PULSED MAGNETIC STIMULATION IN THE TREATMENT OF STRESS URINARY INCONTINENCE IN FEMALE SUBJECTS

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PULSED MAGNETIC STIMULATION IN THE TREATMENT OF STRESS URINARY INCONTINENCE IN FEMALE SUBJECTS

by

LIM RENLY

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To my wonderful parents, Lim Khan San and Lee Kim Hong,

lovely sisters, Tzely and Einly,

caring brother Kewei,

and supportive husband Yong Khee

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LIST OF ABBREVIATIONS

AQoL	Australian Quality of Life questionnaire
ANOVA	Analysis of variance
AUC	Area under curve
AR (1)	Autoregressive order 1
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
EAU	European Association of Urology
ES	Electrical stimulation
EMG	Electromyography
EC	European Commission
FSFI	Female Sexual Function Index
GLMM	Generalised linear mixed model
GRISS	Golombok Rust Inventory of Sexual Satisfaction
IC	Interstitial cystitis
ICC	Intraclass correlation coefficient
ICI	International Consultation on Incontinence
ICIQ	International Consultation on Incontinence Modular Questionnaire
ICIQ-LUTSqol	International Consultation on Incontinence Questionnaire-Lower Urinary Tract Symptoms Quality of Life
ICIQ-UI SF	International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form
ICS	International Continence Society
IEF	Incontinence Episode Frequency

LIST OF ABBREVIATIONS

IIEF	International Index of Erectile Function
IPSS QoL	International Prostate Symptom Score Quality of Life
IQoL	Urinary Incontinence Quality of Life Scale
ISD	Intrinsic sphinteric deficiency
IUGA	International Urogynecological Association
KHQ	Kings Health Questionnaire
LMM	Linear mixed model
LUTS	Lower urinary tract symptom
MCID	Minimal clinically important difference
M_{diff}	Mean difference
MRI	Magnetic resonance imaging
MUI	Mixed urinary incontinence
MUS	Midurethral sling
OAB	Overactive bladder
PASS	Power Analysis and Sample Size Software
PFMT	Pelvic floor muscle training
PFR	Peak flow rate
PGI-I	Patient Global Impression of Improvement
POP	Pelvic organ prolapse
PMS	Pulsed magnetic stimulation
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analyses
PVR	Post-void residual urine volume
QoL	Quality of life

LIST OF ABBREVIATIONS

RCT	Randomised controlled trials
RR	Relative risk
ROC	Receiver operating characteristic
SD	Standard deviation
SE	Standard error
SIMS	Single-incision mini slings
TVT	Tension-free vaginal tape
TVT-O	Transobturator tape
UDI	Urogenital Distress Inventory
UI	Urinary incontinence
UTI	Urinary tract infection
UUI	Urgency urinary incontinence
VAS	Visual Analogue Scale
WHO	World Health Organisation

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STIMULASI MAGNETIK TERDENYUT UNTUK RAWATAN MASALAH INKONTINENS URINARI JENIS STRES DALAM KALANGAN WANITA

ABSTRAK

Stimulasi magnetik terdenyut (PMS) telah digunakan sebagai pilihan rawatan tanpa bedah untuk menangani masalah inkontinens urinari jenis stres (SUI) sejak tahun 1999 disebabkan faktor keselamatan, tidak invasif, dan prosedur rawatan yang mudah. Namun demikian, 'Fifth International Consultation on Incontinence' menekankan bahawa bukti kajian yang sedia ada adalah tidak mencukupi untuk membimbing sebarang cadangan tentang penggunaannya untuk menangani masalah inkontinens urinari, dan kajian klinikal terkawal yang berkualiti tinggi adalah diperlukan. Oleh yang demikian, kajian ini bertujuan menilai keberkesanan PMS untuk rawatan masalah inkontinens urinari. Sebelum kajian di atas dilaksanakan, kajian sistematik telah dijalankan untuk menilai bukti PMS yang sedia ada dalam rawatan pesakit yang didiagnosis mengalami masalah inkontinens urinari. Hasil kajian menunjukkan bahawa PMS mengurangkan simptom masalah inkontinens urinari dalam kalangan wanita untuk jangka masa pendek. Walau bagaimanapun, tanpa kajian klinikal berkualiti tinggi, kesesuaian PMS sebagai pilihan rawatan untuk menangani masalah inkontinens urinari masih diragui. Oleh itu, protokol kajian klinikal yang berkualiti tinggi direka untuk menangani batasan-batasan yang diperhatikan. Seterusnya, indeks yang digunakan untuk menilai kesan masalah inkontinens urinari ke atas kualiti hidup (International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF) dan International Consultation on Incontinence Questionnaire-Lower Urinary Tract Symptoms Quality of Life (ICIQ-LUTSqol)) dan fungsi seksual dikaji dari segi kesahan dan

kebolehpercayaan dalam populasi tempatan. Semua indeks didapati memuaskan dari segi kesahan dan kebolehpercayaan. Dalam tempoh kajian ini, juga dapat diperhatikan kekurangan minat ke atas fungsi seksual pasangan yang mempunyai masalah inkontinens urinari. Justeru, satu kajian keratan rentas telah dijalankan untuk mengkaji pengalaman seksual pasangan dengan atau tanpa masalah inkontinens urinari. Sebagai tambahan, kesan PMS terhadap fungsi seksual pasangan masalah inkontinens urinari turut dikaji. Penemuan awal mendapati bahawa rawatan masalah inkontinens urinari yang berkesan dapat juga menambahbaikkan fungsi seksual kedua-dua pasangan. Bahagian terakhir kajian in melibatkan suatu kajian klinikal rawak, uji kaji dubel-buta dengan kawalan plasebo. Dalam kajian ini, seramai 120 orang pesakit yang menghadapi masalah inkontinens urinari diberi rawatan PMS aktif atau plasebo secara rawak selama 8 minggu. Keberkesanan rawatan ini dinilai dengan menggunakan indeks ICIQ-UI SF. PMS aktif didapati 3.5 kali lebih berkesan dalam mengurangkan simptom masalah inkontinens urinari berbanding plasebo. Sepanjang tempoh susulan selama satu tahun, kajian ini menunjukkan bahawa faedah tersebut dapat dikekalkan untuk jangkamasa tertentu. PMS menunjukkan faedah jangka panjang yang menggalakkan, penerimaan pesakit yang tinggi, pengalaman yang positif dan kadar keciciran yang rendah. Oleh itu, rawatan ini merupakan pilihan rawatan tanpa bedah yang menarik dan memberangsangkan untuk pesakit yang tidak ingin menjalani pembedahan.

