion, which supports the clitoris in women, and the corpora cavernosa in men. Both Nichols and Milley [275] and Zacharin [276-278] have previously suggested that the posterior pubourethral ligaments might support the urethra, and their laxity might contribute to the descent of the urethra in stress incontinence. These studies, however, suggest a different interpretation. Longitudinal and cross-sectional views of the proximal urethra show that the ligaments travel along only the anterior portion of the urethra as they pass beneath the pubis to emerge as the anterior pubourethral ligaments. The vagina and its bilateral attachments forming the lateral sulcus support the posterior part of the urethra. It is more likely that the vaginal wall and its attachments become weaker than the strong condensations of endopelvic fascia forming these ligaments. Therefore, the pubourethral complex, even if attenuated, probably remains stronger than the underlying vaginal wall. Sonographic examination of the prolapsing urethra thus suggests arrest of anterior urethral wall movement by the pubourethral complex, while the vaginal wall continues to rotate, pulling the posterior wall of the urethra along with it.

These anatomical considerations, combined with current knowledge about pudendal nerve activity in normal, prolapse or stress incontinence, suggest an inter-relationship regarding urethral closure and vaginal movement. As intra-abdominal pressure increases, the proximal urethra experiences two kinds of forces, which may lead to opening. The first of these is a shearing force produced by the unequal separation of the anterior and posterior urethral walls from the pubis during straining. This is the effect of vaginal mobility on urethral closure. The second is an expulsive force, produced by the transmission of intra-abdominal forces to the bladder, which must be resisted by the urethra if opening is to be prevented. The urethra

resists this primarily by intrinsic closure of the pudendally innervated striated sphincter, aided by vaginal support.

3D ultrasound has been recently introduced new insights in the image of urethral sphincters. Athanasiou et al [279], using a transvaginal approach, reported a close correlation between the urethral sphincter volume and the degree of incontinence assessed on videocystourethrography (r = .-65; P < .001).

Urethral vasculature has also been postulated to play a role in the continence mechanism and different Doppler parameters have been studied to evaluate correlation with STRESS URINARY INCONTINENCE. However, also for this aspect, results are controversial since some authors [280] reported less periurethral vessels and flow in women suffering from stress urinary incontinence whereas others [281] could not find any difference in the appearance of the urethral vasculature in subjects with or without stress urinary incontinence.

It is likely that these shearing and expulsive forces are generated simultaneously as intra-abdominal pressure rises. One can easily imagine that the urethra can be brought to a continence threshold beyond which urethral closure cannot be maintained.

One can further imagine that repeated episodes of prolapse may eventually stretch, tear or attenuate sphincter mass and contribute to a chronically weakened urethra manifested by low VLPP or low urethral closure pressures, characteristic of ISD.

After severe or prolonged untreated prolapse and stress incontinence, vaginal support alone may not be sufficient to correct the deficiencies of an exhausted sphincter. Although theoretical rather than evidence-based, such considerations may direct future research efforts towards a more integrated hypothesis regarding stress incontinence in women.

The relative contributions of abnormal vaginal mobility and intrinsic urethral function should be considered as part of a continuum rather than a dichotomy. Current research and interest has concentrated mostly on ISD as the primary cause of stress urinary incontinence in women, but the relationship of the many factors affecting urethral support and function should remain a perspective in interpreting emerging findings.

## V. CONCLUSIONS

We are approaching a new classification of stress incontinence which will integrate hypermobility and urethral dysfunction as inter-related elements on a spectrum of change. Certain concepts have stood the test of time, and they are included below, along with conclusions:

1. Many patients with urodynamic stress incontinence show urethral mobility (Level 2), though it is not yet known what it is about that mobility which permits urethral opening during stress.
2. Some patients who present with minimal mobility or who have recurred after successful surgery have primary or residual sphincter insufficiency.
3. Sphincter insufficiency is related to a decline in striated sphincter muscle mass and function as measured by electrophysiological studies of pudendal nerve and sphincter function, and MRI and sonographic estimates of muscle mass (Level 1). If repeated episodes of vaginal traction can be shown to enhance sphincter damage, then the effect of early treatment of stress incontinence and prolapse on future development of ISD should be investigated, since advanced ISD remains difficult to treat.
4. Successful operations can restore urethral position but probably do not restore urethral function. A good surgical outcome probably requires a certain reserve of urethral function. It is in the area of functional understanding of urethral anatomy that the greatest progress is likely to be made.

# D. PELVIC ORGAN PROLAPSE

## I. PATHOPHYSIOLOGY OF PELVIC ORGAN PROLAPSE

Normal pelvic organ support depends on the integrity of the endopelvic fascia, i.e. connective tissue, the pelvic floor muscles and adequate nerve supply. Theoretically, if one of these factors fails, the others might be able to compensate to a certain degree. Our knowledge as to which structure fails and why remains limited. **Table 1** lists structural elements of pelvic organ support, their possible damage and subsequent site of pelvic organ prolapse. In **Table 2** anatomical and functional determinants of normal pelvic organ support are listed. The possible nature of failure and its potential causes, established and theoretical risk factors are also summarised.

For many years vaginal delivery has been considered the most important causal factor in the development of pelvic organ prolapse [282-287]. However, some large community-based epidemiological studies have described pelvic floor symptoms in women who gave birth by caesarean section only [283, 288]. It seems that pregnancy itself plays an important role in the development of pelvic floor dysfunction. Still not sufficiently investigated, the hormonal and enzymatic preparation of the connective tissue to soften and

***Table 1. Structural elements of pelvic organ support, their possible damage and subsequent site of pelvic organ prolapse. The levels of support and anatomical defects are derived from the anatomical studies of DeLancey. [357-359]***

| Structure | Failure / Defects | Anatomical result |
|---|---|---|
| Uterosacral ligaments (Level 1 support) | ?Disruption, ?overdistension and elongation | Uterine prolapse<br>Posthysterectomy vault prolapse |
| • Anterior endopelvic fascia<br>• Lateral attachment at arcus tendineus fascia pelvis with proximal attachment at ischial spine (Level 2 support) | • Attenuation of fascia Disruption from attachment | • Midline cystocele<br>• Paravaginal defect-cystocele<br>• Uterine or vault prolapse |
| Perineum (Level 3 support) | Disruption from endopelvic fascia<br>Disruption of bulbocavernosus muscles | Excessive perineal descent<br>Rectocele |
| Levator ani muscle<br>• Reduced tone/attenuation<br>• Perineal descent<br>• Vertical course of vagina | • Disruption/avulsion from pubic ramus<br>• Paravaginal defect-cystocele | |

***Table 2. Determinants of normal pelvic organ support. Possible sites of failure and possible causes, established and theoretical risk factors.***

| Normal support | Failure | Possible cause / risk factors |
|---|---|---|
| Normal connective tissue including normal tone (smooth muscle cells) | • Reduced tone<br>• Pathological type and cross linking LEVEL OF EVIDENCE 2<br>• Disruption LEVEL OF EVIDENCE 2 | • Genetic LEVEL OF EVIDENCE 2<br>• Pregnancy (connective tissue remodelling) LEVEL OF EVIDENCE 3<br>• Vaginal birth (mechanical) LEVEL OF EVIDENCE 2<br>• Chronic pelvic floor stress (straining, constipation, asthma)<br>• Obesity |
| Normal attachment of connective tissue and pelvic floor musculature | • Disruption, detachment LEVEL OF EVIDENCE 2 | • Vaginal birth LEVEL OF EVIDENCE 1<br>• Hysterectomy, pelvic operations LEVEL OF EVIDENCE 3<br>• Chronic pelvic floor stress LEVEL OF EVIDENCE 3<br>• Pelvic trauma (accidents, falls) LEVEL OF EVIDENCE 3 |
| Normal tone of the pelvic floor muscle | • Hypotonic pelvic floor muscle LEVEL OF EVIDENCE 4 | • Pregnancy, childbirth (ischemic, mechanical, hormonal) LEVEL OF EVIDENCE 2<br>• Reduced connective tissue tone<br>• Chronic pelvic floor stress |
| Normal, nearly horizontal, axis of the vagina | • Vertical course of the vagina LEVEL OF EVIDENCE 3 | • Hysterectomy, pelvic operations including Burch-colposuspension LEVEL OF EVIDENCE 3<br>• Chronic pelvic floor stress<br>• Vaginal birth LEVEL OF EVIDENCE 2 |
| Normal innervation and pre-programming of abdominal capsule and pelvic floor muscle | • Denervation/re-innervation LEVEL OF EVIDENCE 1<br>• Loss of pre-programming LEVEL OF EVIDENCE 4 | • Vaginal birth LEVEL OF EVIDENCE 1<br>• Pelvic trauma/pain<br>• Delayed or lack of pelvic floor contraction during increased abdominal pressure LEVEL OF EVIDENCE 3 |

stretch adequately during vaginal birth might be an imperative factor. Although muscular, neural and connective tissue damage has been demonstrated in women after vaginal deliveries, these changes do not automatically result in pelvic floor dysfunction. Epidemiological studies have also emphasised the contributing effects of ageing, genetic predisposition, obesity, constipation and hormone therapy.

## 1. GENETIC AND ETHNIC PREDISPOSITION

Comparative studies have drawn attention to the higher incidence of pelvic floor dysfunction amongst relatives, most notably amongst identical twins [289-292]. Familial incidence of POP was reported as high as 30% [292].

Genetic variants have been documented that run in families with an increased incidence of pelvic organ prolapse [293]. One study examined gene expression of structural proteins that are related to actin and myosin in five women with and five women without pelvic organ prolapse in the pubococcygeal muscle. There were several genetic differences between subjects and controls with under and overexpression of genes [294]. Altered gene expression of elastin has also been described in women with pelvic organ prolapse [295]. In mice, HOXA11 has been identified as the gene that is responsible for the development of the uterosacral ligaments [296]. In HOXA11-null mice the uterosacral ligaments were absent. HOXA11 and collagen expression were significantly decreased in the uterosacral ligaments of women with pelvic organ prolapse [296].

Also, it has long been suspected and recently been studied that connective tissue diseases like Ehlers-Danlos and Marfan's syndrome predispose to pelvic organ prolapse [297]. Young women with pelvic organ prolapse are more likely to have neurological or connective tissue diseases and congenital abnormalities [298]. Intrinsic joint hypermobility is another well recognised connective tissue disease that is associated with pelvic organ prolapse [299-302].

Differences between ethnic groups have been described in some studies with regard to pelvic floor function. White women seem to have a higher risk of pelvic organ prolapse compared with Afro-American women [303]. However, prolapse is highly prevalent in rural Gambia, West Africa e.g. with 14% of 1067 having moderate to severe prolapse [287]. In one study Hispanic women had an increased risk for prolapse compared to white women [304]. The thickness of the puborectalis muscle measured on perineal ultrasound varies between Caucasian and Chinese women [305].

Signs of a rectocele on ultrasound examination were found in 12% of young nulliparous women in a small observational study raising the question of a congenital fascial defect [306]. Pelvic organ prolapse in young women has also been linked with abdominal hernias [292]. As a deep pouch of Douglas is frequently present in young nulliparous women, without pelvic organ prolapse this implies a congenital variation and may be predisposition [307].

## 2. ALTERATIONS OF COLLAGEN, ELASTIN AND SMOOTH MUSCLE OF THE VAGINAL AND SUPPORTIVE TISSUES

Many studies have found alterations in supportive tissues in women with pelvic organ prolapse [308]. One study revealed that the general amount of collagen in the parametria is reduced in pre and postmenopausal women with pelvic organ prolapse compared with women without prolapse. In biopsies from the vaginal apex there were no differences [309].

Type III collagen is the primary collagen subtype in the vagina and its supportive structures. The ratio of collagen I to III is an indicator of tensile strength. The higher the amount of collagen type III the lower mechanical strength. A lower collagen I/III ratio due to increased type III collagen has been demonstrated in women with pelvic organ prolapse in the vaginal subepithelium and uterosacral and cardical ligaments, independent of age and parity [310-312]. Menopause seems to decrease the collagen I/III ratio [311, 313]. Type I collagen content was similar in women with and without uterine prolapse, but the quality of the fibres was different. In this study, hormonal status did not affect collagen content [314]. Unfortunately there are only cross-sectional studies and the direction of the association between pelvic organ prolapse and increased collagen III is not clear. Is the decreased collagen I/III ratio a response to the prolapse or does it cause it? However, due to the reduced tensile strength of the connective tissue progression of pelvic organ prolapse is likely.

Other studies have focussed on examining active components and factors suggestive of connective tissue remodelling. Active remodelling of vaginal connective tissue in women with prolapse has been suggested as a result of "biomechanical stress" [310]. A higher expression of tenascin -a glycoprotein that is involved in tissue repair – was found in cardinal and uterosacral ligaments of prolapsed uteri [311, 315]. This implies traumatic factors caused by the prolapse. The activity of matrix metalloproteinases (MMP) has been examined in women with and without pelvic organ prolapse with different results emphasising the heterogeneity of pelvic floor dysfunction as well as difficulties with standardisation of specimens, sites and tests [316-318]. Results do however show an active remodelling of the connective tissue in women with prolapse.

Elastin also plays an important role in connective tissue and pelvic floor integrity. As it is thought to be

very stable with little turnover during a woman's lifetime apart from childbirth, demonstrated elastin differences between women with and without pelvic organ prolapse are suggestive of a structural defect rather than a secondary result of prolapse [319].

In mice it has been shown that impaired homeostasis of elastin after parturition due to insufficient LOXL1 expression (lysyl oxidase) leads to prolapse [320]. LOXL1-deficient mice seem to develop prolapse due to a global defect in connective tissues that correlates with inferior biomechanical properties with a decrease of ultimate load at failure [321]. Altered elastin metabolism and elastin gene expression were found in women with pelvic organ prolapse [295, 315, 322] (**Figure 12**).

The significance of highly prevalent smooth muscle in pelvic floor supportive tissues is not clearly understood. In women with normal pelvic organ support smooth muscles fibres in the anterior vaginal wall are organised in "tightly-packed" bundles orientated in circular and longitudinal directions [323]. In comparison, in women with pelvic organ prolapse the bundles were smaller, fewer and disorganised [323]. These features were also demonstrated in biopsies from the upper posterior vaginal wall after hysterectomy in women with prolapse [324]. Loss of smooth muscle content was related to the degree of prolapse [324]. Smooth muscle content was also reduced in the round ligament of women with prolapse [325]. Caldesmon, a protein in smooth muscle that inhibits actin-activated myosin adenosine triphosphatase, plays a role in regulating smooth muscle contractility. As it has been found to be increased in vaginal tissues in women with prolapse, it may have led to impaired smooth muscle contractility and force maintenance [326].

Biomechanical factors have been assessed with different techniques. The tensile strength of the connective tissue is significantly reduced in women with pelvic organ prolapse [327] whereas extensibility was shown to be greater. Interestingly these differences of extensibility were not demonstrated in the skin of the forearms implying that prolapse in these women was related to local rather than systemic connective tissue alterations [328]. Elongation of vaginal apical tissues of women during pelvic reconstructive surgery seems very variable between 15 to 42 mm [329]. The authors concluded that this might be a reason for otherwise unexplained failure of prolapse surgery [329].

## 3. NEUROLOGICAL FACTORS

Intact innervation of the levator ani muscle, anal, and urethral sphincters is critical to normal pelvic function. It has been suggested that neurological damage induced by transvaginal reconstructive surgery results in suboptimal outcome [330]. Perineal terminal motor latency served as a surrogate parameter. However, the authors have reported rather low success rates after bilateral sacrospinous ligament fixation which emphasises the importance of surgical technique [331].

Vaginal birth is an established factor for nerve damage. Prospective EMG studies performed before and after childbirth substantiated the evidence of childbirth induced pelvic floor denervation detecting increased fibre density after vaginal delivery. Ageing leads to further deterioration of pelvic floor denervation [164, 332].

Histologically, there were smaller and fewer nerve bundles in women with posterior vaginal wall prolapse compared with women without prolapse [324]. The density of peptide-containing nerves in the periurethral tissue and in the levator ani muscle in women with prolapse was reduced [333, 334]

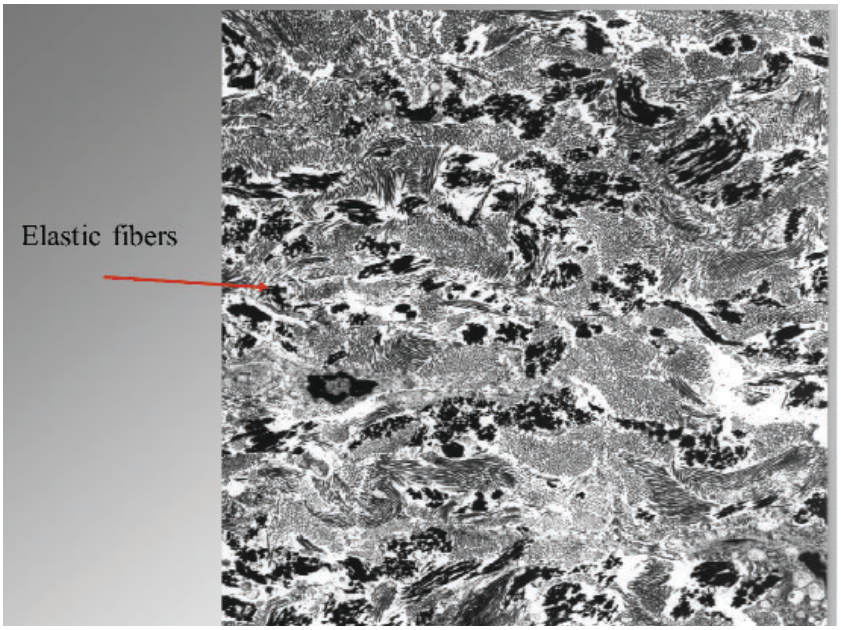


***Figure 12: Tissue sample of a 54 old woman with POP. Black areas show fragmented elastic connective tissue fibres as a sign of pelvic floor tissue defect. [291]***

## 4. PREGNANCY- EPIDEMIOLOGY AND CONNECTIVE TISSUE AND PELVIC FLOOR MUSCLE REMODELLING

Recently some studies have drawn attention to the occurrence of clinically significant pelvic organ prolapse during pregnancy in nulliparous women [335-338]. These studies employed the validated quantitation of pelvic organ prolapse of the International Continence Society. Pelvic organ prolapse stage 2 was found in 26-48% whereas none of the 21 age and race matched non-pregnant controls demonstrated stage 2 prolapse [336, 337]. Prolapse stage increased during pregnancy and persisted postpartum in women who were delivered vaginally [335-338]. The most frequent site of prolapse was the anterior vaginal wall in all of these studies.

