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Prevalence and conservative treatment of urinary incontinence and other urogynecological conditions in women with spinal cord injury

PhD Thesis • Marlene Elmelund

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Preface

This research was conducted between June 2014 and July 2018 at the Clinic for Spinal Cord Injuries, Rigshospitalet and Department of Obstetrics and Gynecology, Herlev and Gentofte Hospital. During this period, I was employed by the Clinic for Spinal Cord Injuries, Rigshospitalet and enrolled as a PhD student at the Graduate School of Health and Medical Sciences, University of Copenhagen.

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List of publications

Manuscripts included in this thesis:

Study I

Elmelund M, Klarskov N, Biering-Sørensen F. Prevalence of urinary incontinence in women with spinal cord injury. Spinal Cord. June 2018.[1]

Study II

Elmelund M, Biering-Sørensen F, Bing MH, Klarskov N. Pelvic organ prolapse and urogynecological assessment in women with spinal cord injury. Spinal Cord. August 2018.[2]

Study III

Elmelund M, Biering-Sørensen F, Due U, Klarskov N. The effect of pelvic floor muscle training and intravaginal electrical stimulation on urinary incontinence in women with incomplete spinal cord injury: An investigator-blinded parallel randomized clinical trial. Int Urogynecol J. March 2018.[3]

Abbreviations

AIS	American Spinal Injury Association impairment scale
IC	Intermittent catheterization
ICIQ-UI-SF	International Consultation on Incontinence Questionnaire – Urinary Incontinence – Short Form
ICIQ-OAB	International Consultation on Incontinence Questionnaire – Overactive Bladder
IVES	Intravaginal electrical stimulation
NDO	Neurogenic detrusor overactivity
NLI	Neurological level of injury
OUP	Opening urethral pressure
PGI-I	Patient Global Impression of Improvement
PFMs	Pelvic floor muscles
PFMT	Pelvic floor muscle training
POP	Pelvic organ prolapse
SCI	Spinal cord injury
SCIBase	Spinal cord injury database
SCI-QoL	International Spinal Cord Injury Quality of Life Basic Data Set
SD	Standard deviation
SUI	Stress urinary incontinence
UI	Urinary incontinence
UUI	Urgency urinary incontinence
QoL	Quality of life

1. Introduction

Spinal cord injury (SCI) is recognized as one of the most devastating medical conditions, resulting not only in physical disabilities due to motor and sensory nerve damage but also cardiovascular, sexual, bowel and urinary function impairments. Despite the abundance of complications following SCI, urinary problems are ranked as some of the most important health complications in this population.[4,5]

Historically, the primary death cause after SCI was renal deterioration. Consequently, management of the neurogenic bladder has been highly prioritized which has led to a decrease in renal-related mortality after the 1970's.[6,7] Hence, neurogenic bladder dysfunction and urinary incontinence (UI) after SCI has gained much attention in the literature but due to an overweight of men among persons with SCI, most of our knowledge is based on research conducted in male SCI populations. However, the anatomical, physiological and psychological differences between the genders underlines the need for research evaluating UI and treatment of UI in spinal cord injured women alone.

There are several treatment options for neurogenic UI. Clean intermittent catheterization (IC), bladder relaxant drugs and intravesical botulinum toxin injections are some of the most common ones, but not all patients are candidates for these treatments and some will need additional treatment. Pelvic floor muscle training (PFMT) and intravaginal electrical stimulation (IVES) are two conservative treatments of UI with few side effects that can be carried out by the patient at home. PFMT is a well-documented, effective treatment of UI in neurologically intact women,[8] whereas IVES has shown more inconsistent results.[9,10] Nonetheless, the two treatments have never been investigated in women with SCI.

Regular gynecological consultations may be a challenge after SCI due to the lack of adequate facilities in gynecological clinics to examine women with mobility impairments and the lack of knowledge regarding complications following SCI among physicians.[11,12] Even in academic literature, information about gynecological conditions following SCI is sparse. It has been suggested that women with SCI may be in increased risk of developing pelvic organ prolapse (POP) due to weakness of the pelvic floor muscles (PFMs), peripheral nerve damage and possible use of increased abdominal pressure during bladder and bowel emptying,[13,14] but this has not previously been investigated.

The aim of this thesis was to add to the knowledge gap on urogynecological conditions following SCI and to explore potential conservative treatments of UI in women with SCI.