PULSED MAGNETIC STIMULATION IN THE TREATMENT OF STRESS URINARY INCONTINENCE IN FEMALE SUBJECTS

ABSTRACT

Pulsed magnetic stimulation (PMS) has been used as a non-surgical option for stress urinary incontinence (SUI) since 1999 due to its established safety, non-invasiveness and simplicity of treatment procedures. However, the Fifth International Consultation on Incontinence (ICI) emphasised that the current evidence is insufficient to guide any recommendation on its use for urinary incontinence, and that well-powered randomised controlled trials are needed. Hence, the present study aimed to evaluate the efficacy of PMS for SUI in a randomized, double-blind, sham-controlled trial. Prior to the above study, a systematic review was conducted to appraise existing evidence on PMS for patients with urinary incontinence. The results showed that PMS provided short-term improvement for incontinence symptoms in women. However, in the absence of high quality trials, the applicability of PMS as a treatment option for urinary incontinence remained uncertain. Thus, a high-quality clinical trial protocol was designed to address the key limitations noted. In the next part of the study, the questionnaires used to assess impact of SUI on quality of life (International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF) and International Consultation on Incontinence Questionnaire- Lower Urinary Tract Symptoms Quality of Life (ICIQ-LUTSqol)) and sexual function (Golombok Rust Inventory on Sexual Satisfaction (GRISS)) were evaluated for their validity and reliability in the local population. All questionnaires demonstrated satisfactory validity and reliability. During the study period, a lack of interest on sexual function of couples with incontinence partners

was noted. Thus, a cross-sectional survey was conducted to investigate sexual experience of couples with or without SUI partners. Additionally, the effects of PMS on sexual function of SUI couples were also studied. The preliminary findings suggested that effective treatment of female's SUI symptoms using PMS resulted in simultaneous improvement in the sexual function of both partners. In the final part of the study, a multicenter, randomized, double-blind, sham-controlled trial was conducted. A total of 120 female SUI subject were randomized to receive either active or sham PMS for 8 weeks. Treatment efficacy was assessed primarily using the ICIQ-UI SF score. Active PMS was found to be 3.5 times more likely to improve SUI symptoms compared with sham. During an additional 1-year of follow-up, the present findings showed that such benefits were sustained over time. The encouraging long-term response rates, high patient acceptance, desirable experience and low dropout rates suggested that PMS is an attractive and promising non-surgical alternative to patients who do not want to undergo surgery.

CHAPTER 1 STRESS URINARY INCONTINENCE

1.1 INTRODUCTION

Urinary incontinence (UI) is a common problem encompassing a constellation of symptoms. It affects the physical, psychological, social and economic well-being of affected individuals and their families (Coyne et al., 2012, Abrams et al., 2015, Su et al., 2015). Recent epidemiological studies have shown that UI affects 25% to 45% of the female population worldwide, with a prevalence of 10% to 40% in Malaysia (Dhillon et al., 2006, Low et al., 2006, Mohd Sidik, 2010, Milsom et al., 2013). This condition is characterised by complaint of involuntary leakage of urine, which should be distinguished from sweating or vaginal discharge.

Although not life-threatening, UI poses negative impacts on all strata of the society and results in various social and medical ramifications. Patients usually continue to endure the life-disrupting consequences as it is often under-diagnosed, overlooked and seldom intervened. In Malaysia, patients are traditionally more conservative and more likely to be hesitant in seeking professional help, with ignorance being the main reason (Low et al., 2006). It is thus necessary to create awareness amongst the population that UI is largely treatable and they should always seek professional help for their UI and other related symptoms.

1.2 DEFINITION AND CLASSIFICATIONS OF URINARY INCONTINENCE

The International Urogynaecological Association (IUGA)/International Continence Society (ICS) defines UI as the complaint of involuntary loss of urine. The three most common types of UI (Haylen et al., 2010, Staskin et al., 2013) affecting patients are:

i) Stress urinary incontinence (SUI)

SUI is the complaint of involuntary loss of urine on effort or physical exertion (e.g., sporting activities), or on sneezing or coughing.

ii) Urgency urinary incontinence (UUI)

UUI is the complaint of involuntary loss of urine associated with urgency.

iii) Mixed urinary incontinence (MUI)

MUI is the complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion or on sneezing or coughing.

Other less common categories of UI (Haylen et al., 2010, Staskin et al., 2013) include:

i) Postural (urinary) incontinence

Postural (urinary) incontinence is the complaint of involuntary loss of urine associated with change of body position, for example, rising from a seated or lying position.

ii) Nocturnal enuresis

Nocturnal enuresis is the complaint of involuntary loss of urine which occurs during sleep.

iii) Continuous urinary incontinence

Continuous urinary incontinence is the complaint of continuous involuntary loss of urine.

iv) Insensible urinary incontinence

Insensible urinary incontinence is the complaint of UI where the woman has been unaware of how it occurred.

v) Coital incontinence

Coital incontinence is the complaint of involuntary loss of urine with coitus. This symptom might be further divided into that occurring with penetration or intromission and that occurring at orgasm.

vi) Incontinence associated with chronic retention of urine

Incontinence associated with chronic retention of urine is the complaint of involuntary loss of urine which occurs in conditions where the bladder does not empty completely as indicated by a significantly high residual urine volume and/or a non-painful bladder which remains palpable or percussable after the individual has passed urine.

vii) Functional incontinence

Functional incontinence is the complaint of involuntary loss of urine that results from an inability to reach the toilet due to cognitive, functional or mobility impairments in the presence of an intact lower urinary tract system.

vii) Multi-factorial incontinence

Multi-factorial incontinence is the complaint of involuntary loss of urine related to multiple interacting risk factors, including factors both within and outside the lower urinary tract such as co-morbidity, medication, age-related physiological changes and environmental factors.