The causes of the development of pelvic organ prolapse during pregnancy might be multifactorial but certainly hormones and enzymes are involved. Progesterone is known to reduce the tone in ureters, bladder and urethra because of its smooth muscle relaxing and estrogen antagonising effects [339]. Relaxin, a peptide hormone similar to insulin, increases markedly during pregnancy. It modifies the connective tissue and has a collagenolytic effect to allow for appropriate stretching during vaginal birth in guinea pigs [340]. As a likely result of connective tissue remodelling in preparation for birth, Landon and colleagues [341] found that the connective tissue of the rectus sheath fascia and the obturator fascia could be stretched to greater length during pregnancy, but it is also much weaker. In some women these changes may be irreversible or further stretching beyond physiological limits may result in permanent dysfunction.

## 5. CHILDBIRTH

Vaginal birth has long been considered the most important risk factor for pelvic organ prolapse. Most epidemiological studies demonstrate an association with parity in general [283, 286, 287, 342-344] and specifically with vaginal birth [168, 283, 303, 345]. Mechanical damage to the pelvic floor musculature, connective tissue and nerve supply occurs particularly during the second stage of labour when the fetal head distends and stretches the pelvic floor. Apart from direct muscle rupture and muscle and connective tissue stretching there might also be biochemical damage to the soft tissue, especially during long second stages. The recent development of three and four dimensional ultrasound has enabled us to directly study pubovisceral muscle detachment after vaginal delivery. Dietz et al., in a small study, revealed levator avulsion in 36% of 39 women after vaginal birth. This injury was associated with stress incontinence [155].

Employing the ICS pelvic organ prolapse standardisation, Sze et al. [337] prospectively studied nulliparous women and found that postpartum, 52% had stage 2 prolapse, 37% of women developed a new prolapse and 15% revealed a more severe prolapse compared to antenatal examinations.

Childbirth in mice has been investigated in an intriguing study analysing the elastin and LOXL1 expression [346]. There is degradation before and a high turnover of elastical fibres after childbirth that allows the tissues to recover. During parturition monocytes are present in the vagina which may induce elastolysis by chemotaxis. Mice injected with elastases into the posterior vaginal wall post partum demonstrated protrusion 2-4 hours later. Fibulin, an elastin-binding protein that is crucial for elastogenesis and effective cross linking is thought to be important for regeneration and to counteract elastin degradation. In 33 of 36 mice with null mutations in fibulin-5 pelvic organ prolapse was found to progress with age. Drewes et al. concluded that there might be different factors initiating prolapse like ageing, smoking and childbirth but the final pathway seems to be a reduction in number of functional elastic fibres [346].

## 6. CAESAREAN SECTION- ONLY PARTIALLY PROTECTIVE

In most post partum as well as long-term studies caesarean section might reduce but not totally prevent urinary and anal incontinence. Pelvic organ prolapse however seemed considerably lower after caesarean section [283, 343] but was still described in a rare prospective study before and 6 weeks after childbirth in 35% of 26 women after caesarean section during active labour compared to 32% of 41 women who had spontaneous vaginal deliveries [337]. The influence of labour versus no-labour pure caesarean delivery on pelvic organ prolapse has been negated in one epidemiological study using validated questionnaires [168].

## 7. OBSTETRICAL AND MATERNAL FACTORS

Age at first delivery may theoretically have an impact on the development of pelvic organ prolapse. However, studies are controversial considering younger age (25 versus 28 years of age) [347] as well as older age (more than 30 years) [348] at first delivery a risk factor. Another large study did not reveal an association at all [303].

A higher birth weight especially more than 4000g has been shown to increase the risk for pelvic organ prolapse in univariate and multivariate analyses [303, 304, 343, 349]. An extensive vaginal rupture has also been associated with prolapse [349].

Instrumental delivery is an established risk factor for anal incontinence but has only been shown in one study to be associated with prolapse [347] A mediolateral episiotomy did not prevent or result in a higher incidence of pelvic organ prolapse three months post partum [303, 350].

## 8. HORMONES

Hormone therapy has been shown to increase urogenital symptoms in some studies [351-353]. Whereas the negative effect of systemic hormone therapy on incontinence status seems established this has not been clearly demonstrated for pelvic organ prolapse. Most epidemiological studies did not reveal a significant association [286, 304, 343]. In a univariate analysis of self-reported prolapse symptoms in a population-based study, current estrogen use increased the risk. However, multivariable regression did not confirm this [303].

In prolapse patients, the cardinal ligaments and levator ani fascia express more estrogen receptors than in women without prolapse [354, 355]. Long term estrogen treatment however led to a decline in estrogen receptor expression [282, 284, 287, 344]. Menopause seems to decrease the collagen I/III ratio [313].

## 9. AGE

Most epidemiological studies have determined age as a main risk factor for pelvic organ prolapse [286, 342, 343, 356]. However, the interaction of age, menopause and hormonal status seems inseparable.

## 10. OBESITY: BODY MASS INDEX AND WAIST CIRCUMFERENCE

Many studies have examined the influence of obesity on pelvic organ prolapse prevalence, some studies also of progression and regression. Body mass index and waist circumference are the most commonly measured variables. An increased BMI increases the risk for prolapse [285, 304, 306, 347, 357] and specifically for progressive rectoceles [342]. Increased waist circumference was associated with more pelvic organ prolapse in some studies [342, 343]. Handa et al. demonstrated this for cystoceles [342]. Whereas some studies do and some do not reveal obesity as a risk factor, no study found overweight protective.

## 11. CONSTIPATION

Similar to obesity, constipation has frequently been described to increase the risk for pelvic organ prolapse [303, 306, 357, 358] and has never been found to be protective.

## 12. CHRONIC PELVIC FLOOR STRESS

Occupational heavy lifting has long been associated with pelvic organ prolapse [359]. Prolapse was more prevalent in labourers or factory workers compared with housewives or service workers [360, 361] Chronic lung disease seems likely to increase prolapse but has rarely been shown to be an independent risk factor [284].

## 13. PREVIOUS OPERATIONS

Whether previous hysterectomy increases the risk for subsequent pelvic organ prolapse is not clear. In some epidemiological studies previous hysterectomy seems to predispose to prolapse and further reconstructive surgery [285, 362] One case-control study (114/6214 women who had undergone hysterectomy, 236/6100 controls randomly selected) looked at the risk factors for reconstructive pelvic surgery. The incidence was 4.3 per 1000 women years if pelvic organ prolapse was grade 2 before the initial hysterectomy but only 0.6 if it was grade 0 or 1. Vaginal hysterectomy itself did not increase the risk [356]. The empirical fact that younger women and women operated on for severe prolapse are more likely to have recurrent prolapse has been confirmed in one follow up study of 389 women [363]. Previous surgery for pelvic organ prolapse appears to be a consistent risk factor.[364, 365]

Isolated enteroceles may occur after pelvic surgery. The classical example is the development of enteroceles after Burch colposuspension in up to 32% [366-369] Symptoms suggestive of a rectocele like digitation to defecate were more frequently observed after hysterectomy [370]. The anterior compartment is the main site of recurrence after sacrospinous fixation. In two comprehensive reviews the apical success rates after a follow up of 12 or more months were 79 – 97% (mean 92%) but the failure rate for cystoceles was 10-30% (mean 21%) [371].

## 14. THE BONY PELVIS

There is evidence from several case control studies that variations in axial and pelvic skeletal structure can be associated with increased risks of POP. These include increasing degrees of thoracic kyphosis, a decrease in lumbar lordosis and in vertical orientation of the pelvic inlet, and an increase in the transverse diameter of the pelvic inlet [372-374]. In a case control study Handa [375] compared 59 women with pelvic floor disorders with controls using standardized pelvimetry techniques during MRI.

After controlling for age, race and parity, using a multiple logistic regression analysis, pelvic floor disorders were significantly associated with a wider transverse inlet (odds ratio 3.4) and a shorter obstetrical conjugate (odds ratio 0.23). The association between early age, advanced stage POP and the severe disruption of pubic bone and pelvic muscle structure in women with bladder exstrophy is well recognized [376].

## 15. CONCLUSION AND RECOMMENDATIONS

There are genetic alterations that predispose to pelvic organ prolapse (LEVEL OF EVIDENCE 2). Differences in collagen type and ratios as well as smooth muscle organisation and neurogenic structures between women with and without prolapse are well-known but the cause and effect remain unclear (LEVEL OF EVIDENCE 2). Altered metabolism and gene expression of elastin is thought to be the cause of pelvic organ prolapse (LEVEL OF EVIDENCE 2) whereas active remodelling of the connective tissue (increase in tenascin e.g.) is likely to be a result of biomechanical stress due to the prolapse (LEVEL OF EVIDENCE 2).

POP increases with age (LEVEL OF EVIDENCE 2). Modifiable risk factors for POP are obesity (increased BMI and waist circumference), occupational heavy lifting and constipation (LEVEL OF EVIDENCE 3). Previous pelvic floor surgery increases the risk of prolapse (LEVEL OF EVIDENCE 2).

Pregnancy itself can lead to prolapse (LEVEL OF EVIDENCE 2). Vaginal delivery increases the risk for prolapse further (LEVEL OF EVIDENCE 1) but caesarean section is only partially protective (LEVEL OF EVIDENCE 2). Obstetrical aspects that are associated with loss of pelvic organ support are birth weight of more than 4000g and instrumental delivery (LEVEL OF EVIDENCE 3). The effect of maternal age at delivery remains unclear. There is no association between episiotomy and POP.

Further research should focus on modifiable risk factors and their impact on the development and prevention of pelvic organ prolapse and its recurrence. The course of pregnancy with hormonal changes cannot be altered and caesarean section is not a universal alternative to vaginal delivery. Although we should aim to make vaginal birth safer for mother and child, the mainstay of prevention of prolapse are modifiable risk factors.

# II. ASSOCIATED PELVIC FLOOR CONDITIONS

Pelvic organ prolapse (POP) has a strong inter-relationship with the urinary tract and urinary incontinence commonly co-exists with POP. Thus, it is important for incontinence specialists to have a well-grounded understanding of POP in order to provide optimal patient care for the many women worldwide whose quality of life is impacted by pelvic floor disorders.

## 1. BLADDER FUNCTION

In a large community-based questionnaire survey, 44% (104/239) of women who had prolapse symptoms (239/3799) also complained of stress urinary incontinence and 37% of overactive bladder [377]. Animal experiments performed by Barrington in the first half of the twentieth century have suggested a mechanism by which urethral relaxation may evoke reflex detrusor contraction: when urine enters a relaxed proximal urethra, the desire to void may be evoked, an extension of his experimental observations in anesthetized rabbits, that water running through the urethra, or mechanical distension of the urethra produced a bladder contraction [378-380]. This mechanism might explain the high co-occurrence-rate of POP and bladder symptoms.

Schick et al [381] looked at 255 women with urodynamic stress incontinence and found a statistically significant correlation between urethral hypermobility and the degree of urethral incompetence assessed with the abdominal leak point pressure. However, with greater degrees of anterior vaginal wall prolapse (Stage III and IV) fewer women have symptoms of stress incontinence [382]. Increased prolapse stages (especially point Ba on the POPQ) are associated with obstructive symptoms, as severe prolapse can descend and obstruct the urethra, making assessment and management of the continence mechanism in such patients problematic [282, 382-384] [385].

Multiple studies have described an occult stress incontinence rate after various methods of reducing the prolapse during preoperative testing of [258-261]. However, Bump et al described an only 4% de novo incontinence rate in women with Stage III or IV prolapse who had been randomized to a bladder neck plication procedure as their only prophylaxis, also concluding that preoperative barrier testing was not useful in identifying women who required a urethropexy [386]. Klutke et al determined that preoperative barrier testing was most useful in identifying those women who do not leak with reduction of the prolapse, since such patients did not undergo urethropexy and had better outcomes with regard to both USI and DO rates [387]. Because of this uncertainty, the least invasive method of bladder neck stabilization seems preferred for such patients [388].

Pelvic organ prolapse can negatively affect voiding function [385, 389], although one study noted that the majority of women with severe prolapse still void effectively [390]. Looking at 228 women with urinary tract disorders and/or prolapse, Dietz et al [391] found that enterocele had the worst effect on voiding function ($P<0.001$), whereas the relationship between anterior vaginal wall prolapse and voiding was complex: using ultrasound the finding of an intact retrovesical angle was related to difficulties in voiding ($P<0.001$);

funnelling and opening of the retrovesical angle was associated with improved voiding (P<0.001). Fitzgerald found that preoperative voiding studies with the prolapse reduced by a pessary was the best predictor of normalization of residuals post operatively [392]. The impact of pelvic organ prolapse on the upper urinary tract is not well described in the surveyed literature, consisting primarily of case reports of acute or chronic renal failure attributed to urethral obstruction by Stage IV uterine or vaginal vault prolapse. Hydroureter and hydronephrosis was demonstrated in such cases, resolving post repair [393-397].

### 2. BOWEL FUNCTION

Bowel symptom like incontinence of flatus and obstructed defecation are common in women with POP. In several surveys, the incidence of anal incontinence ranges from 15-50% ([398-402]. [377, 398, 403-405]. Faecal incontinence was reported in 5-22% of women with prolapse [398, 404, 405] which was significantly more than bowel symptoms in a control group [404]. There were no associations found between prolapse stages and symptoms after adjusting for age and BMI [403, 405].

There are also disparities between the degree of pelvic organ prolapse, pelvic floor symptoms and defecography results [406, 407]. Two series of defecographies in consecutive patients with prolapse and/or evacuation disorders describe defecographic findings that changed the patients diagnosis (though not always the management) in 46 of 62 of cases and noted enteroceles that were not found on physical exam in approximately 50% of cases [408-410]. Sigmoidoceles are present in 4-11% of reported series, and are nearly always missed on physical examination [410, 411]. Their clinical impact and management remain however unclear. Defecography is not a routine investigation in women with POP and interpretation may be difficult in some cases since normal asymptomatic women may have focal defecographic abnormalities demonstrated [407].

The prevalence of abnormal colonic transit time is approximately 20% in patients presenting with evacuation disorders [412]. An abnormal preoperative colonic transit study is the most consistently cited risk factor for failure of rectocele repair to relieve evacuatory symptoms, regardless of the surgical technique [413-415]. Recently Goh et al [416] reviewed the management of rectocele and clearly describe the complexity of clinical conditions resulting from the possible combination of various gynaecological and colorectal symptoms with anatomical abnormalities and the different surgical approaches.

### 3. SEXUAL FUNCTION

Dyspareunia, coital incontinence and vaginal dryness are common complaints in women with pelvic floor disorders [417, 418]. Although sexual dysfunction appears to be more frequently observed in these women, pelvic organ prolapse did not negatively impact on sexual satisfaction when controlled for confounders like age [418-420].

## E. FAECAL INCONTINENCE: GASTROENTEROLOGICAL PERSPECTIVE

Faecal continence is maintained by the structural and functional integrity of the anorectal unit. Consequently, disruption of the normal anatomy or physiology of the anorectal unit leads to faecal incontinence. Faecal incontinence is often due to multiple pathogenic mechanisms and rarely due to a single factor [421].

## I. STRUCTURE AND FUNCTION OF THE ANORECTUM

The rectum is a hollow muscular tube, 12 cm to 15 cm long, composed of a continuous layer of longitudinal muscle that interlaces with the underlying circular muscle [422]. The anus is a muscular tube 2 cm to 4 cm long. At rest, it forms an angle with the axis of the rectum of **approximately 90°**; during voluntary squeeze the angle becomes more acute, approximately 70°; during defecation, the angle becomes more obtuse, about 110° to 130°.

### 1. THE ANAL SPHINCTER

The anal sphincter consists of two muscular components: the internal anal sphincter (IAS), a 0.3 cm to 0.5 cm thick expansion of the circular smooth muscle layer of the rectum, and the external anal sphincter (EAS), a 0.6 cm to 1.0 cm thick expansion of the striated levator ani muscles. Morphologically, both sphincters are separate and heterogenous [423]. The EAS is a predominantly slow-twitch, fatigue resistant muscle [424, 425]. The IAS generates mechanical activity, with a frequency of 15 to 35 cycles per minute, and ultra-slow waves at 1.5 to 3 cycles per minute [426, 427]. The ultra-slow waves generate pressures fluctuating between 20 mm Hg and 50 mm Hg in 10% of control subjects [428-430]. The IAS contributes approximately 70% to 85% of the resting sphincter pressure, but only 40% after sudden distension of the rectum and 65% during constant rectal distension [431]. Thus, the IAS is chiefly responsible for maintaining anal continence at rest [431].

The anus is normally closed by the tonic activity of the IAS. This barrier is reinforced during voluntary squeeze by the EAS. The anal mucosal folds, together with the expansive anal vascular cushions, provide a tight

seal [432, 433]. These barriers are further augmented by the puborectalis muscle, which forms a flap-like valve that creates a forward pull and reinforces the anorectal angle [434].