2. Background

2.1 Spinal cord injury

SCI occurs when there is a damage to the spinal cord, through which the motor and sensory neural pathways travel between the brain and the body. Traffic accidents and falls have been reported as the most common causes of traumatic SCI,[15,16] whereas disc degeneration/prolapse and tumors are the most common causes of non-traumatic injuries.[15,17] Worldwide, the reported annual incidence rate of SCI ranges from 10−58 per million for traumatic injuries,[16,18] and 11−26 per million for non-traumatic injuries.[17,19] As only 18-28% of a traumatic and 50% of a non-traumatic SCI-population are comprised of women, the majority of persons living with SCI are male.[16,17]

The International Standards for Neurological Classification of SCI is an internationally standardized severity assessment score that is used to describe the injury.[20] Firstly, the injury is classified by the neurological level of injury (NLI) which refers to the most caudal segment of the spinal cord with normal sensory and antigravity motor function on both sides of the body.[20] As the spinal cord is shorter than the vertebral column and terminates approximately at the L1-L2 level of the vertebral column in adults, the NLI does not correspond with the skeletal level of injury.

Secondly, the injury is described by the American Spinal Injury Association impairment scale (AIS) which grades the degree of impairment from A to E: AIS A refers to a complete injury with no sensory or motor function preserved in the sacral segments S4-S5, AIS B refers to a sensory incomplete injury with sensory function preserved below the NLI, AIS C refers to a motor incomplete injury with preserved motor function below the NLI where more than half of key muscle functions below the NLI have a muscle grad <3, AIS D refers to a motor incomplete injury with preserved motor function below the NLI where at least half of key muscle functions below the NLI have a muscle grad >3 and AIS E refers to normal sensory and motor function in all segments in a patient with prior deficits.[20]

In Denmark, approximately 150 persons sustain an SCI yearly.[15] There are two national centres treating persons with SCI: the Clinic for Spinal Cord Injuries at Rigshospitalet and the Spinal Cord Injury Centre of Western Denmark in Viborg. The injury is usually classified by NLI and AIS according to the International Standards for Neurological Classification of SCI at the time of discharge after the initial hospitalization in the Clinic for Spinal Cord Injuries, and the

classification is only re-evaluated in the occurrence of changes in symptoms. After the initial hospitalization or visit in the Clinic for Spinal Cord Injuries, all patients from the eastern part of Denmark are offered lifelong follow-up consultations every second year where any health complications, including the lower urinary tract function, are evaluated and managed by an SCI-specialized clinician. Upper and lower urinary tract complications are usually evaluated and managed in cooperation with the Department of Urology, Rigshospitalet.

2.2 Lower urinary tract function

To understand the pathophysiology of the lower urinary tract after SCI, it is important to understand the neurophysiology of the normal functioning lower urinary tract.

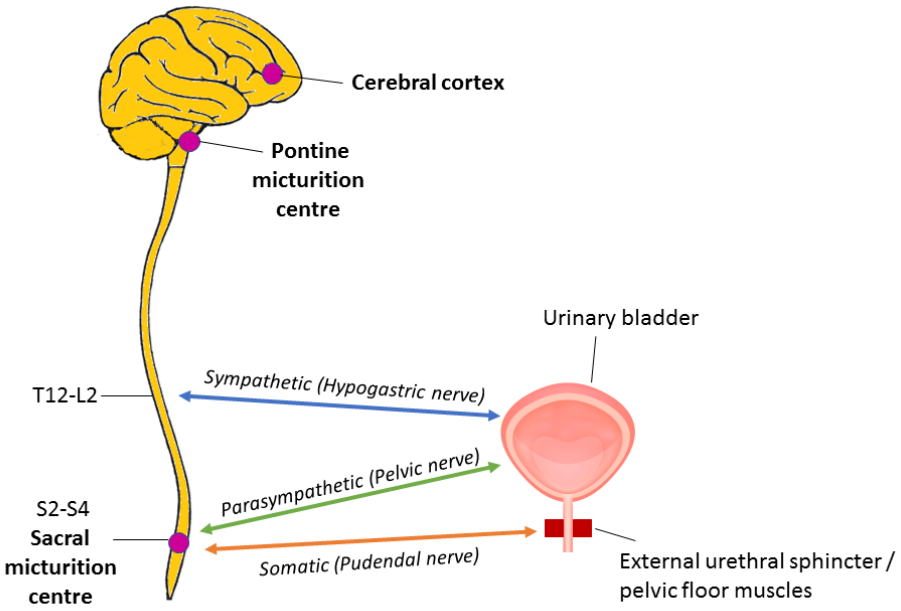

Figure 1. *Neural control of the lower urinary tract function.*

2.2.1 Neurophysiology of the lower urinary tract

The lower urinary tract system is regulated by the central and peripheral nervous system (Figure 1). In the central nervous system, the frontal cerebral cortex, the pontine micturition centre and the sacral micturition centre that is located in the spinal cord segments S2-S4, corresponding to the vertebral level of approximately L1, contribute to the regulation of the bladder. The