1.3 BASIC ANATOMY, HISTOLOGY AND PHYSIOLOGY RELATED TO PELVIC FLOOR MUSCLE

The pelvic floor consists of the levator ani muscles, the coccygeus muscles, and associated connective tissue which span the area underneath the pelvis (Figure 1.1). The pelvic floor has two hiatuses; anteriorly the urogenital hiatus which allow the urogenital apparatus (urethra and vagina) to pass through the pelvic floor into the perineum below and posteriorly rectal hiatus through which the anal canal passes.

The levator ani can be traditionally divided into three sets of fibres according to its bony attachments and muscle fibre direction (Chapple and Milsom, 2012):

- the pubococcygeus muscles which attaches from the pubis and extends to the coccyx at the back
- the puborectalis muscles which surrounds the rectum connecting the pubic bones anteriorly in a U-shaped configuration, and
- the iliococcygeus muscles which arises laterally from the arcus tendinous levator ani and forms a horizontal sheet that spans the posterior opening of the pelvis, providing a shelf on which the pelvic organs lie.

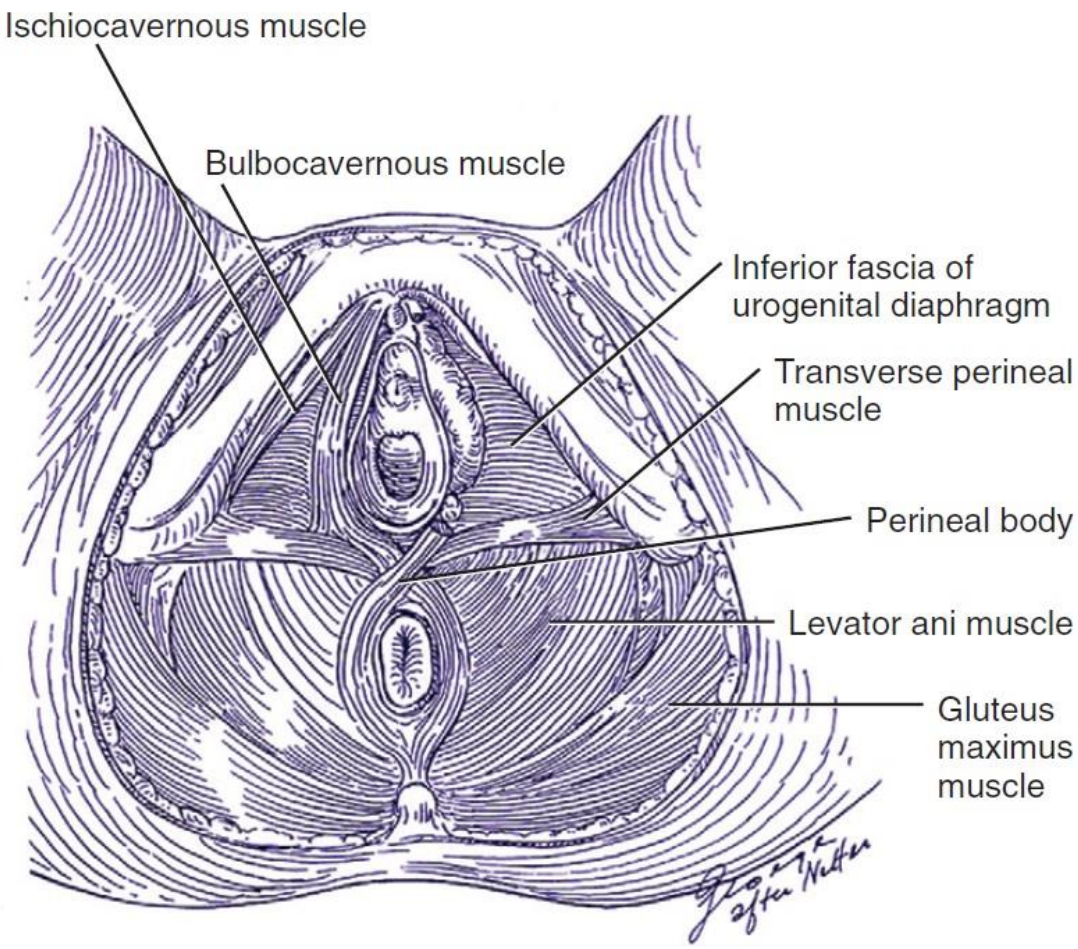

Figure 1.1 Disposition of the levator ani. (Adapted from Chapple and Milsom, 2012)

The levator ani contains not only type I fibres providing resting tone but also type II (fast-twitch) fibres that, under stress, maintain the urethral closure and prevent stretching of the pelvic ligaments (Chapple and Milsom, 2012). The pudendal nerve provides somatic innervation to the striated muscle of levator ani, as well as to the striated muscle within the external anal and urethral sphincters. The levator ani functions to support the pelvic fascia and keeps the rectum and vagina closed via sphincter closing action. It also acts by resisting rises in intra-pelvic pressure during any strain.

Next, the urethra functions to provide an effective continence mechanism and to allow adequate and smooth emptying from the bladder. The urethral sphincter comprises two components including the external striated sphincter and the internal smooth sphincter. The properly functioning sphincters allow narrowing of the urethral space. The urethral mucosa and submucosa which occupies the urethral space function as a filler substance to help in securing closure of the urethral lumen (Wallner et al., 2009). The multifaceted interplay between the extrinsic continence mechanism and the intrinsic continence mechanism ensures that continence is achieved. The intrinsic continence mechanism is formed by contraction of these urethral sphincters while the extrinsic continence mechanism is created by the solid support system consisting of the pelvic floor muscles, organs and structures which surrounds the urethra. In the female, the levator ani muscles are situated lateral to the external sphincter while in the inferior parts of the external sphincter is firmly attached via a tendinous connection to the puborectalis muscles of the levator ani muscles (Plate 1.1). This attachment signifies that the urethral sphincter depends on the levator ani muscles for proper contraction and urethral closure.