### 2. NERVE STRUCTURE AND SENSATION

The anorectum is richly innervated by the sensory, motor, and autonomic nerves and by the enteric nervous system. The principal nerve is the pudendal nerve, which arises from the second, third, and fourth sacral nerves (S2, S3, S4) and innervates the EAS. The pudendal nerve is a mixed nerve that subserves both sensory and motor function [435] Pudendal nerve block creates a loss of sensation in the perianal and genital skin and weakness of the anal sphincter muscle, but it does not affect rectal sensation [431]. It also abolishes the rectoanal contractile reflexes, suggesting that pudendal neuropathy may affect the rectoanal contractile reflex response. It is not completely understood how humans perceive stool contents in the anorectum. Earlier studies failed to demonstrate rectal sensory awareness [436, 437]. But more recent studies have confirmed that balloon distension is perceived in the rectum and that such perception plays a role in maintaining continence [438, 439]. Furthermore, sensory conditioning can improve both hyposensitivity [440, 441] and hypersensitivity [442] of the rectum. Mechanical stimulation of the rectum can produce cerebral evoked responses, [443] confirming that the rectum is a sensory organ. Although there are no organized nerve endings, both myelinated and unmyelinated nerve fibres are present in the rectal mucosa, and the myenteric plexus [437, 444]. These nerves most likely mediate the distension or stretch-induced sensory responses as well as the viscero-visceral, [445] the recto-anal inhibitory, and the recto-anal contractile reflexes [444]. The sensation of rectal distension is most likely transmitted along the S2, S3, and S4 parasympathetic nerves [444]. Rectal sensation and the ability to defecate can be abolished completely by resection of the nervi erigentes [446]. If parasympathetic innervation is absent, rectal filling is only perceived as a vague sensation of discomfort. Even paraplegics or persons with sacral neuronal lesions may retain some degree of sensory function, but virtually no sensation is felt if lesions reach the higher spine [439, 447]. Thus, the sacral nerves are intimately involved with the maintenance of continence. It has been suggested that bowel contents are periodically sensed by anorectal “sampling,”[448, 449] the process by which transient relaxation of the IAS allows the stool contents from the rectum to come into contact with specialized sensory organs, such as the Krause end-bulbs, Golgi-Mazzoni bodies and genital corpuscles, and the sparse Meissner’s corpuscles and Pacinian corpuscles in the upper anal canal [436, 444, 450]. Specialized afferent nerves may exist that subserve sensations of touch, temperature, tension, and friction, but are incompletely understood [444]. Incontinent patients appear to sample rectal contents infrequently [449]. The role of anorectal temperature sensation is also subject to debate [451-453]. The likely role of anal sensation is to facilitate discrimination between flatus and faeces and the fine-tuning of the continence barrier, but its precise role needs to be characterized.

### 3. RECTAL DISTENSION

Rectal distension is associated with a fall in anal resting pressure known as the rectoanal inhibitory reflex. The amplitude and duration of this relaxation increases with the volume of rectal distension [454]. The arrival of flatus mimics sudden rectal distension and this is associated with a fall in anal pressure [455]. Although this process may facilitate discharge of flatus, rectal distension is also associated with an anal contractile response, a subconscious reflex effort to prevent release of rectal contents, such as flatus [456-458].

The amplitude and duration of the rectoanal contractile reflex also increases with rectal distension up to a maximum volume of 30 ml [454]. Abrupt increases in intraabdominal pressure, such as those caused by coughing or laughing, are associated with increases in anal sphincter pressure [459]. This may be achieved through multiple mechanisms, including reflex contraction of the puborectalis [460].

### 4. ANAL ENDOVASCULAR CUSHIONS

The blood-filled vascular tissue of the anal mucosa also plays an important role in producing a more perfect closure of the anus. An in vitro study showed that even during maximal involuntary contraction, the internal sphincter ring was unable to close the anal orifice completely and a gap of approximately 7 mm was left open. This gap was filled by the anal cushions [461]. Anal cushions may exert pressures of up to 9 mmHg and thereby may contribute 10% to 20% of resting anal pressure [462].

## II. PATHOGENIC MECHANISMS AND ETIOLOGY

Faecal incontinence occurs when one or more mechanisms that maintain continence is disrupted to an extent that other mechanisms are unable to compensate. Hence, faecal incontinence is often multifactorial1, [421, 463] In a prospective study, 80% of patients with faecal incontinence had more than one pathogenic abnormality [421]. Although the pathophysiological mechanisms often overlap, they may be categorized under the four subheadings shown in **Table 3**. For each category, the probable cause(s) and the mechanism through which it leads to faecal incontinence is also summarized in Table 3.

*Table 3. Pathophysiologic mechanisms underlying faecal incontinence*

| CATEGORY | CAUSE | MECHANISTIC EFFECT |
|---|---|---|
| **Structural** | | |
| Anal sphincter muscle | Haemorrhoidectomy, anal dilatation | Loss of sampling reflex due to neuropathy |
| Rectum | Inflammation, IBD/ radiation; Prolapse; aging; IBS | Lost accommodation and sensation; hypersensitivity |
| Puborectalis | Excessive perineal descent; aging; trauma | Obtuse anorectal angle sphincter weakness |
| Pudendal Nerve | Obstetrical/surgical injury excessive straining | Sphincter weakness sensory loss/impairment,perineal descent |
| CNS, Spinal cord, ANS | Head or spinal cord injury, Back surgery, MS, DM, stroke, avulsion | Lost sensation/reflexes secondary myopathy, loss of accommodation |
| **Functional** | | |
| Anorectal sensation | Obstet, CNS, ANS injury | Loss of stool awareness, Rectoanal agnosia |
| Faecal impaction | Dyssynergic defecation | Faecal retention and overflow; Impaired sensation |
| **Stool characteristics** | | |
| Volume and consistency | Infection, IBD, IBS, drugs, metabolic abnormalities | Diarrhoea and urgency Rapid stool transport Impaired accommodation |
| Irritants | Bile salt malabsorption/ laxatives | Diarrhoea |
| Hard stool/Retention | Dyssynergia/drugs | Faecal retention and overflow |
| **Miscellaneous** | | |
| Mobility/cognition | Aging, dementia. disability | Multifactorial changes |
| Psychosis | Willful soiling | Multifactorial changes |
| Drugs | Anticholinergics;<br>Laxatives<br>Antidepressants<br>Caffeine/muscle relaxants | Constipation<br>Diarrhoea<br>Alteredsensation/constipation<br>Relaxed sphincter tone |
| Food intolerance | Lactose, fructose, sorbitol | Diarrhoea/flatus malabsorption |

## 1. STRUCTURAL ABNORMALITIES

### *a) Anal sphincter muscles*

Disruption or weakness of the EAS muscle causes urge-related or diarrhoea-associated faecal incontinence. In contrast, damage to the IAS muscle or the anal endovascular cushions may lead to a poor seal and an impaired sampling reflex. These changes may cause passive incontinence or faecal seepage, often under resting conditions. In most patients, both sphincters may be defective. The extent of muscle loss can influence the severity of incontinence.

The most common cause of anal sphincter disruption is obstetric trauma [464, 465] However, it is unclear why most women who have sustained an obstetric injury in their 20's or 30's typically present with faecal incontinence in their 50's. The injury may involve the EAS, the IAS, the pudendal nerves, or a combination of these structures. In a prospective study, 35% of primiparous (normal anti-partum) women showed evidence of anal sphincter disruption following vaginal delivery [465, 466] Other important risk factors include forceps-assisted delivery, prolonged second stage of labour, large birth weight, and occipito posterior presentations [465, 467, 468]. Furthermore, perineal tears, even when carefully repaired, can be associated with incontinence and patients may either present several years following delivery [468]. Episiotomy is believed to be a risk factor for anal sphincter disruption. In one study, medial episiotomy was associated with a nine-fold higher risk for anal sphincter dysfunction [469]. However, in a large 30 year retrospective cohort study, the prevalence of frequent faecal incontinence was 6.9% for women whose index delivery was complicated by anal sphincter disruption, 18% for the control group, and 0% for women who had caesarean section; bothersome incontinence was experienced by 27.6%, 25.8%, and 15.2% of the respective groups. This study suggests that regardless of the type of delivery, faecal or flatus incontinence occurs in a surprisingly large number of middle-aged women. This raises the issue of whether age-related changes that affect the pelvic floor are a predisposing comorbid problem in the pathogenesis of faecal incontinence [470]. Whether anal sphincter pressures change with aging is debatable [471]. In both men and women 70 years of age there was a 30% to 40% decrease in sphincter pressures compared to patients 30 years [472]. In another study, elderly subjects were found to have lower sphincter pressures, [473] but many were taking medications that may have affected muscle function. In contrast, other studies that have examined anal pressures have reported only insignificant decreases with age [474]. However, in all age groups squeeze pressure has been shown to be significantly lower in women than in men [471, 474, 475]. Furthermore, in women, there appears to be a rapid fall in squeeze pressure after menopause [475, 476]. Recently, estrogen receptors have been identified in the human striated anal sphincter [477]. In an experimental study of adult rats, ovariectomy led to atrophy of the striated anal sphincter muscle, [477, 478] which suggests that the strength and vigour of the pelvic floor muscles is influenced by hormones. Also, in older women, pudendal nerve terminal motor latency [PNTML] is prolonged [472, 479] and there is excessive pelvic floor descent on straining [472, 473]. These mechanisms may lead to progressive damage to the striated anal sphincter muscle due to repeated stretch injury during straining [479-481]. An anal endosonography study also showed that aging was associated with an increase in the thickness and echogenecity of the internal sphincter muscle [482].

Other causes of anatomic disruption include iatrogenic factors such as anorectal surgery for haemorrhoids, fistula, or fissures. Anal dilation or lateral sphincterotomy may result in permanent incontinence due to fragmentation of the anal sphincter apparatus [483, 484]. Contrary to the belief of many surgeons, haemorrhoidectomy can cause incontinence by inadvertently damaging the IAS [485] or through the loss of endovascular cushions. Accidental perineal trauma or a pelvic fracture may also cause direct sphincter trauma leading to faecal incontinence. Interestingly, a study of homosexual men showed that although the anal resting pressure of the subjects was lower and the anal sphincters were thinner than those of controls, there was no evidence of sphincter injury from ano-receptive intercourse [486]. These results suggest that anal intercourse may not cause sphincter trauma, at least in men. Finally, in the absence of traumatic structural defects, internal sphincter dysfunction may also occur because of myopathy, [464] internal sphincter degeneration, [487] or as a complication of radiotherapy [488].

### *b) Puborectalis muscle*

Sir Allan Parks believed that the pressure exerted by the anterior rectal wall together with the puborectalis muscle was fundamental to maintaining continence as it formed a flap valve mechanism [489]. This concept was disputed in another study that imaged the rectum radiologically while simultaneously measuring rectal and anal canal pressures, as well as anal electromyogram (EMG) activity, during defecation manoeuvres [490]. The authors concluded that continence was maintained primarily by increased activity of the EAS muscle and the puborectalis muscle and that rectal pressures were consistently lower than those generated within the anal canal [490]. Similar observations were made by another group [491].

Also, after successful sphincter repair, continence was associated with higher sphincter pressures and not with an altered anorectal angle [492]. These findings suggest that an obtuse anorectal angle may represent an epiphenomenon in patients with

incontinence. The nerve supply for the upper portion of the puborectalis muscle arises from direct branches of the anterior S3 and S4. Thus, the puborectalis muscle and the external anal sphincter have separate neurological innervation. Consequently, pudendal blockage does not abolish voluntary contraction of the pelvic floor [493] but completely abolishes EAS function.11, [431, 493] It has been suggested that continence can be preserved following division of the EAS and IAS provided the puborectalis muscle is intact [494]. Moreover, division of the puborectalis muscle posteriorly does not produce incontinence as long as anal sphincter pressures are normal [495]. Thus, although the puborectalis plays an integral role in maintaining continence, its precise role is poorly understood.

***c) Neuropathy***

An intact innervation of the pelvic floor is essential for maintaining continence. Sphincter degeneration secondary to pudendal neuropathy and obstetric trauma may cause faecal incontinence in women [481]. The neuropathic injury is often sustained during childbirth, probably due to stretching of the nerves during elongation of the birth canal or through direct trauma during the passage of the fetal head. The nerve damage is more likely to occur when the fetal head is large, when the second stage of labour is prolonged, and when forceps are applied, especially high forceps delivery or if there is prolonged labour [465, 468, 481, 491, 496, 497]. Damage to the innervation of the pelvic floor musculature is usually asymmetrical [498]. Subsequent vaginal deliveries may further damage the pudendal nerves [466]. In another study of women who sustained obstetric sphincter injury, the only risk factor associated with the development of faecal incontinence was prolonged PNTML [499].

## III. AUTONOMIC NEUROPATHY

The role of extrinsic autonomic innervation is somewhat controversial. Animal studies have shown that the pelvic nerves convey relaxatory fibres to the rectum [500]. Consequently, these nerves may play a role in accommodating and storing faeces and gas [501]. Damage to the pelvic nerves may lead to impaired accommodation and rapid transit through the rectosigmoid region, overwhelming the continence barrier mechanisms. Sympathetic efferent activity, as studied by stimulating the pre-sacral sympathetic nerves, tends to relax the IAS, [501, 502] whereas parasympathetic stimulation may cause contraction of the anal sphincter. The upper motor neurons for voluntary sphincter muscle lie close to those innervating the lower limb muscles in the parasagital motor cortex adjacent to the sensory representation of the genitalia and perineum in the sensory cortex [497]. Consequently, damage to the motor cortex from central nervous system (CNS) lesions may lead to loss of bowel control and to incontinence. In some patients with neurogenic incontinence there is damage to both the sensory and motor nerve fibres, resulting in sensory impairment [438, 503, 504]. This can impair conscious awareness of anal filling [505] as well as the associated reflex responses in the striated pelvic floor sphincter muscles. Approximately 10% of patients with faecal incontinence may have lesions more proximal than the intrapelvic or perianal nerves. The primary abnormality in these patients is cauda equina nerve injury [497] which may be occult and not evident through clinical evaluation. These patients have a prolongation of nerve conduction along the cauda equina nerve roots without an abnormality in PNTML muscles [497, 506, 507]. In a minority of patients, however, there is a combination of peripheral and central lesions [506]. Other disorders such as multiple sclerosis, diabetes, and demyelination injury (or toxic neuropathy from alcohol or traumatic neuropathy) may also lead to incontinence [508-514].

***a) Rectal accommodation and reservoir function***

The rectum is a compliant reservoir that stores stool until social conditions are conducive for its evacuation [514, 515]. If rectal wall compliance is impaired, a small volume of stool material can generate high intrarectal pressure that can overwhelm anal resistance and cause incontinence [516]. Etiologies include radiation proctitis, ulcerative colitis, [516, 517] or Crohn's disease, an infiltration of the rectum by tumour or following radical hysterectomy [518]. Likewise, rectal surgery, in particular pouch surgery, [519] and spinal cord injury, [520, 521] may also be associated with loss of rectal compliance.

## IV. FUNCTIONAL MECHANISMS

### 1. ANORECTAL SENSATION

An intact sensation not only provides a warning of imminent defecation, but also helps to discriminate between formed stool, liquid faeces, or flatus. Elderly persons, [522] physically and mentally challenged individuals, and children with faecal incontinence [523] often show blunted rectal sensation. This impaired sensation may lead to excessive accumulation of stool, causing faecal impaction, mega-rectum (extreme dilation of the rectum), and overflow [522, 523]. Impaired rectal sensation may also occur as a result of neurological damage such as multiple sclerosis, diabetes mellitus, or spinal cord injury [511, 520]. Less well known is the fact that analgesics (particularly opiates) and antidepressants may also impair rectal sensation and produce faecal incontinence. That the rectum is important in preserving continence has been shown elegantly through surgical studies in which preservation of the distal 6 cm to 8 cm of the rectum,

along with its parasympathetic nerve supply, helped subjects avoid incontinence [450]. In contrast, both rectal sensation and the ability to defecate can be abolished completely by resection of the nervi erigentes [446]. An intact "sampling reflex" allows the individual to choose whether to discharge or retain rectal contents. Conversely, an impaired "sampling reflex" may predispose a subject to incontinence [449]. However, the role of the sampling reflex in maintaining continence remains unclear. In children who have had colonic pull through surgery, some degree of sensory discrimination is preserved [524].

Because the anal mucosal sensory zone is absent, it has been suggested that sensory receptors (possibly located in the puborectalis muscle) may play a role in facilitating sensory discrimination [524]. Also, traction of this muscle is a more potent stimulus for triggering both defecation and rectal distension [524].

## F. CHILDBIRTH AND FAECAL INCONTINENCE

Pregnancy and childbirth have a significant impact on the emotional and physical wellbeing of a woman. It is reported that as many as 91% of women report at least one new symptom eight weeks post-partum [525]. A fall in maternal mortality accompanied by an increase in female life expectancy (80 years in the UK) has now shifted the focus of attention towards identification of factors that may minimise morbidity. Although pre-existing bowel symptoms may be aggravated during pregnancy and childbirth, the development of symptoms *de novo* is a more frequent occurrence. Obstetric trauma is the most common cause of faecal incontinence.

However the onset of symptoms may occur many years after delivery with a peak incidence in the perimenopausal years. This may reflect the effect of contributory factors such as the process of aging, the effect of the menopause or progression of neuropathy. This section focuses on the association between obstetric trauma and faecal incontinence. However to avoid confusion, the term anal incontinence is used to include incontinence to flatus, liquid and solids.

Anal incontinence has been reported to occur between 5 [465, 526] to 26 [527] percent of women during the first year following vaginal delivery. In a Canadian study [528] involving 949 consecutive women who delivered vaginally, 26% reported anal incontinence while 3% reported faecal incontinence. They identified forceps delivery and third/fourth degree tears as independent risk factors. In a population based study of 8774 women in Oregon, USA, more than 25% reported faecal incontinence within 6 months of childbirth [529].