peripheral nervous system consists of parasympathetic nerve fibers from the sacral spinal cord and sympathetic nerve fibers from the thoracic and lumbar spinal cord that innervate the detrusor muscle and the bladder neck area, including the internal urethral sphincter, with afferent and efferent nerve fibers. Together, these fibers take part of the spinal-bladder reflex that facilitates the storage and voiding phases of the bladder. In addition, somatic afferent and efferent nerve fibers in the pudendal nerve, originating from the sacral spinal cord (Onuf's ganglion), innervate the external urethral sphincter and PFMs. In a neurologically intact bladder, inhibiting impulses are sent from the frontal cortex via pons to the sacral micturition centre to prevent the detrusor muscle from contracting during the filling phase. At the same time, the urethral sphincter remains contracted to prevent urinary flow. During voiding, the cortical inhibition ceases and the detrusor muscle contracts by excitation of the parasympathetic efferent innervation of the bladder and inhibition of the sympathetic efferent innervation of the bladder. In addition, the pontine micturition centre controls the coordination between the detrusor and the external sphincter during voiding, facilitating sphincter relaxation and a non-obstructed urine flow through the urethra.[21,22]

Though not fully understood, a pro-continence reflex has also been acknowledged. Upon contraction of the urethral sphincter and PFMs, afferent nerve fibers in the pudendal nerve send a signal to the lumbosacral spinal cord which causes inhibition of the parasympathetic efferent nerve fibers and activation of the sympathetic efferent nerve fibers, ultimately resulting in relaxation of the bladder.[23-25]

2.2.2 Neurogenic bladder dysfunction

Inevitably, the normal bladder function is disturbed by damage to the neural pathways in the spinal cord. A temporary spinal shock phase begins initially after a traumatic SCI and is characterized by loss of sensory, motor and reflex activity below the level of injury, resulting in complete painless urinary retention.[22,26] This phase typically lasts 6-12 weeks.[27] After recovery from the acute spinal shock phase, a chronic neurogenic bladder dysfunction usually develops (Figure 2).