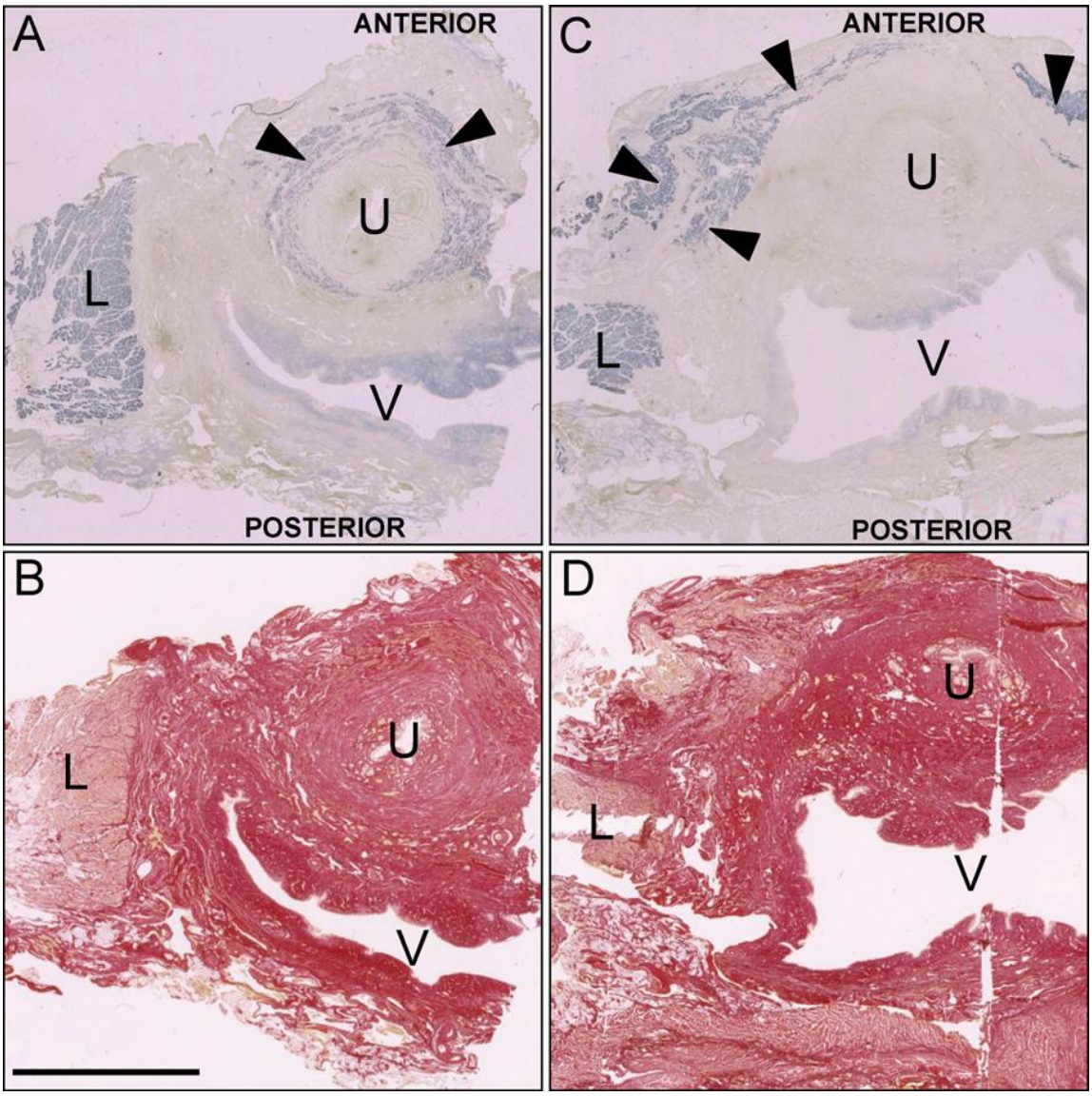

Plate 1.1 The anatomical relationship of the external urethral sphincter (EUS) to the levator ani muscle (LAM) in adults. Panels (A) through (D) show transverse sections through the EUS and the LAM of an adult female (54 yr): (A) superior part of the EUS (arrowheads), section stained immunohistochemically for striated muscle; (B) sequential section stained with sirius red for connective tissue; (C) inferior part of the EUS (arrowheads), section stained immunohistochemically for striated muscle; (D) sequential section stained with sirius red for connective tissue. Note in (C) that in the adult, the anatomical relationship between the inferior part of the EUS and the LAM is still maintained. The contrast of images (A) and (C) was increased digitally. L = levator ani muscle; U = urethra; V = vagina. (Adapted from Wallner et al., 2009)

1.4 EPIDEMIOLOGY

Despite an absence on a universal consensus on the definition of quality of life (QoL), the constitution of the World Health Organisation (WHO) defines health as "a state of complete physical, mental, and social well-being not merely the absence of disease" (WHO, 1948). Thus, it is imperative to acknowledge the general well-being of patients who seek treatment via assessing the improvement in their QoL rather than merely measuring changes in the severity of the disease. Although not a life-threatening disease, SUI impairs patients' QoL considerably (Ragins et al., 2008). When compared to other diseases, UI was reported to reduce QoL, similar to severe chronic diseases such as stroke, arthritis, and chronic kidney disease (Schultz and Kopec, 2003, Horng et al., 2013).

Various factors were found to predispose UI. These include (Hunskaar, 2008, Ebbesen et al., 2013, Milsom et al., 2013):

- Increasing age. There is a steady increase in UI throughout the adult lifespan.
- Obesity. It is one of the most clearly established risk factor for UI in women.
- Pregnancy and parity
- Mode of delivery. Vaginal delivery is significant risk factors for UI compared to caesarean section.
- Hysterectomy. Hysterectomy by any route appears to be associated with development of subsequent UI symptoms, but the evidence is inconsistent.
- Diabetes is a risk factor for UI although no mechanism has been established.

The prevalence of UI has been controversial, ranging from 5% to 69%, with most studies in United States of America and Europe reporting a prevalence of any UI in the range of 25% to 45% (Hannestad et al., 2000, Irwin et al., 2006, Milsom et al., 2013). UI is at least twice as prevalent in women compared with men, and SUI accounts for about half of all incontinent cases in women. In Asia, the prevalence of SUI is 0.9% in Korean men and 20.7% in Korean women (Lee et al., 2011), 18% in the Taiwanese population (Chen et al., 2003) and 33% in the Japanese population (Ueda et al., 2000). The considerable variability in prevalence estimate is presumably attributed to confoundment in survey and epidemiological research, difference in definitions and measurements used, reporting bias as well as discrepancy in selection criteria and study population. Quantification of the true global impact is thus made difficult due to the heterogeneity of the available published data.