### I. NEUROGENIC TRAUMA

The mechanism that maintains continence is complex and affected by various factors such as mental function, lack of a compliant rectal reservoir, enhanced colonic transit and changes in stool consistency and volume. However the most important factors appear to be an anatomically intact anal sphincter complex and neurological function. In about 80% of women with presumed "idiopathic" anorectal incontinence there is histological evidence of denervation of the striated pelvic floor muscles, particularly the puborectalis and external anal sphincter (EAS) [530]. This feature has also been demonstrated electrophysiologically by means of an increased fibre density in patients with idiopathic faecal incontinence indicating re-innervation following denervation [531]. Another finding in these patients is a conduction delay in pudendal nerves as measured by pudendal nerve terminal motor latency (PNTML) [532].

Although Hertz in 1909 suggested that pelvic floor damage may result from a normal vaginal delivery, objective scientific evidence for this was only produced in 1984 [245] and a follow-up of 14 patients 5 years later [332]. These authors studied 122 women, 71 after delivery with manometry, perineometry, PNTML and EMG, and 51 before and after delivery with EMG. This study demonstrated an increase in anal sphincter striated muscle fibre density in the vaginal delivery group at 2 months post-partum indicating evidence of re-innervation following denervation. The fibre density was not altered following elective caesarean section. Thirty three percent of primiparae and 50% of multiparae had prolonged PNTML within 48 hours of delivery. However by 2 months, the PNTML had returned to normal in 60% of these women, indicating that damage to pudendal nerve conduction is reversible. Multiparity, forceps delivery, increased duration of the second stage of labour, third degree perineal tears and high birth weight were important factors leading to pudendal nerve damage. In the 5 year follow-up study of 14 women, only multiparae who did not have a forceps delivery were selected; the denervating process was found to be progressive in the majority of women and 5 women suffered from stress incontinence of urine, 3 of whom were also incontinent to flatus.

In another prospective neurophysiological study, Allen et al [157] reported on 96 nulliparous women with EMG, PNTML and vaginal pressure measurements during pelvic floor contraction. They found evidence of re-innervation in the pelvic floor muscles of 80% of primiparae 2 months after vaginal delivery. The only obstetric factors associated with re-innervation were a high birth weight and a longer active stage of labour. Forty five of the original 96 women were studied again 6 years later and they concluded that changes in

pelvic floor neurophysiology occur with time and do not appear to be related to further childbearing [533].

A third prospective study [534] measured anal pressures, anal sensation and the perineal plane in 72 antenatal women and repeated 72 hours postpartum and in 41 women 2 months postpartum. Anal sensation was unchanged. Cornes et al [535] measured anal sensation in 96 primiparae within 10 days after delivery and measurements were repeated in 74 women 6 months after delivery. They found that at 6 months anal sensation had returned to normal. Anal sensation remained unchanged after caesarean section. In women who had a torn EAS, only impairment of sensation in the upper anal canal persisted at 6 months. More than half the women who admitted to persistent anal incontinence had normal anal sensation. Chaliha et al [536] measured anal electrosensitivity before and after childbirth and found it unchanged. Anal sensation in isolation therefore probably plays a minor role in the development of obstetric related faecal incontinence.

## II. MECHANICAL TRAUMA

Until the recent advent of anal ultrasound, mechanical trauma to the anal sphincters was only suspected when there was history of a difficult vaginal deliveries and particularly recognised third or fourth degree tears collectively known as obstetric anal sphincter injuries (OASIS). Consequently, when anal endosonography was performed in patients believed to be suffering from "neurogenic" faecal incontinence unsuspected internal anal sphincter (IAS) and EAS defects were identified [537]. The sonographic appearance of EAS defects has been verified histologically to represent fibrosis [538] while the appearance of IAS defects have been validated prospectively in patients undergoing lateral internal anal sphincterotomy [539]. Trauma as identified by ultrasound may be unrecognised (previously referred to as occult) or recognised OASIS.

### 1. UNRECOGNISED (OCCULT) ANAL SPHINCTER TRAUMA

Sultan et a [465]l performed the first prospective study (before and after childbirth) to demonstrate both "occult" anal sphincter trauma (Figure 10) and pudendal nerve damage during childbirth in both primiparous and multiparous women (n=150). In 35% of primiparous and 44% of multiparous women anal sphincter defects were identified at 6 weeks postpartum by anal endosonography that were not present before vaginal delivery. Thirteen percent and 23% respectively developed defecatory symptoms (faecal urgency and/or anal incontinence) after delivery. Only 2 of the 150 women (both primiparous) had recognised tears of the anal sphincter at the time of delivery. A strong association was demonstrated between the presence of any defect and the development of symptoms. Only 4% of multiparous women sustained new sphincter damage following a subsequent delivery. The single independent factor associated with anal sphincter damage was forceps delivery. The 23 women delivered by caesarean section remained asymptomatic and none developed sphincter defects. No relationship was demonstrated between PNTML measurements and defecatory or urinary symptoms.

Donnelly et al [540] interviewed 219 nulliparae regarding bowel habit in the third trimester and performed anal vector manometry. At 6 weeks postpartum 184 women returned and the same bowel symptom questionnaire was completed and anal vector manometry plus PNTML measurements were performed. Anal endosonography was performed in 81 women with altered faecal continence or abnormal physiology. Instrumental vaginal delivery and a passive second stage of labour prolonged by epidural analgesia were significantly associated with the greatest risk of anal sphincter trauma and impaired faecal continence. As instrumental delivery is a known risk factor (8 fold increased risk of sphincter trauma), early use of oxytocin was recommended to shorten the second stage. A continuation of the same study [541] reported that PNTML was prolonged and the squeeze pressure increment was reduced in women who had a caesarean section in the late first stage (>8cm cervical dilatation) or second stage.

Chaliha et al [536]measured anal sensation and manometry in 286 nulliparae during the third trimester and repeated it in 161 women postpartum when anal endosonography was also performed. Anal endosonography revealed sphincter defects in 38% of women and this was associated with the presence of a lowering of anal squeeze and resting pressures. Threshold anal electrosensitivity remained unchanged and bore no relationship to symptoms. Postpartum sphincter defects were associated with perineal lacerations and vaginal delivery.

Abramowitz et al [542] performed a prospective study of 233 women who had anal endosonography performed before and 6 to 8 weeks after childbirth Of the 233 women (118 primiparae) 202 had a vaginal delivery. Postpartum anal incontinence in the 233 women was reported by 13% of primiparae and 8.5% of multiparae and anal sphincter defects in 21% and 12% respectively. However the prevalence of anal sphincter defects amongst those who had a vaginal delivery (n=202) was 26% and 13% respectively. Previous studies [543, 544] including others mentioned in **Table 4 and 5** have shown that the first delivery is at greatest risk for anal sphincter trauma but this study is at variance as it claimed that secundiparous females have the same risk as primiparous women. However this finding remains unsubstantiated and is further disputed by a subsequent prospective study [544].

***Table 4. Prospective studies before and after vaginal delivery of "occult" anal sphincter injury and anal incontinence but excluding faecal urgency.***

| **Study** | **Parity** | **Vaginal delivery** Numbers | FU in weeks postpartum | Sphincter Defects | Anal incontinence |
|---|---|---|---|---|---|
| Sultan et al<br>93 [465] | Primi<br>Multi | 79<br>48 | 6<br>6 | 33%<br>44% | 5%<br>19% |
| *Donnelly et al 98 [540] | Primi | 168 | 6 | 35% | 25% |
| Rieger et al 98 [550] | Primi | 37 | 6 | 41% | 8% |
| Zetterstrom et al 99 [551] | Primi | 38 | 9 | 20% | 18% |
| *Fynes et al 99 [545] | Multi | 59 | 6-12 | 37% | 17% |
| Abramowitz et al 00 [542] | Primi<br>Multi | 202<br>including multi | 8 | 26%<br>13% | 15%<br>10% |
| Chaliha et al 01 [536] | Primi | 130 | 12 | 19% | 13% |
| Belmonte-Montes et al 01 [548] | Primi | 78 | 6 | 13% | ? |
| Nazir et al 02 [547] | Primi | 73 | 20 | 19% | 25% |
| Willis et al 02 [546] | Primi<br>+Multi | 42 | 12 | 10% | 5% |
| MEAN (excluding Willis et al) | Primi<br>Multi | | | 28%<br>31% | 16%<br>15% |

*modified continence score questionnaire used and may include urgency

***Table 5. Postnatal studies of "occult" anal sphincter injury sustained during vaginal deliv-ery and anal incontinence excluding faecal urgency.***

| **Study** | **Parity** | **Vaginal delivery** Numbers | FU in weeks postpartum | Sphincter Defects | Anal incontinence |
|---|---|---|---|---|---|
| *Varma et al 99 [549] | 78<br>31 | Primi<br>Multi | 4 weeks<br>4weeks | 11.5%<br>19% | 0%<br>0% |
| Damon 00 [552] | 197 | Primi | 3 months | 34% | 6% |
| **Faltin 00 [553] | 150 | Primi | 3 months | 28% | 15% |

*Ultrasound performed < 1 week after delivery

** Anal ultrasound performed immediately after delivery before perineal repair

Fynes et al [545] undertook a prospective study of 59 previously nulliparous women through 2 successive pregnancies and found that 34% had anal sphincter injury after their first delivery but only 2 new injuries occurred after the second delivery confirming the findings in Sultan's study [465]. An important finding in this study was that 42% of women (5 of 12) who had occult sphincter injury during their first delivery (squeeze pressure increment < 20mmHg or anal sphincter defect > one quadrant) developed anal incontinence after the second delivery.

Willis et al [546] performed anal vector manometry, endosonography, PNTML and rectal sensitivity at the 32 weeks and 6 weeks postpartum. Using the Kelly-Holschneider score they reported anal incontinence in 5% and identified occult injuries in 19%. PNTML and rectal sensitivity was unaffected by vaginal delivery.

Nazir [547] et al performed vector manometry and endoanal ultrasound in 73 nulliparous woman at 25 weeks and 5 months postpartum (Table 4). There was no correlation between vector manometry and anal endosonography or clinical variables.

Belmonte-Montes [548] performed anal endosonography in 98 nulliparous women 6 weeks before and 6 weeks after delivery and after excluding 20 third degree tears found occult sphincter injuries in 13%. Seventy five percent of women with defects were symptomatic and there was a good correlation between defects and symptoms. However it is not clear how many with occult defects were symptomatic (Table 4).

In 3 further studies [549-551] anal ultrasound was performed only after delivery and defects were identified in 11.5 to 34% (Table 5). Varma et al [549] studied 159 postnatal women (105 primiparous and 54 secundiparous) and found occult anal sphincter defects in 11.5% of primiparous and 19% of secundiparous vaginal deliveries but 80% of forceps deliveries. None of their patients suffered faecal incontinence but only 72% of questionnaires were returned. However their cohort had a high caesarean section rate (25%) and a low forceps rate (4%).

Some 15 years after having first coined the term "occult" OASIS Sultan [465] questioned whether the 28% sonographic anal sphincter defects (**Table 6**) were genuine occult defects in that they were not visible following delivery. They therefore conducted a prospective study [585] in which 241 women having their first vaginal delivery had their perineum re-examined by an experienced research fellow and endoanal ultrasound was performed immediately after delivery and repeated 7 weeks postpartum. When OASIS was identified by the research fellow, the injuries were confirmed and repaired by the duty registrar or consultant. The prevalence of clinically diagnosed OASIS increased from 11% to 25% (n=59). Every clinically diagnosed injury was identified by postpartum endoanal ultrasound. However there were 3 women with sonographic defects in whom the injury was not identified clinically. Two of these had only small IAS defects that were not considered clinically significant. The other was a combined defect of both the IAS and EAS and while this could be classified as an occult tear it is most probably an undiagnosed tear. At 7 weeks no *de novo* defects were identified by ultrasound. This study concluded that most sphincter defects that have previously been designated as "occult" injuries (Table 6) were in fact OASIS that could have been identified by a trained clinician [586] and that less than one percent are genuine occult OASIS (if they exist). Interestingly, 87% of midwives and 27% of junior doctors failed to recognise OASIS clinically. Although it is likely that some of these injuries would have been detected at the time of suturing the tear, it is concerning that clinical recognition of OASIS is suboptimal [586]. However this finding is not unique as Groom and Patterson [587] also found that the rate of third degree tears rose to 15% when all "2$^{nd}$ degree tears" were re-examined by a second experienced person.

These studies [585, 587] confirm inadequate training that was previously highlighted by Sultan et al [588] who reported that 91% of doctors who had done at least 6 months of training in obstetrics and 60% of midwives indicated inadequate training in perineal anatomy and 84% and 61% respectively reported inadequate training in identifying 3$^{rd}$ degree tears. Another possible reason for under-diagnosis is that tears of the anal sphincter have been wrongly classified and therefore anal sphincter tears have been under-reported. Any involvement of the anal sphincter should be classified as third degree. However 41% of doctors and 16% of midwives classified a torn anal sphincter as a 2nd degree tear [588]. Sultan and Thakar [589] reviewed every relevant text book (n=65) in the library of the Royal College of Obstetricians and Gynaecologists (RCOG) and found that there was a lack of consistency in classification and in about 40% the classification was omitted or wrong. Furthermore previous classifications were incomplete because they did not incorporate depth of EAS rupture or involvement of the IAS. This therefore has epidemiological, clinical and medicolegal implications. If a third degree tear is incorrectly classified as second degree, then inappropriate repair could result in sub-optimal outcome (see below). Sultan [590] has therefore proposed the following classification [591] that has been incorporated into the 29$^{th}$ RCOG green top guidelines [585] and the first edition of this book:

**First degree:** laceration of the vaginal epithelium or perineal skin only.

**Second degree:** involvement of the perineal muscles but not the anal sphincter.

***Table 6. Prevalence of anal incontinence following primary repair of obstetric anal sphinc-ter rupture (faecal incontinence ie. excluding flatus incontinence only is shown in paren-theses)***

| Authors (n=33) | Year | Country | N | Follow-up Months | Anal (Faecal) incontinence |
|---|---|---|---|---|---|
| Sangalli et al [554] | 2000 | Switzerland | 177 | 13 years | 15% (10%) |
| Wood J et al [555] | 1998 | Australia | 84 | 31 | 17%* (7%) |
| Walsh et al [556] | 1996 | UK | 81 | 3 | 20% (7%) |
| Sander et al [557] | 1999 | Denmark | 48 | 1 | 21% (4%) |
| Pretlove et al [558] | 2004 | UK | 41 | ? | 22% (22%) |
| Crawford et al [559] | 1993 | USA | 35 | 12 | 23% (6%) |
| Sorensen et al [560] | 1993 | Denmark | 38 | 3 | 24% (?) |
| Mackenzie et al [561] | 2003 | UK | 53 | 3 | 25% (7%) |
| Nichols et al [562] | 2005 | USA | 56 | 3 | 25% (11%) |
| Nielsen et al [563] | 1992 | Denmark | 24 | 12 | 29% (?) |
| Go & Dunselman [564] | 1988 | Netherland | 20 | 6 | 30% (15%) |
| Fenner et al [565] | 2003 | USA | 165 | 6 | 30% (?) |
| DeLeeuw et al [566] | 2001 | Netherland | 125 | 14 years | 31% (?) |
| Wagenius et al [567] | 2003 | Sweden | 186 | 4 years | 33% (25%) |
| Uustal Fornell et al [568] | 1996 | Sweden | 51 | 6 | 40% (16%) |
| Poen et al [569] | 1998 | Netherland | 117 | 56 | 40% (?) |
| Sultan et al [468] | 1994 | UK | 34 | 2 | 41% (9%) |
| Zetterstrom et al [527] | 1999 | Sweden | 46 | 9 | 41% (2%) |
| Sorensen et al [570] | 1988 | Denmark | 25 | 78 | 42% (?) |
| Tetzschner et al [499] | 1996 | Denmark | 72 | 24-48 | 42% (17% ) |
| Williams et al [571] | 2003 | UK | 124 | ? | 42% (?) |
| Norderval et al [572] | 2004 | Norway | 156 | 25 | 42% (17%) |
| Garcia et al [573] | 2005 | USA | 26 | 3 | 42% (15%) |
| Kammerer-Doak et al [574] | 1999 | USA | 15 | 4 | 43% (13%) |
| Haadem et al [575] | 1988 | Sweden | 62 | 3 | 44% (?) |
| Rieger et al [576] | 2004 | Australia | 51 | 3 | 45% (25%) |
| Bek & Laurberg [577] | 1992 | Denmark | 121 | ? | 50% (?) |
| Davis et al [578] | 2003 | UK | 52 | 3.6 | 50% (?) |
| Fitzpatrick et al [579] | 2000 | Ireland | 154 | 3 | 53% (6%) |
| Nazir et al [580] | 2003 | Norway | 100 | 18 | 54% (17%) |
| Gjessing H et al [581] | 1998 | Norway | 35 | 12-60 | 57% (23%) |
| Savoye-Collet et al [582] | 2003 | France | 21 | 4 | 57% (29%) |
| Goffeng et al [583] | 1998 | Sweden | 27 | 12 | 59% (11%) |
| Nygaard et al [470] | 1997 | USA | 29 | 30 years | 59% (28%) |
| Pinta et al [584] | 2004 | Finland | 52 | 15 | 61% (10%) |
| Mean | | | | | 39% (14%) |

*Includes 2 with secondary sphincter repair

**Third degree:** disruption of the anal sphincter muscles (**Figures 13 & 14**) and this should be further subdivided into:

**3a:** <50% thickness of external sphincter torn.

**3b:** >50% thickness of external sphincter torn.

**3c:** internal sphincter torn also.

**Fourth degree:** Third degrees tear with disruption of the anal epithelium.

An isolated rectal tear without involvement of the anal sphincter is rare and should not be included in the above classification.