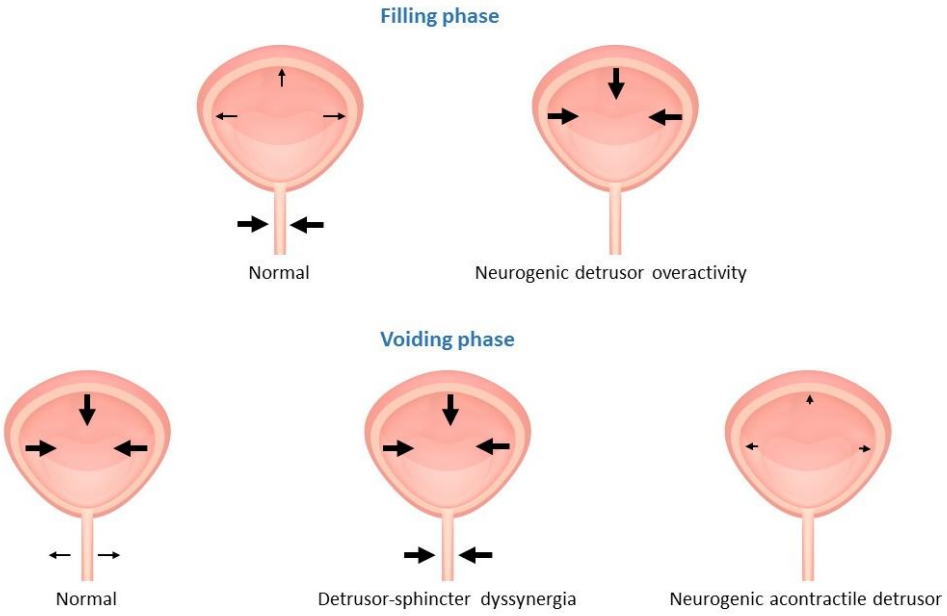

Figure 2. *Examples of neurogenic bladder dysfunction.*

Depending on the NLI, the pathophysiology of the neurogenic bladder dysfunction varies. SCI with neurological level above the sacral micturition centre traditionally results in neurogenic detrusor overactivity (NDO), which is involuntary detrusor contractions during the storage phase (diagnosed with a filling cystometry). Due to disturbance of the pontine control of the micturition reflex, a suprasacral SCI may also lead to detrusor-sphincter dyssynergia, which is involuntary contractions of the urethral and/or periurethral striated muscles simultaneous with detrusor contractions. In contrast, SCI with neurological level at or below the sacral spinal cord usually results in an acontractile detrusor, which is a non-contracting bladder during voiding (diagnosed with a pressure-flow study) that may or may not be accompanied by impaired sphincter deficiency.[22,26] Nonetheless, in clinical practice, the neurogenic bladder dysfunction may not always correlate with the NLI as described above, especially in persons with an incomplete injury or multiple level injuries, and therefore urodynamic evaluation of the bladder function is recommended.[28,29]

Neurogenic bladder dysfunction with increased detrusor pressure has previously been associated with renal deterioration and upper urinary tract complications,[30] and until the 1970's, renal deterioration was the main cause of death in persons with SCI.[6]

2.3 Urinary incontinence

According to the International Urogynecological Association and the International Continence Society, UI can be defined by the symptom (the complaint of involuntary loss of urine), the sign (objectively verified UI) and/or the urodynamic finding.[31]

Most prevalence studies report of the symptom of UI, and results show that symptoms of UI are common among women, affecting approximately 25-46%.[32-34] Stress urinary incontinence (SUI) is the most frequent subtype of UI. Symptoms of SUI are leakage of urine during effort, physical activity or when sneezing or coughing, and SUI has been associated with increasing age, vaginal delivery and obesity.[31,34] Other common subtypes of symptomatic UI are urgency urinary incontinence (UUI), which is UI concurrent with a sudden compelling desire to pass urine that is difficult to defer, and mixed UI, which is symptoms of both UUI and SUI.[31]

2.3.1 Neurogenic urinary incontinence

The subtype of UI after SCI depends on the type of neurogenic bladder dysfunction: NDO can cause NDO incontinence, also referred to as reflex UI, that occurs with or without any sensation of urgency or awareness.[26] Conversely, neurogenic acontractile detrusor and/or a non-relaxing urethral sphincter can cause UI associated with chronic urinary retention, which has previously been referred to as overflow UI.[24-25] Finally, an incompetent urethral sphincter or paralysis of the PFMs can cause neurogenic SUI.[25] The reported prevalence of symptomatic UI in persons with SCI varies in the literature from 34% to 73%,[5,35] depending on the definition of UI, study population and study design. In a meta-analysis including four studies, the estimated prevalence of UI in SCI persons with NDO was 52%.[36] In a Danish study including patients with traumatic SCI, a total of 43% reported UI varying from less than once a week to daily.[37] All studies were conducted in SCI populations comprised primarily by men.

In patients with SCI, increasing severity of UI has been associated with decreasing QoL in terms of social function and emotions,[38] and UI was identified as a predictor of dissatisfaction with sexual life after SCI.[39]

2.3.2 Treatment of urinary incontinence after spinal cord injury

Treatment of the neurogenic bladder dysfunction and UI aims at improving continence and QoL as well as protecting the upper urinary tract.[40] The treatment is primarily conservative. Firstly, it includes timed bladder emptying, controlled fluid-intake and avoidance of urinary tract infections.[41] Secondly, if the bladder is not emptied adequately and safely, alternate bladder emptying methods should be applied and IC is recommended as first-line treatment. Nonetheless, other bladder emptying methods may be used including suprapubic or transurethral indwelling catheter, bladder reflex triggering and bladder expression by external expression or abdominal straining, though these methods are not recommended.[41,42]

Thirdly, treatment of incontinence after SCI includes pharmacotherapy, and especially anticholinergic drugs are widely used in persons with NDO incontinence. However, the treatment has a considerably high incidence of adverse events (fatigue, constipation, dry mouth etc) and a recent meta-analysis conducted in neurologically intact women revealed a relatively limited effect compared with placebo.[41,43]