The International Data Base population predicts that the worldwide population of age ≥65 will increase by 160% between 2008 and 2040, with a steady elevation of life expectancy within the general population (Kinsella et al., 2009). Furthermore, the worldwide estimate of SUI is forecasted to rise by 20.7% to 167 million (by 2018), with the regional burden presumed to be the largest in Asia (Irwin et al., 2011).

1.5 ETIOLOGY AND PATHOGENESIS OF STRESS URINARY INCONTINENCE

As mentioned previously, the complex interplay between the extrinsic and intrinsic continence mechanism ensures that continence is achieved. The essential factors required for the urethra to remain closed at rest and during increased abdominal pressure include properly functioning sphincters, well-vascularised mucosa and submucosa and a healthy and intact vaginal wall support.

The common causative factors of SUI are childbirth, injury to the urinary system and surgery of the pelvic area. During pregnancy, the pelvic structures undergo anatomical, hormonal and functional alterations. During the subsequent vaginal childbirth, the pelvic floor experiences momentous stretching, tearing and avulsion to make way for the newborn to go through it causing a longer and wider levator hiatus. A recent systematic review showed a pooled prevalence of 33% of any postpartum UI in the first three months postpartum, in which the prevalence was double in the vaginal delivery group (31%) compared to the caesarean section group (15%) (Thom and Rortveit, 2010). Nevertheless, caesarean section no longer exhibited significant protective effects against UI after multiple deliveries (MacLennan et al., 2000, Rortveit et al., 2003).

The mechanism underlying SUI is usually due to urethral hypermobility or intrinsic sphinteric deficiency (ISD), but often both coexist. In urethral hypermobility, the urethra fails to close when the pelvic floor muscles becomes weak, resulting in it moving too much (hypermobile). The primary urethral weaknesses in the functioning of the pelvic muscles is based on DeLancey's theory of urethral support, the so-called

hammock theory (DeLancey, 1994, DeLancey, 1996). DeLancey found that the urethra lies in a position where it can be compressed against like a hammock layer on which the bladder and urethra rest. In this model, it is suggested that the urethra is compressed against the posterior position of the vagina, which provides a backboard against rises in the intra-abdominal pressure and thus prevent loss of urine. When the supporting structures is relaxed or lost, the bladder neck and urethra may encounter a rotational descent away from its retropubic position during periods of activity, resulting in increases in abdominal pressure. If the pressure of the bladder exceeds the pressure on the urethra, the urethra opens concomitantly, and leakage ensues. Surgical operations designed to stabilise or elevate the sub-urethral vaginal wall may help preserve continence (Richter et al., 2010, Mostafa et al., 2013, Khan et al., 2015).

ISD is a less common component of SUI focusing on the chronically weakened urethra characterised by low urethral closure pressure. In recent years, it became clear that urethral hypermobility and ISD are not mutually exclusive conditions (Chapple and Milsom, 2012). Urethral hypermobility may occur commonly without significant ISD, while ISD alone is rare, but there is typically a mixture of both in SUI patients. The paradigm shift away from simple categorisation of SUI followed in part because of the development of the concept of Valsalva leak point pressure and from the analysis of long-term results of SUI (McGuire, 1995, Leach et al., 1997).

1.6 DIAGNOSIS

History

The general history taking includes a detailed account from patients on any possible precipitating factors of urinary loss, time of onset and duration of symptoms and degree of bother, which should be characterised and quantified as accurately as possible (Staskin et al., 2013). The patient's medical history should include questions relevant to neurological and congenital abnormalities as well as information on previous urinary tract infections and pelvic surgery. The patient's medical history should provide information on menstrual status, obstetric history, medications which could possibly affect the lower urinary tract and any significant co-morbidities which can produce symptoms mimicking SUI.

Physical examination

Physical examination should include abdominal, pelvic, perineal and a focused neurological examination, and showing incontinence when that is a complaint (Kobashi, 2012, Blaivas, 2000). Perineal examination allows description of the skin (such as presence of atrophic vaginitis, pelvic organ prolapse or any anatomic abnormalities).

Pelvic organ prolapse (POP)

POP is defined as the descent of one or more of the anterior vaginal wall, posterior vaginal wall, the uterus (cervix), or the apex of the vagina (vaginal vault or cuff scar after hysterectomy) (Abrams et al., 2002). The presence of any such sign should be correlated with relevant POP symptoms. More commonly, this correlation would occur at the level of the hymen or beyond, wherein the hymen is considered as the

fixed point of reference for prolapse description (Bump et al., 1996, Haylen et al., 2010).

POP can be divided into five stages (Figure 1.2):

i) Stage 0: No prolapse is demonstrated.

ii) Stage I: Most distal portion of the prolapse is more than 1 cm above the level of the hymen.

iii) Stage II: Most distal portion of the prolapse is 1 cm or less proximal to or distal to the plane of the hymen.

iv) Stage III: The most distal portion of the prolapse is more than 1 cm below the plane of the hymen.

v) Stage IV: Complete eversion of the total length of the lower genital tract is demonstrated.