## 2. RECOGNISED OBSTETRIC ANAL SPHINCTER INJURIES

Primary repair of OASIS (third and fourth degree tears) are usually performed by obstetricians using the end-to-end repair technique [468]. However as shown in Table 6, anal incontinence occurs in 39% (range15 to 61%) and in addition, urgency can affect a further 6 [468] to 28% [579]. Frank faecal incontinence affected 14% [468] (range 2 [527] to 29% [581]). In five studies [468, 569, 574, 579, 583] anal endosonography was performed to demonstrate persistent anal sphincter defects following repair in 40 to 91% of women. The extent of the sphincter injury may be related to outcome of repair. However in some studies (Table 6) the data was not interpretable [560], incomplete [583] or inclusive of symptoms other than anal incontinence [575]. Forceps delivery, first vaginal delivery, large baby, shoulder dystocia and a persistent occipito-posterior position have been identified as the main risk factors for the development of OASIS [468, 542, 543, 569].

The most popular method of EAS repair is the end-to-end technique but colorectal surgeons prefer the overlap technique for secondary repair because of better outcome [592]. It is now known that like other incontinence procedures, outcome can deteriorate with time and one study has reported 50% continence at 5-year follow-up [593]. However, at least one third of women in this study had more than one attempt at sphincter repair and therefore these findings cannot be extrapolated to that following primary repair of acute injury [593]. Sultan et al [592] were the first to describe the overlap technique for acute EAS rupture and in addition advocated the separate identification and repair of the IAS. Until then very little importance was given to torn IAS during primary repair. However subsequently in a study involving 500 consecutive women with OASIS it has been shown that sonographic evidence of IAS injury was predictive of faecal incontinence [594]. When a patient presents with faecal incontinence, it is almost impossible to perform a successful IAS repair highlighting the importance of identification and repair immediately after delivery [591]. Compared to matched historical controls [468] who had an end-to-end repair, Sultan et al [592] found that anal incontinence could be reduced from 41% to 8% when the overlap technique was used for EAS repair with separate repair of the torn IAS [592] and therefore they recommended a randomised trial.

The first published randomised trial by Fitzpatrick et al [579] reported no significant difference between end-to-end and overlap repair although there appeared to be trend towards more symptoms in the end-to-end group. However there were methodological differences in that the torn IAS was not identified and repaired separately and they used a constipating agent for 3 days after the repair. Unfortunately they included partial EAS tears in their randomised study. A true overlap [591, 592] is not possible if the sphincter ends are not completely divided and it would be expected that if an overlap is attempted, the residual intact sphincter muscle would have to curl up and hence there would be undue tension on the remaining torn ends of muscle that would be overlapped. This technique would therefore go against the general principles of surgery of deliberately placing tissue under avoidable tension [591].

Garcia et al [573] also performed a randomised trial of the two techniques and took great care to include only complete ruptures of the EAS (full thickness 3b,3c and 4$^{th}$ degree tears). There were 23 women in the end-to-end group and 18 in the overlap group. Unfortunately only 15 and 11 women respectively returned for follow-up which was only at 3 months. No significant difference was found between the groups in terms of symptoms of faecal incontinence or transperineal ultrasound findings. However the authors acknowledged that the major limitations of their study were that randomization was inaccurate and that their study was underpowered.

Recently, Williams et al [595] performed a factorial randomized controlled trial (n=112) in which women were randomized into 4 groups: overlap with polyglactin (Vicryl;Ethicon, Edinburgh, UK); end-to-end repair with Vicryl; overlap repair with polydiaxanone (PDS; Ethicon, Edinburgh, UK); end-to-end repair with PDS. This trial was specifically designed to test the hypothesis regarding suture related morbidity (need for suture removal due to pain, suture migration or dyspareunia) using the two techniques. At six weeks there were no differences in suture related morbidity. The authors claim that there were no differences in outcome based on repair technique. Unfortunately the majority of patients included in this trial were partial tears of the EAS (3a tears and as mentioned above, a true overlap [591, 592] cannot be performed if the EAS is only partially torn. Furthermore their follow up rate at 12 months was only 54%. This data therefore needs to be interpreted by caution.

Fernando et al [596] performed a randomized

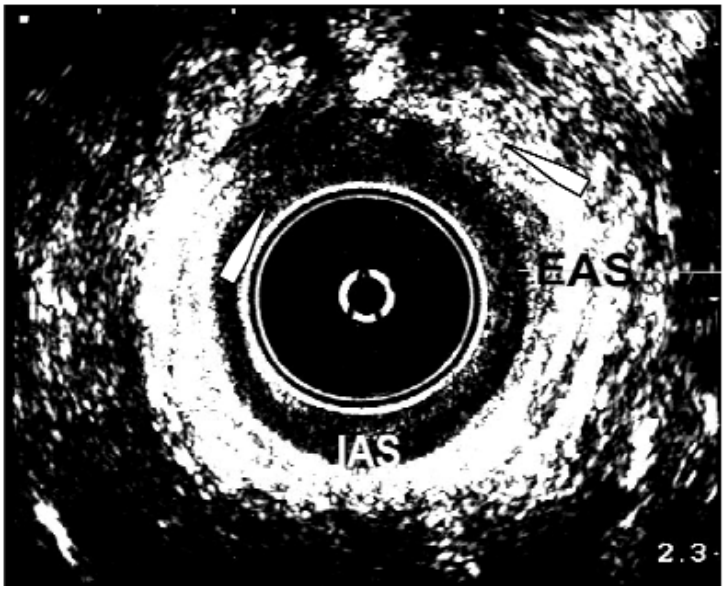


***Figure 13: Anal ultrasound image of the mid anal canal. EAS = external anal sphincter. IAS = internal anal sphincter. The area between the arrows at 10 and 1o'clock represents an external anal sphincter defect***

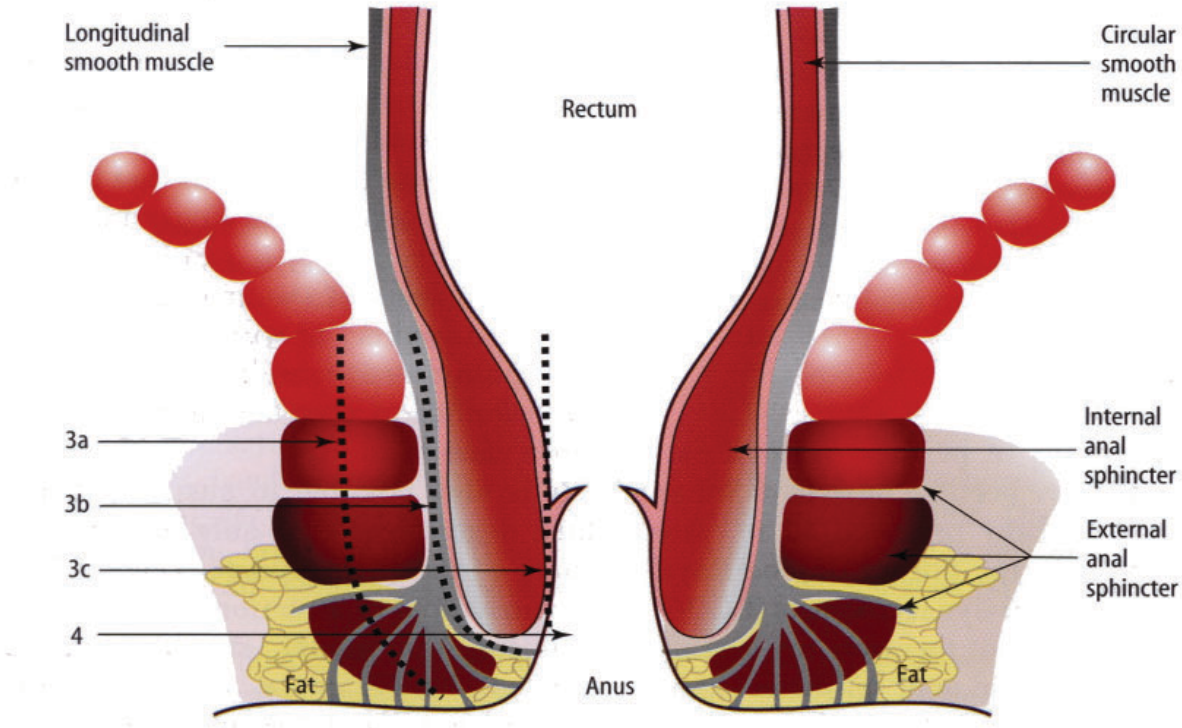


*Figure 14: Schematic representation of 3rd and 4th degree tears (with permission from Springer) [620]*

controlled trial of end-to-end vs overlap technique. The study had adequate power (n=64) and the primary outcome was faecal incontinence at one year. All repairs were performed by two trained operators and superficial partial tears of the EAS (3a) were excluded. At 12 months (81% follow-up rate), 24% in the end-to-end and none in the overlap group reported faecal incontinence (p=0.009). Faecal urgency at 12 months was reported by 32% in the end-to-end and 3.7% in the overlap group (p=0.02). There were no significant differences in dyspareunia and quality of life between the groups. At 12 months 20% reported perineal pain in the end-to-end and none in the overlap group (p=0.04). During twelve months 16% in end-to-end and none in the overlap group reported deterioration of defecatory symptoms (p=0.01). Further calculation revealed that four women need to be treated with the overlap technique to prevent one woman with OASIS developing faecal incontinence. On the basis of this randomized trial one can conclude that the overlap technique of external sphincter repair accompanied by separate repair of the torn internal sphincter is performed by trained clinicians it is superior to the end-to-end repair. However as the other randomized trials included 3a tears and did not evaluate operator expertise [595] it remains to be established whether the same results would be obtained when the repair is performed by trainees.

### 3. MANAGEMENT OF SUBSEQUENT PREGNANCY AFTER OASIS

All women who sustained a third/fourth degree tear should be assessed in hospital by a senior obstetrician 6 to 8 weeks after delivery. Some centres have established dedicated multidisciplinary perineal clinics. It is important that a careful history is taken regarding bowel, bladder and sexual function. As these symptoms are embarrassing, a structured questionnaire may be useful. A careful vaginal and rectal examination should be performed to check for complete healing, scar tenderness and sphincter tone [585, 597, 598]. Mild incontinence (faecal urgency or flatus incontinence) may be controlled with dietary advice, constipating agents (loperamide or codeine phosphate), physiotherapy or biofeedback. However women who have severe incontinence should, in addition, be offered secondary sphincter repair by a colorectal surgeon. Asymptomatic women must be advised to return if symptoms develop [591].

There are no randomised studies to determine the most appropriate mode of delivery. Women who have had a successful secondary sphincter repair for faecal incontinence should be delivered by caesarean section [599]. Some women with faecal incontinence may choose to complete their family prior to embarking on anal sphincter surgery. It remains to be established whether these women should be allowed a vaginal delivery as it could be argued that damage has already occurred and risk of further damage is minimal and possibly insignificant in terms of outcome of surgery.

Until recently [591] the management in a subsequent pregnancy after OASIS has not been discussed in any detail [589]. It has been suggested that a caesarean section should be performed even after transient anal incontinence [499] but this has been questioned [599].

In order to counsel women with previous 3rd/4th degree tears appropriately, we find it useful to have a symptom questionnaire, anal ultrasound and manometry results. If vaginal delivery is contemplated then these tests should be performed during the current pregnancy unless performed previously and found to be abnormal. In a prospective study over a 5 year period, Scheer et al [600] found that when women who had no evidence of significant anal sphincter compromise based on anal endosonography and manometry were allowed a vaginal delivery (the others offered caesarean section) there was no deterioration in symptoms, anorectal function or quality of life. Although 11% of textbooks recommend a prophylactic episiotomy [589] there is limited evidence that an elective episiotomy prevents subsequent anal sphincter disruption [566] while other studies have indicated that episiotomy may increase the prevalence of anal sphincter disruption.

## III. INSTRUMENTAL VAGINAL DELIVERY

Although only 4% of women delivered by forceps sustain a $3^{rd}/4^{th}$ degree tear, up to 50% of those that do tear have an instrumental delivery [468]. Vacuum extraction is associated with fewer $3^{rd}/4^{th}$ tears than forceps and this view is supported by 2 large randomised studies [601, 602]. A UK study [601] where mediolateral episiotomy is practised reported severe vaginal lacerations in 17% of forceps compared to 11% of vacuum deliveries and a Canadian study [602] where midline episiotomy is practised reported 3 $3^{rd}/4^{th}$ tears in 29% of forceps compared to 12% of vacuum deliveries. In a Cochrane review (ten trials) [603] use of the vacuum extractor instead of forceps was associated with significantly less maternal trauma (odds ratio 0.41, 95% confidence interval 0.33 to 0.50) and with less need for general and regional anaesthesia. There were more deliveries with vacuum extraction (odds ratio 1.69, 95% confidence interval 1.31 to 2.19) and fewer caesarean sections were carried out in the vacuum extractor group. However the vacuum extractor was associated with an increase in neonatal cephalhaematomas and retinal haemorrhages. Serious neonatal injury was uncommon with either instrument.

The reduction in cephalhaematomas and retinal haemorrhages seen with forceps may be a com-

pensatory benefit. A 5 year follow-up of infants who participated in a randomised study of forceps and vacuum delivery has confirmed that there is no difference in terms of neurological development and visual acuity with use of either instrument [602]. "Occult" trauma to the anal sphincter has also been identified more frequently in forceps delivery occurring in up to 80 percent [465, 549, 604]. A small randomised study (n=44) confirmed this by identifying occult anal sphincter defects in 79% of forceps compared to 40% of vacuum deliveries [604]. Trauma occurs more frequently when a second instrument is used to attempt vaginal delivery [604] and therefore if delivery fails with the appropriate technique and vacuum cup, one should resort to a caesarean section. Metal cups appear to be more Stress Urinary Incontinencetable for 'occipito-posterior', transverse and difficult 'occipito-anterior' position deliveries [605]. The soft cups seem to be appropriate for straightforward deliveries as they are significantly more likely to fail to achieve vaginal delivery (odds ratio 1.65, 95% confidence interval 1.19 to 2.29). Although, they were associated with less scalp injury (odds ratio 0.45, 95% confidence interval 0.15 to 0.60), there was no difference between the two groups in terms of maternal injury. Farrell et al [606] performed a prospective study of 690 primigravid women and found that forceps delivery was associated with a higher incidence of flatal incontinence (RR 2.6) compared to vaginal delivery and both flatal (RR 2.6) and faecal (RR 3.6) incontinence compared to caesarean delivery. Vacuum delivery did not increase the risk of flatus incontinence. MacArthur et al [526] performed the largest questionnaire based multicenter study to establish the prevalence of faecal incontinence at 3 months post-partum. They reported a prevalence of 9.2%, with 4.2% reporting it more often than rarely. Forceps delivery was associated with almost twice the risk of developing faecal incontinence whereas vacuum extraction was not associated with this risk. Thakar and Eason [607] performed a meta-analysis and demonstrated that one anal sphincter injury is avoided for every 18 women delivered by vacuum extraction instead of forceps.

## IV. EPISIOTOMY

There is now considerable observational data to indicate that a reduction in episiotomy rate is not associated with an increase in OASIS [608]. The Cochrane database [185] shows that restricting the use of episiotomy is associated with less posterior trauma. Although anterior perineal trauma was increased it had no effect on the development of urinary incontinence. Henrikssen et al [609, 610] performed an observational study in which they noted that when midwives who previously had a high episiotomy rate reduced their rate, the prevalence of OASIS also reduced. However this beneficial effect was abolished when midwives with a low rate of episiotomy attempted to reduce it even further. Based on this evidence, it was suggested that the ideal episiotomy rate should lie between 20 to 30% and no more. Midline episiotomies are more popular in North America as it is believed that they are more comfortable and recovery is less complicated. However Coats et al [611] performed a quasi-randomised study of 407 primiparae and found 12% of midline episiotomies extended into the anal sphincter compared to 2% of mediolateral episiotomies. Although the perineum was significantly less bruised in the midline group and sexual intercourse commenced earlier, pain and wound breakdown was similar in both groups. However care needs to be taken to ensure that mediolateral episiotomies are performed correctly as Andrews et al [612] have shown that only 22% of doctors and no midwife made the incision commencing from the posterior fourchette with a 40 to 60 degree angle from the midline. Another study demonstrated for every six degrees away from the midline there was a 50% reduction in OASIS [613].

## V. DELIVERY TECHNIQUES

Pirhonen et al [614] compared the frequency of anal sphincter rupture in low risk deliveries between two Scandinavian countries (26 541 vaginal deliveries) and found the risk to be 13 times higher in Sweden (Malmo) *vs* Finland (Turku). They speculated that the only explanation for this was a difference in manual support given to the baby's head during crowning and pushing the perineum under the chin. The following interventions with randomized controlled trials evidence regarding effectiveness demonstrated no effect on OASIS: antenatal perineal massage, pelvic floor exercises in pregnancy, water births, positions during labour and birth, epidural analgesia, early vs delayed pushing with epidural and second stage pushing advice [607].

## VI. TRAINING

McLennan et al [615] who surveyed 1177 fourth year residents and found that the majority of residents had received no formal training in pelvic floor anatomy, episiotomy or perineal repair and supervision during perineal repair was limited. Stepp et al [616] found that textbooks used in American practice offered little in terms of prevention and repair of perineal trauma. There is evidence from one study [588] that perineal anatomy is poorly understood by midwives and trainee doctors, who perform the bulk of deliveries in the UK. In this study 41% of trainees and 16% of midwives incorrectly classified a partial or complete tear of the EAS as 'second degree'. Inconsistency in classification of tears would allow many injuries to pass, unre-

cognised. It has been shown that hands-on workshops on perineal repair (www.perineum.net) can change practice [617, 618] and therefore intensive and focused training in perineal anatomy and repair should therefore become an essential module in the programme for trainees.