Finally, surgical procedures may be offered when conservative treatments fail. In patients with NDO incontinence, intravesical injection with botulinum toxin is considered a safe and effective treatment,[41] but with an average effect-duration of nine months, the treatment needs to be repeated.[44,45] Alternate surgical procedures are also available. Bladder augmentation cystoplasty can increase the bladder volume and reduce the intravesical pressure during filling by placing a segment of bowel tissue in the bladder (enterocystoplasty) or by autoaugmentation.[46,47] Patients with neurogenic SUI may be offered an autologous or synthetic sling procedure. The mid-urethral sling procedure is a well-established effective and safe treatment of SUI in women in general. However, the evidence of its use in patients with neurogenic SUI is very limited, but some small studies have demonstrated good results.[48,49] Alternatively, the minimal-invasive peri-urethral injection therapy, a bladder neck closure or insertion of an artificial urinary sphincter can be used,[41] though the latter has been associated with a substantial complication and revision rate.[50,51] Ultimately, urinary diversion using the Mitrofanoff or Monte procedures (a continent abdominal wall stoma) or the non-continent urinary diversion, e.g. the ileoureterostomy, can be considered in selected patients, especially if the patient is in high risk of developing renal failure. In a study including 29 patients, 96% became continent after a continent urinary diversion combined with a bladder augmentation. Nonetheless, in this group of patients, 13 post-operative complications were reported including stenosis, bladder stones, bowel obstruction and formation of fistulae.[52]

2.3.3 Pelvic floor muscle training

PFMT refers to the exercise of the striated muscles that form the floor of the pelvis through which the urethra, the vagina and the anus pass (Figure 3).

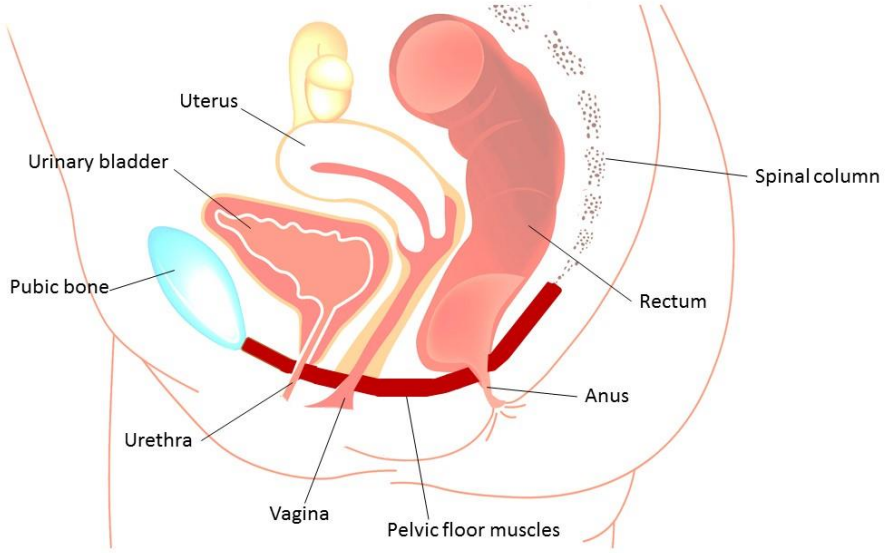

Figure 3*. Cross-sectional image of the organs and structures in the female pelvis.*

PFMT was first described as treatment of SUI in the late 1940's by the American gynecologist, Arnold Kegel.[53] Today, PFMT is a well-documented, first-line treatment of SUI. A PFMT-program is usually performed repeatedly over an extended period, and may be performed as individualized PFMT, group PFMT, supervised PFMT or home PFMT.[54]

The mechanism of action is believed to be two-fold: PFMT during effort or exertion increases the urethral pressure, preventing urine loss during increased abdominal pressure. Secondly, PFMT improves the tone of the PFMs which limits the descent of the PFMs during increased intraabdominal pressure, preventing urine loss. However, PFMT has also shown good results on UUI with an effect equivalent to or better than anticholinergic medication.[55] It is hypothesized that PFMT reduces UUI by the so-called urge suppression strategy (pro-continence reflex) where PFMT conducted during an urgency episode inhibits or suppresses the bladder contraction via Onuf's ganglion in the sacral micturition centre, and inhibits the parasympathetic excitatory pathway of the micturition reflex.[24,56,57]

2.3.4 Electrical stimulation

Electrical stimulation is another treatment option of UI in women. There are several types of electrical stimulation that can be used to treat UI, including suprapubic, transvaginal/anal, sacral or tibial nerve stimulation.[58,59] IVES is a non-invasive, transcutaneous type of electrical stimulation that is applied using a vaginal probe (Figure 4).