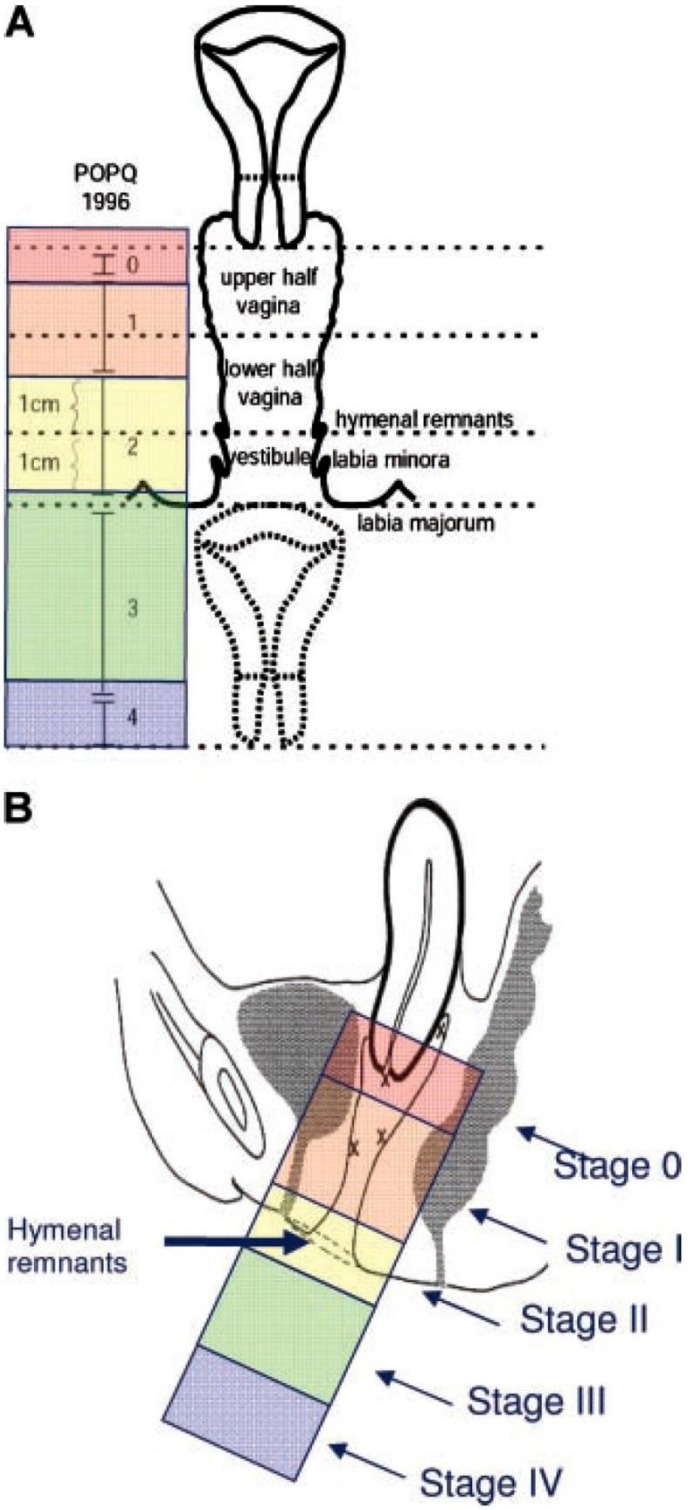

Figure 1.2 A,B: Prolapse staging—0, I, II, III, and IV (uterine—by the position of the leading edge of the cervix) (Haylen et al., 2010).

Urine analysis

It is generally agreed that urine analysis is a fundamental test that should be carried out in the assessment of all incontinent patients (Kobashi, 2012). Urinary infections can simulate any lower urinary tract pathologic conditions including SUI. The value of urine analysis is exemplified by the findings that 60% of females without detrusor overactivity will develop detrusor overactivity at the time of urinary tract infection (Staskin et al., 2013). Furthermore, results from the urine analysis can help in identifying the presence of microbiota, pyuria, hematuria, proteinuria or glucosuria which can be suggestive of conditions that can cause secondary incontinence.

Micturition diary

The micturition time chart is an important self-monitored adjunct to medical history that records patients' voiding habits. Selected variables provide objective information on the incontinence episodes, pad use, fluid intake, distribution of voiding between daytime and night-time and each voided volume (Lose et al., 1998). Nevertheless, the accuracy of micturition diary depends largely on the patient's ability to follow instructions and the reproducibility of this method may be questionable although it may improve with an increasing number of days of self-recording.

Pad test

The pad test quantifies the amount of urine lost over the duration of testing, by measuring the increase in the weight of the perineal pads (weighed pre- and post-testing) used. This may serve as a guide to the severity of incontinence. Different durations from a short (20 minutes) test to a 24- and 48-hour tests have been used

with provocation varying from normal everyday activities to defined regimens (Lose et al., 1988, O'Sullivan et al., 2004, Wu et al., 2006).

Pelvic floor muscle function

Pelvic floor muscle function can be qualitatively defined by the tone at rest and the strength of a voluntary or reflex contraction classified as strong, normal or weak. Pelvic floor muscle contractions can be assessed by visual inspection, digital palpation, electromyography, dynamometry, perineometry, or ultrasound. Factors to be assessed include pelvic floor muscle strength, muscular endurance, repeatability, duration, coordination, and displacement (Haylen et al., 2010).

The ICS reports in the standardisation of terminology of pelvic floor muscle function and dysfunction provides a fuller description of the assessment of pelvic floor muscle function including the following (Messelink et al., 2005):

i) Normal pelvic floor muscles: Pelvic floor muscles which can voluntarily and involuntarily contract and relax.

ii) Overactive pelvic floor muscles: Pelvic floor muscles which do not relax, or may even contract when relaxation is functionally needed, for example, during micturition or defecation.

iii) Underactive pelvic floor muscles: Pelvic floor muscles which cannot voluntarily contract when this is appropriate.

iv) Non-functioning pelvic floor muscles: Pelvic floor muscles where there is no action palpable.

Uroflowmetry and post void residual

Uroflowmetry represents a simple non-invasive test to assess the emptying function of the bladder. Ideally, the uroflowmetry studies are conducted in a completely private uroflowmetry room. The patient voids into the uroflowmetry device when they have a normal but strong desire to empty their bladder. Various parameters are obtained from this test including patterns of urine flow, urine flow rate, voided volume, maximum and average flow rate, voiding time and time to maximum flow. The interpretation of the uroflowmetry results are best referenced to the Liverpool nomogram wherein under the 10th centile of the nomogram has been determined as having the most useful discriminatory ability for diagnosis of voiding difficulty (Haylen et al., 1989, Haylen et al., 2008) (Figure 1.3). A normal female voiding procedure is a bell-shaped curve on the uroflowmetry (Figure 1.4).

The post-void residual urine volume (PVR) is defined as the volume of urine left in the bladder at the end of micturition (Abrams et al., 2002). The ultrasonography provides an accurate estimate of the PVR (Lucas et al., 2012a). Clinicians generally consider a PVR of up to 50ml as normal, while a PVR of more than 200ml is regarded as problematic (Blaivas, 2000). A large PVR may be caused by either urethral obstruction or impaired detrusor contractility (Blaivas, 2000).