## VII. IRRITABLE BOWEL SYNDROME (IBS)

IBS affects 3-17% in selected populations and the cause remains unknown. Donnelly et al [619] recruited 312 primiparous women and reported that 11% of young primiparous women (n= 34 of 208) suffered from pre-existing IBS prior to their first pregnancy. Twenty four percent reported symptoms of impaired faecal continence in the puerperium but symptoms were found significantly more frequently in those with IBS compared to those with normal bowel habit (71% vs 18%). However women suffering from IBS are no more likely to incur mechanical or neurologic injury to the anal sphincter. Women with IBS delivered by caesarean section did not have altered continence postpartum. However 6 months postpartum there were no symptomatic differences between those with IBS and those without but only 90 of the 107 women who had either impaired faecal continence or abnormal anal manometry were studied. Treatment is directed towards the predominant symptom and although antispasmodics such as hyoscine, mebeverine and dicyclomine are used widely to relax intestinal smooth muscle, they should be avoided during pregnancy.

## VIII. CONCLUSIONS AND RECOMMENDATIONS

a) Compared to forceps the vacuum extractor is associated with less perineal and anal sphincter trauma and should therefore be the instrument of choice. **(Level 1)**

b) Compared to midline episiotomy, mediolateral episiotomy is associated with a lower risk of anal sphincter rupture (12% vs 2%). **(Level 1)**

c) Liberal use of episiotomy is not beneficial **(Level 1)** and restricting the rate of episiotomy to about 30% may reduce the risk of trauma to the anal sphincter.**(Level 4)**

d) A prolonged active second stage of labour is associated with denervation of the pelvic floor and one study has suggested that this also occurs with a prolonged passive second stage of labour with epidural analgesia. In these circumstances, early use of oxytocics in the second stage of labour may be useful. **(Level 4)**

e) Selective use of caesarean section particularly in those who have evidence of compromised anal sphincter function and those who have had previous successful continence or prolapse surgery. **(Level 5)**

f) Modification in techniques of delivery of the baby may reduce anal sphincter injury and further research is needed **(Level 5)**

g) A more focused training program for doctors and midwives needs to implement. There is a poor understanding of perineal and anal sphincter anatomy and hence identification of anal sphincter trauma, incorrect classification and poor outcome of repair **(Level 5)**

h) In experienced hands the overlap technique of external anal sphincter repair is superior to the end-to-end technique and further studies await completion to establish whether these findings can be generalized **(Level 1)**

# G . PATHOPHYSIOLOGY OF INCONTINENCE IN MEN

Urinary incontinence in men as in women may be caused by either an abnormality of the bladder, an abnormality of the bladder outlet (sphincter), or a combination of both [621-623]. Changes in bladder ultrastructure and function that can occur as a result of neurological disease or aging (that can cause detrusor overactivity or underactivity) are similar in men and women. However there are causes of bladder and sphincter dysfunction that are unique to men. Many of these center around benign and malignant diseases of the prostate and their treatment. For example, the prevalence of detrusor overactivity and impaired compliance causing incontinence is associated with obstruction (usually caused by benign prostatic obstruction) far more often in men than in women. Also sphincter incontinence does not generally occur as the result of aging or other associated normal conditions such as pregnancy and childbirth, but rather is usually attributed to surgery or radiation of the prostate (for benign or malignant conditions) or neurological injury. Extra-urethral incontinence, which is very rare in men, is caused only by urinary fistula. Because of embryological considerations, ectopic ureter in the male does not cause incontinence as its insertion into the lower urinary tract is always proximal to the distal urethral sphincter.

In this section, we will focus on the Pathophysiology of incontinence as it relates to prostatic obstruction and its treatment and the treatment of prostate cancer.

## I. CONTINENCE MECHANISM IN THE MALE

The proximal urethral sphincter (PUS) extends from the bladder neck through the prostatic urethra above the verumontanum. The distal urethral sphincter (DUS) extends from the prostatic urethra below the verumontanum through the membranous urethra. DUS includes the rhabdosphincter (intrinsic skeletal and smooth muscle) and extrinsic paraurethral skeletal muscle. (Modified from Hadley HR, Zimmern PE, Raz S: The treatment of male urinary incontinence. In Walsh PC, Gittes RF, Perlmutter AD (Eds) Campbell's Urology, Eds 5. B.: London,WB Saunders, 1986, p 2658) [624] (**Figure 15**).

For simplicity, the normal male urinary sphincter mechanism may be divided into two functionally separate units, the proximal urethral sphincter (PUS) and the distal urethral sphincter (DUS) [624]. The PUS consists of the bladder neck, prostate and prostatic urethra to the level of the verumontanum. It is innervated by autonomic parasympathetic fibres from the pelvic nerve. This portion of the continence mechanism is removed during prostatectomy, leaving only the DUS to prevent urinary leakage. The DUS extends from the verumontanum to the proximal bulb and is comprised of a number of structures that help to maintain continence. The male DUS urethral sphincter complex is composed of the prostato-membranous urethra, cylindrical rhabdosphincter (external sphincter muscle) surrounding the prostato-membranous urethra, and extrinsic paraurethral musculature and connective tissue structures of the pelvis. The rhabdosphincter is a concentric muscular structure consisting of longitudinal smooth muscle and slow-twitch (type I) skeletal muscle fibres which can maintain resting tone and preserve continence [625, 626]. The striated muscle of the rhabdosphincter is considerably thicker ventrally and thins dorsally. Skeletal muscle fibres of the rhabdosphincter have been shown to intermingle with smooth muscle fibres of the proximal urethra, suggesting a dynamic and coordinated interaction [627]. The rhabdosphincter is invested in a fascial framework, and supported below by a musculofascial plate that fuses with the midline raphe, which is also a point of origin for the rectourethralis muscle [627]. Superiorly, the fascial investments of the rhabdosphincter fuse with the puboprostatic ligaments [628]. This dorsal and ventral support probably contributes to the competence of the sphincter. The striated fibres of the extrinsic paraurethral muscle (levator ani complex), on the other hand, are of the fast-twitch (type II) variety [625]. During sudden increases in abdominal pressure, these fibres can contract rapidly and forcefully to provide continence. Continence has been showed to be maintained after inducing paralysis of the striated sphincter [629] indicating that this structure is not solely responsible for continence. Unlike in the female where urethral support can be compromised as a result of childbirth and aging, in the male compromise to the rhabdosphincter usually occurs after trauma or surgery (e.g. prostatectomy). The striated muscle fibres of the rhabdosphincter intermingle with smooth muscle fibres of the proximal urethra and in fact have been shown to be inseparable from each other in the

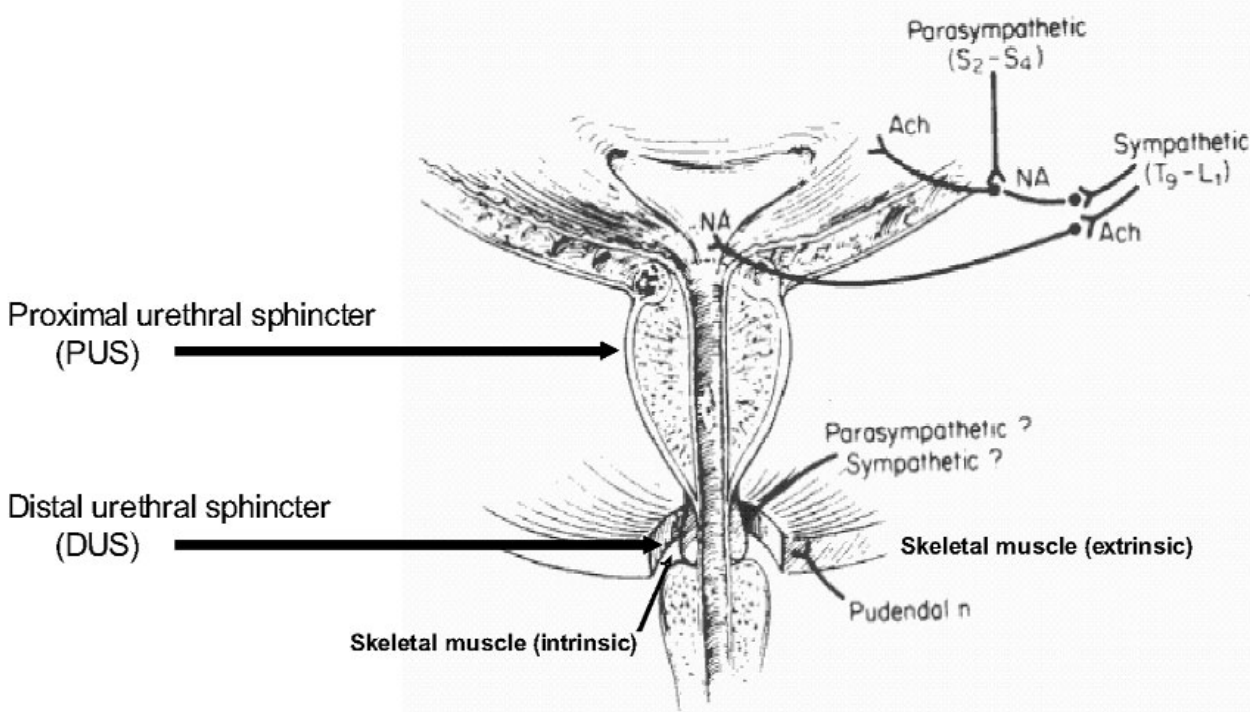


***Figure 15: Functional anatomy of the male continence mechanism.***

human male fetus [630]. However the smooth muscle fibres, which are continuous with the bladder, are divided during radical prostatectomy and the muscular vesico-prostatico-urethral continuance is interrupted. Thus continence is maintained primarily by the striated muscle of the rhabdosphincter (**Figure 16**).

The innervation of the DUS has been extensively studied; however, the exact details remain a point of controversy amongst anatomists. It is generally agreed that the DUS is innervated by both the autonomic (via the pelvic nerve) and somatic (by the pudendal nerve) nervous systems. Nerve fibres are seen proximally in a dorsolateral position (5 to 7 o'clock), while more distally, they are located primarily laterally, and at varying distances from the urethra [627, 631]. The intrinsic smooth muscle of the proximal urethra receives parasympathetic innervation from pelvic nerve branches of the inferior hypogastric plexus [631, 632]. The rhabdosphincter may also receive somatic innervation. Hollabaugh and colleagues described the so-called "putative continence nerves" as branches of the pelvic nerve travelling under the endopelvic fascia which pick up intrapelvic branches of the pudendal nerve, given off before it enters the pudendal canal [631]. It has also been proposed that somatic innervation from the pudendal nerve after it exits the pudendal canal is primarily sensory in origin, facilitating reflex contraction of the sphincter complex to maintain continence. [633].

A recent elegant histological and immunohistochemical study with three dimensional reconstruction in the male fetus has confirmed mixed autonomic and somatic innervation [630]. Unmyelinated (autonomic) nerve fibres destined for smooth muscle fibres run alongside of the myelinated (somatic) fibres. The majority of the unmyelinated fibres approach the smooth muscle layers at 5 and 7 o'clock while the majority of myelinated fibres penetrate the striated sphincter at 3 and 9 o'clock.

Structure and innervation are important components of sphincter function. In addition, Tuygun and associates [634] have found a much higher incidence of periurethral (or peri-sphincter) fibrosis in incontinent vs. continent men after prostatectomy. Using MRI at least 6 months after prostatectomy they discovered that all 22 incontinent men had periurethral fibrosis while only 4/14 (29%) continent men did.

In summary, sphincter continence is dependent on the integrity of the PUS and/or DUS, its support structures and neural innervation. Following removal of the PUS with prostatectomy, continence is maintained by the DUS mechanism, consisting of soft tissue supportive structures, smooth muscle, and striated muscle. The smooth muscle and slow twitch skeletal muscle of the rhabdosphincter is probably most responsible for sphincter continence; however, skeletal muscle contractions of the periurethral and paraurethral muscle are likely assist. After radical prostatectomy, the integrity or continuity of the smooth muscle fibres is lost, which may have a significant effect on their contribution to continence. Damage to the innervation (parasympathetic and somatic) of the

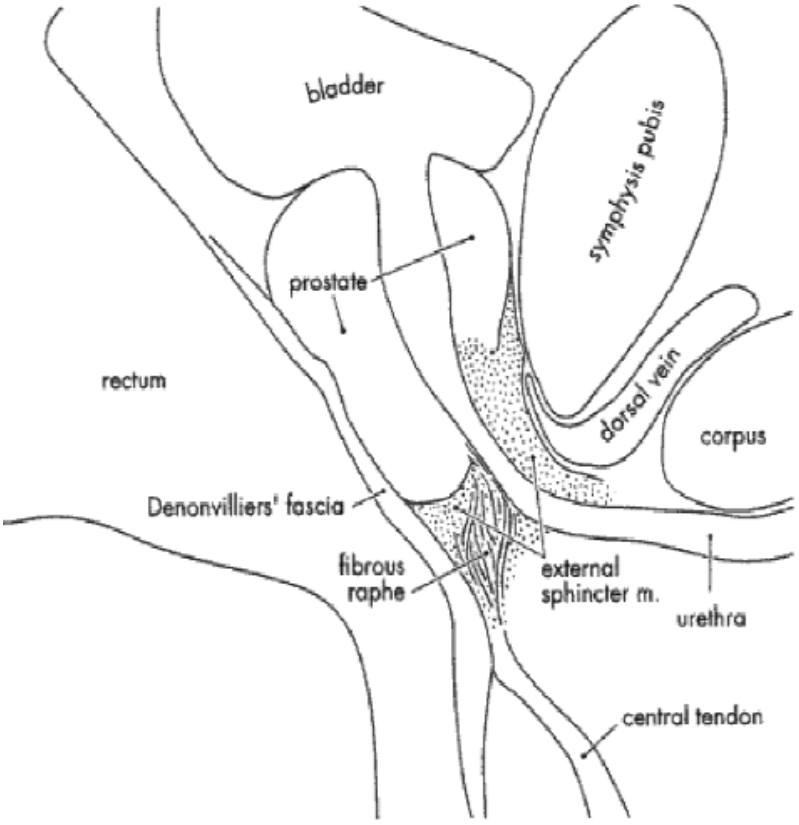


***Figure 16 : The rhabdosphincter is invested in a fascial framework, and supported below by a musculofascial plate that fuses with the midline raphe, which is also a point of origin for the rectourethralis muscle. Superiorly, the fascial investments of the rhabdosphincter fuse with the puboprostatic ligaments. This dorsal and ventral support likely contributes to the competence of the sphincter. (From Burnett AL, Mostwin JL. In situ anatomical study of the male urethral sphincter complex: relevance to continence preservation following major pelvic surgery. J Urol 1998; 160:1301-1306). [627]***

smooth and skeletal muscle may indirectly contribute to post-prostatectomy incontinence. In addition compromise of the sphincter support mechanism or post operative changes such as fibrosis can compromise sphincter function.

## II. INCONTINENCE ASSOCIATED WITH BPH AND ITS TREATMENT

Benign prostatic hyperplasia (BPH) and benign prostatic obstruction (BPO) and their treatments have long been associated with incontinence in men. Detrusor overactivity (DO), impaired compliance and urge incontinence are prevalent in men with BPO. In men undergoing urodynamic testing detrusor overactivity is present in 40-80% of patients with obstruction [635-637]. In addition, impaired compliance, another potential cause of incontinence has been shown to have a high correlation with outlet obstruction in men [638]. Thus even before treatment of BPH and BPO there is a notable incidence of bladder dysfunction and incontinence.

Incontinence after the treatment of BPH may be related to persistent bladder dysfunction, new onset bladder dysfunction or sphincter dysfunction (injury). Turner-Warwick et al. [639] first directed attention to the relationship of bladder outlet obstruction, the symptoms of frequency, urgency and urge incontinence (now commonly known as LUTS: Lower Urinary Tract Symptoms) and the correlation of these symptoms with detrusor overactivity seen on cystometry. They noted that in 75% of men, symptoms were relieved by prostatectomy. Leng and McGuire [640] showed improvement in compliance after relief of obstruction in 7/9 men with severely impaired compliance ($\leq$ 5 ml/cmH2O), but only one man was restored to "normal" compliance. Several contemporary explanations for the cause of persistent overactivity after obstruction endure. These include denervation supersensitivity of the bladder muscle [33, 89, 641], alterations in collagen composition of the obstructed bladder [642], emergence of altered and increased sensory reflexes mediating the micturition reflex [22, 51], and physical changes in detrusor myocytes affecting electrical transmission [39]. In addition, the bladder itself and particularly the trigone may be inadvertently resected during surgery, causing bladder dysfunction. Causes of sphincter damage after transurethral or open prostatectomy for BPH include direct damage to endolumenal tissue distal to the verumontanum because of surgical error or loss of landmarks, unexpected infiltration of the sphincter by carcinoma with loss of urethral compliance, and electrocautery or thermal injury to the sphincter [643].

Recently, Han et al [644] conducted a retrospective data analysis using a managed care data set (Integrated Healthcare Information Services National Benchmark Database) from 1997 through 2003. They identified a cohort of men this BPH using International Classification of Diseases, Ninth Revision (ICD-9) codes. From a total of over 12 million men, 411,658 men with BPH (3.3%) were identified. The group then determined the nature of incontinence in these men with BPH focusing on its incidence, prevalence, and management. Furthermore they stratified patients by therapeutic subgroups of watchful waiting, alpha blockers, 5-alpha reductase inhibitors and surgery. Of the total cohort, 2.7% had a diagnosis of incontinence. Most of these men (87.5%) did not have prior BPH surgery, but of those who did have surgery 12.5% were diagnosed with incontinence. The rates were almost identical whether the procedure was transurethral resection or incision, laser, transurethral needle ablation, transurethral microwave therapy or open prostatectomy. The rate of incontinence was 1.4% for both stress and mixed incontinence, 4.5% for urge incontinence and 6.5% for unspecified incontinence. Incontinence rates for men on watchful waiting, alpha-blockers, 5-alpha reductase inhibitors and combination therapy were 6.4%, 5.7%, 5.1%, and 6, 5% respectively. This study provides some interesting data but must be interpreted with caution. The diagnosis of incontinence was limited by what the patient and provider considered incontinence and was often not confirmed by objective testing. Furthermore one cannot assume cause and effect related to treatments as many of these men may have sought treatment because they were incontinent. Nevertheless, the relationship of BPH and incontinence can clearly be inferred.

Until the last decade, transurethral resection of the prostate and open prostatectomy accounted for the majority of surgical procedures to treat BPO. In 1989, the American Urological Association published two major series on TURP and its complications. The AUA cooperative study included 3,885 patients from 13 teaching centres and private practices [645], while the second consisted of a survey of all practicing urologists in the United States of whom 2,716 urologists responded [646]. Rates of post-TURP incontinence requiring a pad or collection device were 0.4% in the first and 3.3% in the second study. The AUA Cooperative study also reported mild stress incontinence in 1.2% [647]. In 1994, the Agency for Health Care Policy and Research published clinical guidelines for the diagnosis and treatment of benign prostatic hyperplasia. The guidelines panel reviewed 27 articles about transurethral prostatectomy and 30 articles reporting open prostatectomy to analyze treatment outcomes. The panel reported that the risk of total incontinence, defined as complete loss of voluntary control over micturition was of great concern to patients facing a treatment decision for BPH. In an overall ranking of 15 different outcomes, the panel's proxy judges ranked total incontinence of urine as the fourth most important outcome influencing a

treatment decision. After TURP, 2.1 % of patients experienced stress incontinence, 1.9 % had urge incontinence, and 1.0% had total incontinence. The panel attempted to abstract data on urge incontinence, but found very few studies reporting this particular outcome, therefore a statistical analysis was not performed. For open prostatectomy stress incontinence occurred in 1.9%, urge incontinence in 0.5% and total incontinence in 0.5% of patients.

Most studies evaluating post TURP and open prostatectomy incontinence have found a significant incidence of sphincter and bladder dysfunction. The incidence of sphincter dysfunction ranges from 20-92% and bladder dysfunction from 56-97% [648-653]. The relatively high incidence of sphincter dysfunction may seem somewhat surprising as the incidence of DO before treatment is so high and it persists in 18-59% after surgery to relieve obstruction [636, 639]. Therefore one might expect that a large number of patients would have persistent detrusor overactivity and urge incontinence. However, in large series, sphincter dysfunction appears to be the main cause of incontinence. The high incidence of sphincter dysfunction is likely to represent a selection bias, e.g. large numbers of patients referred to tertiary centres for treatment of stress incontinence. Nitti et al [654] evaluated patients with voiding dysfunction after TURP and found that of those who had incontinence 75% had bladder dysfunction, while only 20% had sphincter dysfunction (the cause of incontinence could not be identified in 5%). Twenty-seven percent of incontinent patients with bladder dysfunction also had obstruction.

In the past decade, alternatives to TURP for the treatment of BPH have emerged. Most notably are thermal therapies and laser resection/enucleation of the prostate. Thermal therapies are considered “less invasive” and outcomes in most series are not comparable to traditional TURP with respect to efficacy. However some laser treatments provide similar efficacy in well selected patients, at least in the short term. Studies that have evaluated holmium laser enucleation (HoLRP), holmium laser resection (HoLRP) or potassium titanyl phosphate (KTP) laser vaporization of the prostate have shown a similar incidence of incontinence. Two randomized controlled trials of holmium laser versus TURP have shown rates of stress incontinence to be very similar. Westenberg, et al [655] showed the incidence of stress incontinence with or without urge incontinence to be 7% for HoLRP versus 6.7% for TURP at a minimum of 4 years follow-up. Kuntz and colleagues [656] found just 1% stress incontinence in each group at 12 months. They also showed a similar rate of resolution of preoperative urge incontinence for both groups (81% versus 85%). Two other prospective non-randomized trials of HoLEP found 0.6% -2.5% incidence of stress [657]. Two randomized controlled trials of KTP (green light) laser versus TURP reported 0% and 1% stress incontinence in each group respectively [658, 659] while a third randomized trial did not mention incontinence [660] .Retrospective studies on Green light showed a 2-3.3% incidence of stress incontinence [661, 662]. Te et al [663] reported 1 year results of green light in the first US multicenter prospective trial. At 12 months 2 of 139 men had persistent new onset urge incontinence. They reported no stress incontinence.

## III. INCONTINENCE ASSOCIATED WITH RADICAL PROSTATECTOMY

### 1. INCIDENCE

The incidence of incontinence after radical prostatectomy has been a source of controversy over the past several decades as reported rates have varied greatly depending on the definition and methodology of data collection. The incidence has probably declined over the past two decades, owing to advances in surgical technique and to earlier recognition of lower stage disease in younger patients, however the prevalence of post-prostatectomy incontinence has risen; paralleling the increase in surgical procedures performed annually [664].

In 1991, Foote et al tabulated data from series published between 1977 and 1990, and reported a range of incontinence rates from 2.5 to 87 percent after radical prostatectomy [665]. In general, older single-institution studies utilizing physician assessments to determine incontinence rates report relatively low rates (5-8%) [666-671] .A variety of definitions of incontinence were used, making comparison of data difficult. Since then, validated patient questionnaires have been developed, which help to standardize definitions of incontinence, allow easier comparison between institutions, and assess of the impact of incontinence on quality of life. This eliminates physician bias perhaps improving accuracy [672-674], although it introduces the cave at that questionnaire-based data may reflect subjective urine leakage but does not correlate with bother or actual urine, especially for mild degrees of incontinence [675, 676]. As expected these studies show the incidence of incontinence to be significantly higher, 13-65%, depending upon the definition.

In the past several years robotic radical prostatectomy has gained popularity. Similar to what is seen with open radical prostatectomy the continence rates tend to increase with longer follow-up and may continue to improve even beyond 12 months [677]. The continence rates from several large recently published series ranged from 68 to 97% at 12 months post surgery [677-681], 20 - 27% achieving immediate continence following catheter removal [678, 680, 681]. Recently anterior vesicourethral reconstruction [682], posterior vesicourethral reconstruction [683] and total reconstruction [684] have been described to increase the continence rate and hasten time to recovery of

continence. As in earlier open prostatectomy series, robotic series tend to be single institution studies with physician reported outcomes and continence status based on no or 0-1 pads.

In 1993, The American College of Surgeons Commission on Cancer reviewed the reported results of 2,122 patients treated by radical prostatectomy performed at 484 institutions in 1990 [685]. Only 58% reported complete continence, 23% reported occasional incontinence not requiring pads, 11.2% wore 2 or fewer pads per day, 4% wore more than 2 pads per day, and 3.6% were completely incontinent. Fowler et al [686] published the results of an outcomes study on a series of Medicare patients with less encouraging results. In this series patients age >65 surveyed by mail, telephone, and personal interview, over 30 percent reported currently wearing pads or clamps to deal with wetness; over 40 percent said they dripped urine during cough or when the bladder was full; 23 percent reported daily wetting of more than a few drops. Six percent had surgery after the radical prostatectomy to treat incontinence.

There appear to be differences in physician vs. patient reported outcomes and centres of excellence versus community surgeons' outcomes. When trying to interpret all of the data, it is clear that the varying definitions of incontinence make comparisons impossible. Even using the definition of pad free as totally continent has its limitations. Rodriguez et al [687] found that 70% of men who attained "pad-free continence" after radical prostatectomy have occasional incontinence. Conversely, Lepor et al [688] asked the single question "Do you consider yourself continent?" at 3-24 months after surgery. 97.1% of men answered yes. They found that the best correlation of objective measures with a positive were 0 *or* 1 pad, total control *or* occasional dribbling, and no *or* slight problem from incontinence on the UCLA/RAND questionnaire [688]. There is a dearth of good quality prospective studies evaluating incontinence after prostatectomy in an objective manner. One such study compared continence in patients undergoing open versus laparoscopic radical prostatectomy at one year, using a 24 hour pad test, symptom scores and quality of life measures [689]. Incontinence was defined as a pad weight of > 8 grams/24 hours. There were no difference in objective and subjective measures between the two groups. Urinary incontinence was present in 13% of open and 17% of laparoscopic cases. In practical terms incidence of incontinence that produces bother, no matter what its degree, is the true parameter of interest. However, because of the individual variability of bother and the way data has been collected, we must realize the limitations of the historical data in the literature. **Tables 7 and 8** highlight the reported rates of post-prostatectomy incontinence

***Table 7. Incidence rates of incontinence following radical retropubic prostatectomy based on physician assessment in single institution studies.***

| Reference | N | F/U (mo) | Mean age/ (range) | Subjective Leakage | Pad Use |
|---|---|---|---|---|---|
| Patel, et al (2007) [678] | 500 | 12 | 63.2 | N/A | 3% (not all patients had 12 month data) |
| Catalona, et al (1999) [666] | 1328 | 50 | 63 (38-79)<br>40-49: 53<br>50-59: 358<br>60-69: 632<br>70+: 282 | N/A | 8% |
| Eastham, et al (1996)[667] | 581 | 24 | 63 med | Stress: 5%<br>Severe: 4% | N/A |
| Geary, et al (1995) [668] | 458 | >18 | 64.1 +/- 0.3 | N/A | 1-2pads/day - 8.1%<br>3-5 pads/day - 6.6%<br>Total Incont - 5.2% |
| Zincke, et al (1994) [671] | 3170 | 12 | 65.3 (31-81) | N/A | 3 or more pads/day:<br>Pre 1988 - 7.9%<br>Post 1988 - 5% |
| Leandri, et al (1992) [669] | 398 | 12 | 68 (46-84) | STRESS URINARY INCONTINENCE - 5%<br>Total - 0 | 5% |
| Steiner, et al (1991) [670] | 593 | 12 | ? (34-76) | STRESS URINARY INCONTINENCE - 8%<br><br>Total - 0 | <1 pad/day - 2.2%<br>1 pad/day - 3.5%<br>2 pads/day - 1.5%<br>>2pads/day - 0.5% |

***Table 8. Incidence rates of incontinence following radical retropubic prostatectomy based on data gathered from validated patient questionnaires.***

| Reference | N | F/U (mo) | Age (range) | Subjective Leakage | Pad Use |
|---|---|---|---|---|---|
| Lepor, et al (2004) [688] | 621 | 24 | 58.7 (37-75) | Patients considered "continent" on self assessment | 0-1 pad/24 hours |
| Stanford, et al (2000) [690] | 1291 | 18 | <65 - 56%<br>>65; -44% | Occasional - 40%<br>>Occasional - 8.4% | 1-2 pads/day -18.3%<br>>3 pads/day - 3.3% |
| Kao, et al (2000) [691] | 1069 | N/A | 63.6 (30 -77) | 65.6% | 33% |
| Wei, et al (2000) [672] | 217 | 12 | 62.3 (40-80) | Any leakage - 47%<br>>1 episode/day - 65% | 13% (>1PPD) |
| Fontaine, et al (2000) [692] | 116 | 51.6 | 65.2 (48-76) | 14.4% | 19.8%<br>1 pad/day - 74%<br>2 pads/day - 13%<br>>3 pads/day - 13% |
| Walsh, et al (2000) [693] | 59 | 18 | 57 (36-67) | N/A | 7% |
| McCammon, et al (1999) [673] | 203 | 40.3 (12-144) | 63.7 (43-73) | 61.8% | 23.7% |
| Bates, et al (1998) [694] | 87 | 22 (7-87) | 65 (49-73) | 69% | 24%<br>1 pad/day - 60%<br>2 pads/day - 15%<br>>3 pads/day - 25% |
| Talcott, et al (1997) [695] | 94 | 12 | 61.5 | 13% | 39% |
| Donnellan, et al (1997) [675] | 51 | 12 | ? | Mild - 14%<br>Moderate - 4%<br>Severe- 2% | Pad test<br>Mild - 6%<br>Moderate - 6%<br>Severe - 4% |
| Jonler, et al (1996) [696] | 86 | 22.5 (12-48) | 64 (49-75) | Some- 59%<br>>Few drops - 30% | 47% |
| Goluboff, et al (1995) [650] | 480 | 36.4 (12-106) | 62.6 | Occasional, no pads- 56.6%<br>Daily incontinence: 8.2% | Regular use - 8.2% |
| Fowler, et al (1993) [686] | 757 | >24 | 65-69 - 51%<br>70-74 - 39%<br>>74 - 10% | Some: 47%<br>>Few drops and every day - 23% | 31% |

in large contemporary series using physician-gathered and self-reported data respectively. Most large series are on radical retropubic prostatectomy as opposed to radical perineal prostatectomy.

## 2. RECOVERY OF CONTINENCE AFTER RADICAL PROSTATECTOMY

While the majority of patients experience incontinence immediately following RRP, in most this is transient with a gradual improvement over time. Most studies report progressive return of continence up to one year after surgery and in general intervention for incontinence is usually delayed until one year after surgery unless absolutely no progressive improvement is seen. Thus, most prostatectomy series report continence rates at 1 year. Lepor and Kaci [688] showed that continence may continue to improve up to 24 months based on objective and subjective measures. They showed modest improvements in bother (UCLA RAND questionnaire) pad usage and total control rates between 12 and 24 months. Pad weights were not determined so it is possible that some "improvements" could have been related to patient tolerance and expectations over time. Smither et al [697] objectively assessed the natural history of post radical prostatectomy incontinence using a standardized I hour pad test. They showed a rapid improvement in urinary control during the first 18 weeks post-RRP with a flattening of the recovery curve beyond that point. Minimal incontinence defined as $\leq$ 1 gm on a 1 hour pad test was as demonstrated in 3,37,66, 85, 87 and 91% of patients at 2, 6, 18, 30, 42, and 54 weeks. They concluded that the 18 week marker appears to be the time point after which the majority of patients have achieved urinary control, although a small percentage will have continued objective improvement.

## 3. RISK FACTORS

An increased risk towards post-prostatectomy incontinence in older men is supported in theory by anatomical observations. With advancing age, there is evidence of atrophy of the rhabdosphincter [627] and neural degeneration [698]. Several studies have shown advancing age to be a risk factor for postoperative incontinence [666, 667, 669, 671, 690, 699]. Steiner, et al [670] found no correlation between age and continence status, but only 21 of the 593 patients were 70 years or older. Catalona et al [666] reported that "Recovery of urinary continence occurred in 92% (1,223 of 1,325 men) and was associated with younger age ($p<0.0001$).

Most large series have found no correlation between the stage of disease and incontinence rates [666, 667, 672, 676]. However, in certain cases, the stage of disease may affect the surgical technique (i.e. nerve sparing) and rates may be higher, but this appears to be a reflection on surgical technique and not disease stage [667].

Authors of several single-institution studies have argued that surgeon experience and surgical technique are important determinants of post-operative incontinence rates [631, 650, 667, 700, 701] and many have found that changes in their own technique have led to reduced rates of incontinence or a reduced time to continence recovery [631, 667, 684, 702-704]. This includes procedural modifications such as, nerve - sparing (probably secondary to a more careful dissection) bladder neck preservation, preservation of anterior urethral ligamentous attachments and urethrovesical junction reconstruction.

Patients who have undergone prior radiation for prostate cancer are at high risk of developing incontinence after radical prostatectomy. Rates of significant incontinence after salvage prostatectomy range from 57-64% [705, 706]. Sanderson and colleagues [707] reported that 45% of men underwent artificial urinary sphincter placement after salvage prostatectomy and another 31% without an artificial sphincter had incontinence greater than occasional dribbling. This has prompted some to recommend urinary diversion at the time of salvage radical prostatectomy [708].

## 4. ETIOLOGY AND PATHOPHYSIOLOGY OF POST RADICAL PROSTATECTOMY INCONTINENCE: SPHINCTER VS. BLADDER DYSFUNCTION

There is fairly extensive literature on urodynamic investigation of post prostatectomy incontinence. While it is well established that both bladder and sphincter dysfunction may be present after radical prostatectomy, most studies agree that sphincter dysfunction (stress incontinence) is the main cause. [648, 698, 709-712]. In these series the incidence of sphincter dysfunction ranges from 88–98.5%, with associated bladder dysfunction (detrusor overactivity and less commonly impaired compliance) in 26-46%. Bladder dysfunction, on the other hand, was present in 34–45% of patients but was the sole cause of incontinence in only 1.5–4%. Bladder dysfunction when present in association with sphincter dysfunction may not always be clinically significant. Ficazzola and Nitti [710] found that although 46% of patients had bladder dysfunction, incontinence on urodynamic study was demonstrated in only 27%. Even in those patients, sphincter dysfunction was the main cause of incontinence in the overwhelming majority. Groutz and colleagues [709] found a 33% incidence of bladder dysfunction, but found that it was the main cause of incontinence in only 7.25%. Two earlier series reported a higher incidence of bladder dysfunction [649, 650]. Some authors feel that in some patients with severe intrinsic sphincter deficiency bladder dysfunction may occur as a result of filling the bladder to volumes that it is not accustomed to holding [710]. Filling to capacity may produce detrusor overactivity or decreased accommodation. Thus, bladder dysfunction is in a

sense an artefact. This may explain why the outcomes for artificial urinary sphincters for the treatment of stress incontinence are not adversely affected by the presence of detrusor overactivity [713, 714]. In addition bladder dysfunction may be chronic and stem from obstructive uropathy present before prostatectomy. **Table 9** summarizes the urodynamic findings in eight series. It must be emphasized that patient selection, urodynamic technique and timing of urodynamic evaluation maybe responsible for the differences seen among the different studies. It is also important to note that most of these studies are preformed in men seeking treatment for there incontinence. However, it appears that sphincter dysfunction is the main cause of post-radical prostatectomy incontinence, but bladder dysfunction may be present in a significant number of men (though rarely alone) and must not be completely discounted when planning treatment.