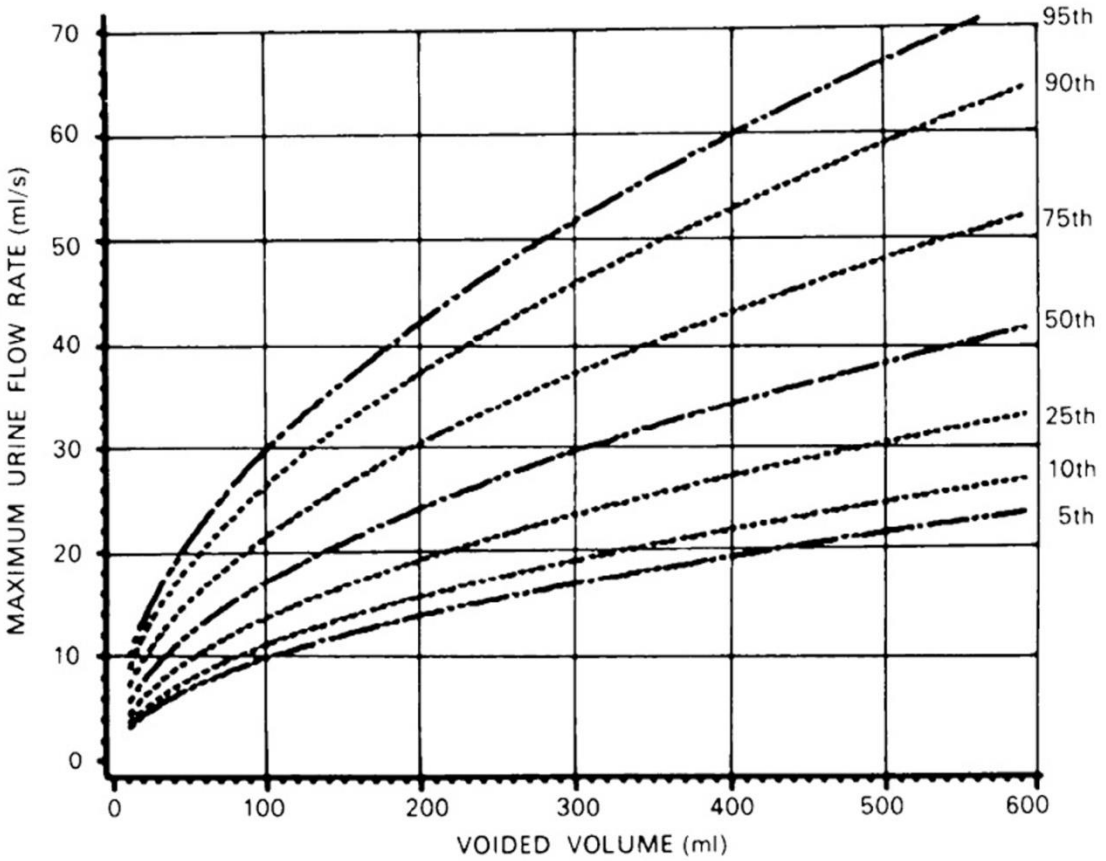

Figure 1.3 Liverpool nomogram for maximum urine flow rate in women. Equation: Ln(maximum urine flow rate)=0.511 + 0.505 x Ln(voided volume); root mean square error=0.340 (Adapted from Haylen et al., 2008).

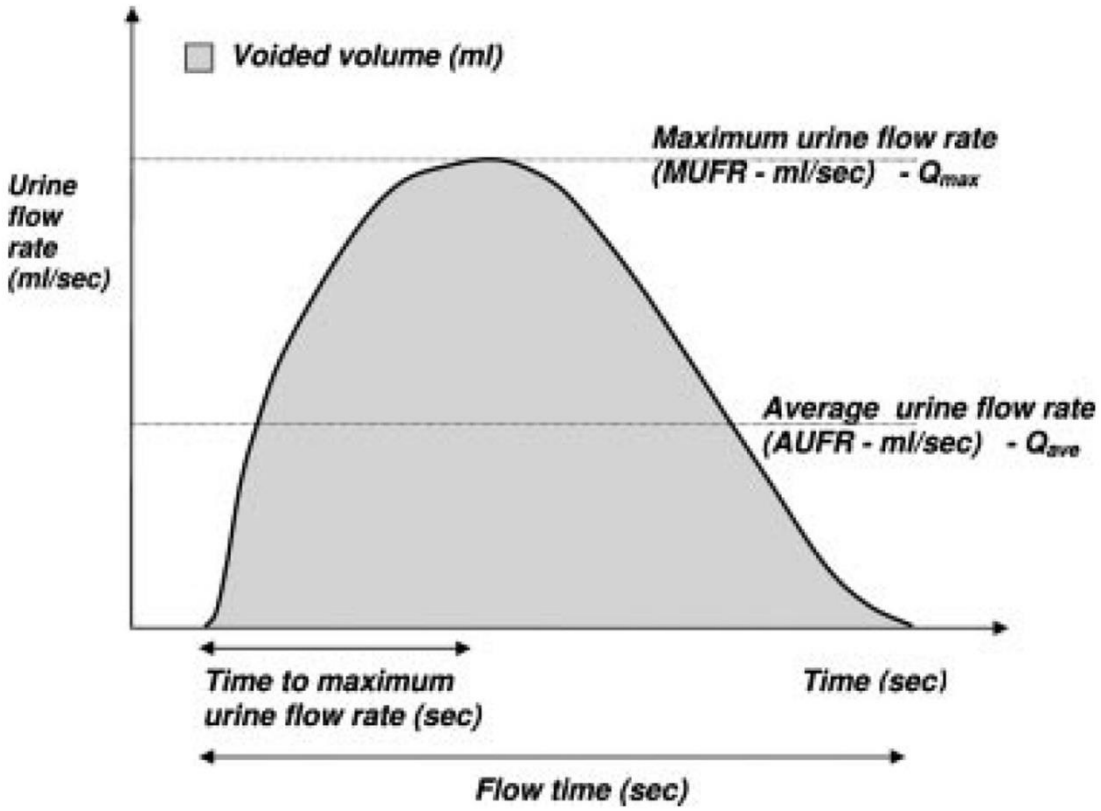

Figure 1.4 A schematic representation of urine flow over time (Haylen et al., 2010).

Urodynamic evaluation

The urodynamic testing was developed as an extension of patient history and physical examination to objectively measure and document the entire lower urinary tract function especially when it can significantly change clinical diagnoses and have therapeutic consequences (Sirls et al., 2013). A urodynamic evaluation consists of filling cystometry and pressure flow study (voiding cystometry).

Filling cystometry is the method by which the pressure/volume relationship of the bladder is measured during bladder filling (Abrams et al., 2002). It is an invasive test involving catheter placements into the bladder and another placed rectally or vaginally to measure abdominal pressure. The filling phase starts when filling commences and ends when the patient and urodynamicist decide that 'permission to void' has been given (Abrams et al., 2002). It can assess bladder sensation, bladder capacity, detrusor activity and bladder compliance.

Pressure flow studies of voiding are the method by which the relationship between pressure in the bladder and urine flow rate is measure during bladder emptying (Abrams et al., 2002). The voiding phase starts when 'permission to void' is given or when uncontrollable voiding begins, and ends when the patient considers voiding has finished (Abrams et al., 2002).

1.7 OUTCOME MEASURES

Scientific evaluation of outcome measures of therapeutic interventions is based on assessments conducted before and after treatment. Outcome measures are principally categorised as primary and secondary outcome measures. Primary outcome measures are those viewed by the researchers to be of central interest, and the anticipated changes are used to estimate sample size (Brubaker, 2013). There can be several secondary outcome measures which are not the main focus of the study objectives. These outcomes are seldom used in sample size calculations and are typically exploratory. Until a universal outcome tool has been established, multiple outcome measures that are valid and clinically relevant are intrinsic for assessment of SUI in clinical trials (Thuroff et al., 2011).

Symptoms and health related quality of life

It is crucial to assess multidimensional aspects of QoL. The two main types of health related QoL questionnaires include disease-specific and generic questionnaires. Disease-specific questionnaires measure one particular facet of health status such as symptoms (e.g. UI), social well-being (e.g. sexual function), psychological well-being (e.g. depression) and cognitive function (e.g. mental status evaluation) (Brubaker, 2013). Examples of disease-specific questionnaires include the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF) (Avery et al., 2004), International Consultation on Incontinence Questionnaire- Lower Urinary Tract Symptoms Quality of Life (ICIQ-LUTSqol) (Abrams et al., 2006), Urogenital Distress Inventory and Incontinence Impact Questionnaire (Shumaker et al., 1994). The generic questionnaires are designed to evaluate broad aspects of health across populations, rather than patients

with particular medical conditions. The relative insensitivity of generic measures on effect of urinary symptoms on QoL and on its improvement after treatment dictates the necessity to use both generic and condition-specific QoL measures in clinical trials. Examples include EQ-5D (Group, 1990), Patient Global Impression of Improvement (PGI-I) (Yalcin and Bump, 2003) and SF-36 (Brazier et al., 1992).

Given the plethora of questionnaires available to assess the impact of UI on QoL, researchers and clinicians are often overwhelmed by multitude of options when selecting outcome measures. The International Consultation on Incontinence developed the ICI Modular Questionnaire project (ICIQ) with the aim to develop universally applicable standard guide for selection of questionnaire for use in clinical practice and research (Abrams et al., 2006, Coyne and Kelleher, 2010). The ICIQ-UI SF was developed as a brief and robust measure to assess the impact of symptoms of incontinence on QoL and treatment outcome. It consists of 4 items to assess the prevalence, frequency and perceived cause of UI, and its impact on everyday life. The ICIQ-UI SF has undergone extensive psychometric testing and is graded A (highly recommended by the International Consultation of Incontinence) as an outcome measure in research trials (Kelleher et al., 2013). The ICIQ-LUTSqol is a 20-item questionnaire derived from the King's Health Questionnaire to assess in detail the impact of UI on patients' lives with particular reference to social effects.

The PGI-I is single-item questionnaire comprising seven choices, ranging from "very much better" to "very much worse". Published data indicate that this single-item questionnaire is valid and reliable for assessment of baseline severity and treatment response in patients with SUI (Yalcin and Bump, 2003).

Micturition diary

Symptoms relevant to SUI (incontinence episodes and complications) can be measured using a self-completed incontinence diary. However, accuracy is difficult to evaluate as there is no available gold standard against which the test results can be compared. Reproducibility depends on the parameter used, and improves with an increase in the number of days that the self-recording is obtained. Two or 3 days of recording (not necessarily consecutive) will generally provide more useful clinical data (Haylen et al., 2010). Similarly, it is recommended that a diary is kept for a minimum of three days as an outcome measure in clinical research (Lose et al., 1998).

Pad weighing tests

Pad tests can be divided into short-term tests, generally performed under standardised conditions as office tests, and long-term tests, generally performed by the patient at home during 24 to 48 hours. Accuracy is difficult to assess. Reproducibility is generally poor, but improves if the circumstances are standardised as much as possible. A commonly used pad test is known as the one-hour pad test and should be conducted according to guideline as described by the International Continence Society (Abrams et al., 1988). For long-term tests, the test period should be sufficiently long (Lose et al., 1998).

Pelvic muscle activity

This is the force of voluntary pelvic muscle contraction determined in direct (e.g. digital or air pressure) or indirect (e.g. surface electromyography) measures (Lose et al., 1998). Several techniques have been proposed for the evaluation of the pelvic

floor muscle strength: digital palpation using various scoring systems, perineometry measuring intravaginal pressure or electromyographic (EMG) activity generated during a contraction and perineal ultrasound assessing elevation of the bladder neck during pelvic floor muscle contraction (Peschers et al., 2001).

Uroflowmetry

Maximum and average flow are directly dependent upon voided volume. Consequently, interpretation and comparison of flow rates require that the voided volume is taken into account. Flow rate depends to a lesser extent on age and sex, while parity, weight, menstrual cycle phase, or menopause status seem not to influence flow rate Researchers should describe their methodology and provide reproducibility data or indicate their absence (Lose et al., 1998).

Cystometry

Cystometry variables include sensation, compliance, capacity, and activity of the bladder. The investigation can be carried out in a stationary or ambulatory setting. Data obtained are method-dependent. Accuracy is difficult to assess, since variation in various parameters is significant (Lose et al., 1998).

Electromyography (EMG)

EMG recordings are performed to examine the activity (behavior) of pelvic and sphincter muscles during different maneuvers, particularly during bladder filling and voiding (Lose et al., 1998). Both surface and intramuscular electrodes may be used for recording. The reliability of EMG recordings is poorly determined.