The majority of evidence in the literature supports the conclusion that sphincter damage is the primary cause of incontinence after total prostatectomy. Direct exposure and manipulation of the sphincter during radical prostatectomy would suggest that sphincter damage is the most likely cause of incontinence. Successful treatment with the artificial urinary sphincter and male sling procedures also indirectly suggests that primary sphincter injury is the major cause of incontinence, since outcome is usually not complicated by bladder dysfunction. Bladder dysfunction after prostatectomy may have been present preoperatively, for example due to pre-existing outflow obstruction, may be caused by the operation itself, or may be due to age related changes in bladder function. Many patients who have prostate surgery have pre-existing bladder dysfunction, which may or may not be symptomatic. While it is obvious how overzealous TURP with resection into the trigone can cause detrusor overactivity; it is less apparent how radical prostatectomy affects detrusor function. Some have suggested that denervation of the urethra or the bladder may occur during radical prostatectomy. John et al [715] studied trigonal innervation by biochemical markers and found that "urinary incontinence was associated with decreased trigonal innervation, a high sensory threshold and low maximal urethral closure pressure".

## IV. INCONTINENCE RELATED TO RADIATION THERAPY FOR PROSTATE CANCER

Radiation therapy, whether external beam or brachytherapy, can be a cause of voiding dysfunction and incontinence. Sometimes this is a direct effect of the radiation or it can be related to the treatment of other sequelae such as urinary retention. The initial response to is primarily oedema and then gradually degeneration, fibrosis and disorganization overcomes the bladder musculature. While radiation is primarily delivered to the prostate, portions of the bladder may also be affected. Perivascular fibrosis of blood vessels may then cause vascular occlusion followed by ischemia of the bladder wall which can then progress to fibrosis within 6 to 12 months [716]. Choo et al. [717], found that urodynamic bladder capacity decreased by an average of 54 ml, 18 months after radiation therapy. Blaivas et al [718] evaluated 47 men with symptomatic LUTS after brachytherapy and found that 71% were incontinent and 85% had detrusor overactivity. Similarly, radiation can cause damage to the distal urinary sphincter which can result in incontinence. However, this usually does not manifest until the patient undergoes treatment such as transurethral resection or incision of the prostate which compromises the proximal urethral sphincter.

Urinary retention and increased obstructive LUTS are other common problems that radiation therapy and

***Table 9. Summary of several urodynamic contemporary series on post-radical prostatec-tomy incontinence with regard to sphincter and bladder dysfunction.***
****This study considered urodynamic diagnoses of obstruction and impaired contractility so that patients with sphincter insufficiency and impaired contractility or obstruction without bladder dysfunction are not included in this group. From Nitti [731]***

| | N | Sphincter Dysfunction | | Bladder Dysfunction | |
|---|---|---|---|---|---|
| | | Total (%) | Alone (%) | Total (%) | Alone (%) |
| Leach, et al [649] | 162 | 82 | 40 | 36 | 14 |
| Goluboff, et al [650] | 25 | 60 | 8 | 90 | 40 |
| Chao & Mayo [698] | 74 | 96 | 57 | 43 | 4 |
| Gudziak, et al [712] | 37 | 97 | NA | NA | 3 |
| Desautel, et al [711] | 35 | 95 | 59 | 39 | 3 |
| Ficazzola & Nitti [710] | 60 | 90 | 53 | 45 | 3 |
| Winters, et al [648] | 92 | 98.5 | 59 | 29 | 1.5 |
| Groutz, at al [709] | 83 | 88 | 33* | 34 | 4 |

particularly brachytherapy is urinary retention. The incidence of retention has been reported to range from to be 2% to 30% after brachytherapy [719-722]. Most patients with retention will have resolution of their obstruction within weeks others go on with surgical procedures. A retrospective review of over 2,100 Medicare patients who underwent brachytherapy for prostate cancer found that 8.3% required a surgical procedure to relieve bladder outlet obstruction post-brachytherapy [723]. Flam, et al [724] reported that 19 of 600 (3.1%) patients receiving brachytherapy required TURP. Kollmeier and colleagues [725] reported a similar rate of 2% in 2050 men. Most authors have found significant rates of post TURP incontinence after radiation. Incontinence following TURP after brachytherapy has been reported in 0-70% and is often severe. [724-726]. External beam radiation is also is a risk factor as Green et al [727] reported a 33% incidence of incontinence following TURP in patients post-irradiation for prostate cancer. Some authors have emphasized that incontinence can be minimized by performing a limited resection [728] or by performing TURP within 2 years of brachytherapy [725]. In the latter study, two of 24 patients (8%) that underwent TURP within 2 years of treatment were incontinent and 5 of 14 patients (36%) that underwent TURP 2 years or more after brachytherapy were incontinent (p=0.04). However, others suggest that delaying TURP until 5 years after radiation can actually reduce the risk of incontinence [729, 730].

## V. CONCLUSIONS

Incontinence in the male as in the female can be broadly divided into that which is caused by bladder dysfunction and that which is caused by sphincter dysfunction. The pathophysiology of incontinence as it relates specifically to the male is fairly well described; however advances in science and anatomy will undoubtedly provide a more intricate understanding in the future. For example, the causes of sphincter insufficiency are known (i.e. damage to muscle, nerve and/or supporting structures) but clinicians are not able to accurately assess the exact cause of sphincter insufficiency in any given patient. Therefore much of our understanding of post treatment incontinence "pathophysiology" is derived from reports of incontinence (incidence/prevalence) after surgery or radiation In addition investigators have not done a good job in defining the incidence of incontinence related to interventions for prostatic disease, whether benign or malignant. Problems have been two-fold: first in defining incontinence and what is bothersome/significant and second in accurately reporting data. New technologies for the treatment of BPH have provided us with Level 1 evidence regarding the incidence of incontinence in trials comparing new technology to TURP and Level 2 evidence through meta-analysis and prospective series. Data regarding the incidence of post radical prostatectomy and post radiation incontinence has been less robust and of a lower quality – level 2-4. Even the level 2 evidence lacks a consistent definition.

## VI. RECOMMENDATIONS

Level of evidence 1 regarding the incidence of post prostatectomy and post radiation incontinence is needed. It is hoped that the advent of new technologies will prompt controlled trials of different therapies for prostate cancer with incontinence as a primary endpoint. These studies must start with a standardized definition of incontinence and how it affects quality of life, thus objective and subjective measures will be necessary. Such an understanding will allow clinicians to better select, prepare and treat patients and ultimately prevent or at least limit incontinence.

# H. CAUSES OF TRANSIENT INCONTINENCE IN OLDER ADULTS

## I. BACKGROUND

Transient causes probably accounts for one-third of incontinent cases among community-dwelling older people (>65 years old), up to one-half of cases among acutely-hospitalized older people, and a significant proportion of cases among nursing home residents [732-734]. Most causes of transient incontinence in the older population lie outside the lower urinary tract but two points are worth emphasizing. First, the risk of transient incontinence is increased if, in addition to physiologic changes of the lower urinary tract, the older person also suffers from pathologic changes. Overflow incontinence is more likely to result from an anticholinergic agent in a person with a weak or obstructed bladder, just as urge incontinence is more likely to result from a loop diuretic in someone with detrusor overactivity and/or impaired mobility [735, 736].

This fact may explain why some controversy persists regarding some causes of transient incontinence. It also emphasizes that continence depends on the integrity of multiple domains-mental state, mobility, manual dexterity, medical factors, and motivation, as well as lower urinary tract function. Although in younger individuals incontinence usually results from lower urinary tract dysfunction alone, incontinence in older patients often results from deficits in multiple domains that together result in incontinence [737]. Attention to any one or more of these risk factors can restore

continence or at least improve it. Second, although termed “transient,” these causes of incontinence may persist if left untreated, and so they cannot be dismissed merely because the incontinence is of long duration.

## II. QUALITY OF DATA

In older people, continence status is often not absolute, especially in those who are frail. Infrequent leakage of small amounts may appear and disappear, and reporting accuracy varies as well [738].

Furthermore, ethical constraints and methodological issues preclude robust investigations of the conditions commonly impugned as causes of transient incontinence. Thus, it is not surprising that evidence supporting the association between these conditions and transient incontinence consists predominantly of case reports and case series.

## III. RESULTS OF LITERATURE REVIEW

Transient causes of incontinence in older people are shown in **Table 10** and can be recalled using the mnemonic **DIAPPERS** [739]

***Table 10. Causes of Transient Incontinence in Older People***

| | |
|---|---|
| **D** | **Delirium** |
| **I** | Infection (UTI, symptomatic) |
| **A** | Atrophic urethritis/vaginitis |
| **P** | Psychological (e.g. severe depression, neurosis) |
| **P** | Pharmacologic |
| **E** | Excess urine output |
| **R** | Restricted mobility |
| **S** | Stool impaction |

### 1. DELIRIUM

“D” is for delirium, a confusional state characterized by fluctuating inattentiveness and disorientation. Its onset occurs over hours to days, as contrasted with dementia, which develops over years. Delirium can result from almost any medication and from virtually any acute illness, including congestive heart failure, deep vein thrombosis, or infection. Many of these conditions may present atypically in older patients, and if the patient becomes confused because of them, incontinence may be the first abnormality detected [740]. Delirium leads the list because, if unrecognized, it is associated with significant mortality. Thus, in this case, meticulous medical evaluation - not cystometry- is crucial.

### 2. URINARY INFECTION

Symptomatic urinary infection is another cause of incontinence, although it is an uncommon one [732]. However, asymptomatic urinary infection, is much more common in older people [741, 742].

### 3. ATROPHIC VAGINITIS

Atrophic vaginitis in older women is frequently associated with lower urinary tract symptoms, which occasionally include incontinence. As many as 80% of such women attending an incontinence clinic are reported to have physical evidence of atrophic vaginitis, characterized by vaginal mucosal atrophy, friability, erosions, and punctuate haemorrhages. Atrophic vaginitis has been associated with urgency and occasionally a sense of “scalding” dysuria, but both symptoms may be relatively unimpressive. More recent epidemiologic and clinical studies have called these beliefs into question since they have demonstrated an association with estrogen treatment and the onset of incontinence. Unfortunately, limitations in their design allow for the possibility of both bias and confounding factors. Further research is warranted.

### 4. MEDICATIONS

Pharmaceuticals are one of the most common causes of incontinence in older people, with several categories of drugs commonly implicated [743] (**Tables 11 and 12**). Of note, many of these agents also are used in the treatment of incontinence, underscoring the fact that most medications used by older people are “double-edged swords.” The first category of relevant drugs is the long-acting sedative/hypnotics, such as diazepam and flurazepam, which can cloud an older patient’s sensorium. “Loop” diuretics, such as furosemide or bumetanide, by inducing a brisk diuresis,

***Table 11. Important anticholinergic drugs and drug side effects in the elderly***

| Drugs | Anticholinergic Effects |
|---|---|
| Antipsychotics | Dry mouth |
| Tricyclic Antidepressants (not SSRI’s) | Constipation |
| Anti-parkinsonian agents | Confusion |
| First generation (sedating) antihistamines | Drowsiness, fatigue |
| Anti-arrhythmics (disopyramide) | Tachycardia |
| Antispasmodics | Inhibit detrusor contractility |
| Opiates | Urinary-retention; Blurred-Vision;Increased ocular pressure |

***Table 12. Common Medications Affecting Continence***

| Type of Medication | Examples | Potential Effects on Continence |
|---|---|---|
| Sedatives/Hypnotics | Long-acting benzodiazepines (e.g.diazepamflurazepam) | Sedation, delirium, immobility |
| Alcohol | | Polyuria, frequency, urgency, sedation, delirium, immobility |
| Anticholinergics | Dicyclomine, disopyramide, antihistamines, (sedating ones only, e.g., Benadryl®) | Urinary retention, overflow incontinence, delirium, impaction |
| Antipsychotics | Thioridazine, haloperidol | Anticholinergic actions, sedation, rigidity, immobility |
| Antidepressants (tricyclics) | Amitriptyline, desipramine; not SSRI's | Anticholinergic actions, sedation |
| Anti-Parkinsonians | Trihexyphenidyl, benztropine mesylate, (not L-dopa or selegiline) | Anticholinergic actions, sedation |
| Narcotic analgesics | Opiates | Retention, impaction, sedation, delirium |
| Adrenergic ·antagonists) | Prazosin, terazosin, doxazosin | Urethral relaxation may precipitate stress incontinence in women |
| Adrenergic ·agonists) | Nasal decongestants | Urinary retention in men |
| Calcium channel blockers | All dihydropyridines* | Urinary retention; nocturnal diuresis due to fluid retention |
| Potent diuretics | Furosemide, bumetanide (not thiazides) | Polyuria, frequency, urgency |
| NSAIDsThiazolidinediones | Indomethacin,COX-2 inhibitors, Rosiglitazone, pioglitazone | Nocturnal diuresis from fluid retention |
| Angiotensinconverting enzyme(ACE) inhibitors | Captopril, enalapril, lisinopril | Drug-induced cough precipitates stress incontinence in women and some men after prostatectomy |
| Vincristine | | Urinary retention from neuropathy |

(Adapted from: Resnick, N. M., Geriatric Medicine. In: Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DJ (eds), Harrison's Principles of Internal Medicine. McGraw-Hill, 1994; p. 34.)[745]

can also provoke leakage. Drugs with anticholinergic side effects are a particular problem and include major tranquilizers, antidepressants, antiparkinsonian agents (e.g., benztropine mesylate or trihexyphenidyl), first generation (sedating) antihistamines, anti-arrhythmics (disopyramide), antispasmodics, and opiates. By decreasing detrusor contractility, they can cause urinary retention and overflow incontinence. They also can cause confusion. Anticholinergic agents are particularly important to ask about for two reasons. First, older patients often take more than one of them at a time. Second, they are contained in many non-prescription preparations that older people frequently take without consulting a physician.

Adrenergically-active agents have also been associated with incontinence. Many alpha-adrenoreceptor antagonists (used mainly for treatment of hypertension) block receptors at the bladder neck and may induce stress incontinence in women [744]. Older women are particularly at risk because their urethral length and closure pressure normally decline with age. Thus, prior to considering other interventions for stress incontinence in a woman taking such a drug, substitution of an alternative agent should be tried and the incontinence re-evaluated. Calcium channel blockers can cause incontinence. As smooth muscle relaxants, they can increase residual volume, especially in older adults with impaired detrusor contractility. The increased residual urine may occasionally lead to stress incontinence in women with a weak urethral sphincter, or to overflow incontinence in men with concurrent urethral obstruction. Finally, angiotensin converting enzyme inhibitors, by inducing cough (the risk of which is age-related), may precipitate stress incontinence in older women whose urethra has shortened and sphincter weakened with age.

### 5. DIURESIS

Excess urinary output can also cause incontinence, especially in individuals with impaired mobility, mental state, or motivation, particularly if they also have detrusor overactivity. Causes of excess output include excess intake, diuretics (including theophylline-containing fluids and alcohol), and metabolic abnormalities (e.g., hyperglycemia and hypocalcaemia). Nocturnal incontinence can be caused or exacerbated by disorders associated with excess nocturnal excretion, such as congestive heart failure, peripheral venous insufficiency, hypoalbuminemia (especially in malnourished older people), and drug induced peripheral oedema associated with NSAIDs, thiazolidinediones, and some calcium channel blockers (e.g., dihydropyridines such as nifedipine, isradipine, and nicardipine). The role of caffeine and timing of drinking fluids (e.g. in the evening or before bedtime) is still not clear, but should nonetheless be considered a possible contributing cause for nocturia and nocturnal incontinence.

### 6. RESTRICTED MOBILITY

Restricted mobility is an easily understood but frequently overlooked cause of incontinence. In addition to obvious causes, restricted mobility may be associated with orthostatic or postprandial hypotension, poorly-fitting shoes, poor physical state, or fear of falling, all of which are common geriatric conditions.

### 7. FAECAL IMPACTION

Finally, faecal impaction has been implicated as the cause of incontinence in up to 10% of older patients seen in acute hospitals or geriatric incontinence clinics. One possible mechanism involves stimulation of opioid receptors [746]. A clue to the presence of faecal impaction is the onset of both urinary and faecal incontinence, usually associated with oozing of loose stool around the impaction.

## IV. SUMMARY

Apart from re-challenge data for alpha adrenergic agents (Level of Evidence = 2), the level of evidence for most of these causes is Level 3-4. Nonetheless, because they are easily addressed and contribute to morbidity beyond the lower urinary tract, they are worth identifying even if the evidence is not strong.

## V. RECOMMENDATIONS

Despite the current lack of compelling data, these seven “transient” causes of urinary incontinence should be searched for in older incontinent patients before embarking on more complex assessment and management. Their prevalence is high, their treatment straightforward, and they contribute to morbidity beyond the urinary tract. Moreover, addressing them may improve the incontinence even if it does not eliminate it, and it may make the incontinence more amenable to subsequent therapy. (Grade of recommendation C)

## VI. RESEARCH PRIORITIES

Further research should be performed on the mechanisms, prevalence, incidence, and remission rates of each of the known causes of transient incontinence, and possible additional causes should be identified as well. Since older people are heterogeneous, studies should be conducted among several subgroups, including independent and homebound community-dwelling older people, bedbound and mobile institutionalized older people, and acutely hospitalized older people.

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