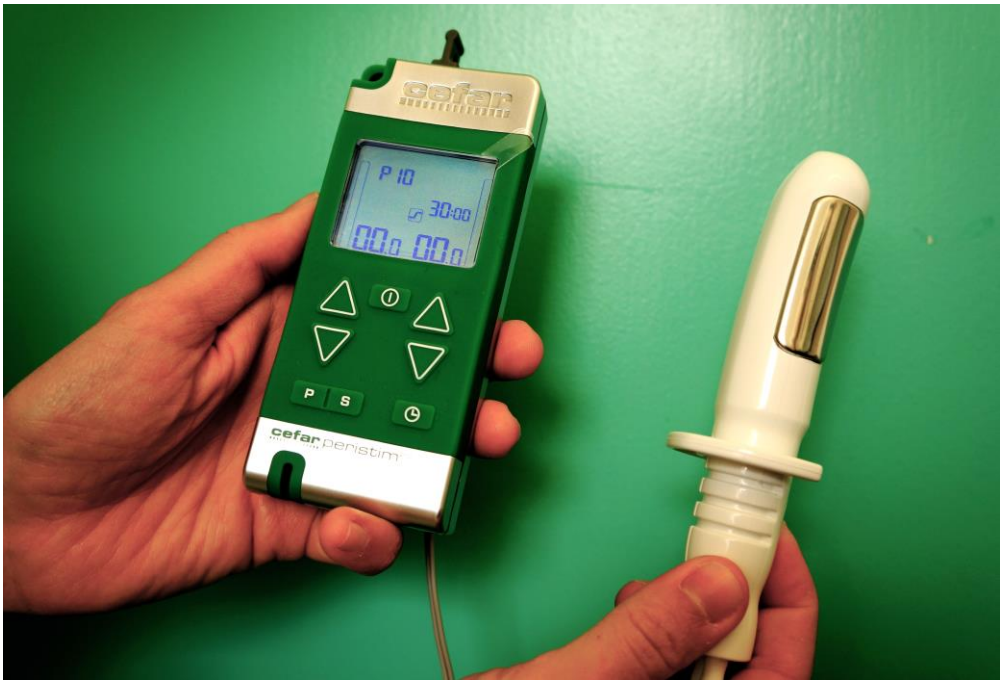

Figure 4*. Electrical stimulation devices used in study III, showing the stimulator (left) and the intravaginal probe (right).*

Though the mechanism of action is not fully understood, it is believed that IVES has a neuro-stimulative and neuro-modulative effect: At frequencies of 40-50 Hz, it stimulates the pudendal efferent motor fibers which facilitates contraction of the PFMs and thereby aids in the treatment of SUI. On the contrary, IVES at frequencies of 5-10 Hz modulates the pudendal afferent nerves in the pelvic floor muscle area which causes relaxation of the bladder due to inhibition of the parasympathetic efferent nerve fibers, ultimately aiding in the treatment of UUI.[23,60] Though IVES has been described in the treatment of both SUI, UUI and mixed UI, the evidence of treating SUI and mixed UI with electrical stimulation in neurologically intact women is inconsistent,[10,58] and a recent guideline from the European Association of Urology concluded that it is unknown if electrical stimulation is more effective than sham stimulation or if electrical stimulation adds to the benefit of PFMT.[9] On the contrary, some studies have shown that in women with UUI, the effect of

IVES is comparable or superior to anticholinergic medication.[61-63] The effect of IVES on UI in adults with a neurological disorder is less well examined with only two randomized clinical trial studies available: One study showed results statistically in favour of IVES combined with PFMT compared with PFMT alone after multiple sclerosis,[64] while the other study found that IVES combined with PFMT was not superior to PFMT on symptoms of UI after multiple sclerosis.[65]

2.4 Pelvic organ prolapse

Another common urogynecological issue is POP which refers to the downward displacement of the pelvic organs, including the uterus and/or the different vaginal compartments with their neighboring organs e.g. the bladder or rectum. POP can be described by symptoms, anatomical findings and any relevant diagnostic investigations.[66] The most common symptom of POP is the feeling of a vaginal bulge or 'something coming down' through the vaginal introitus, though other symptoms can also occur, including heaviness or pain in the pelvis, lower backache and sexual, urinary or anorectal symptoms.[66]

The anatomical findings include the descent of the anterior vaginal wall (anterior compartment prolapse), posterior vaginal wall (posterior compartment prolapse), the uterus/cervix or apex of the vagina (apical compartment prolapse) or a combination (Figure 5).[66]

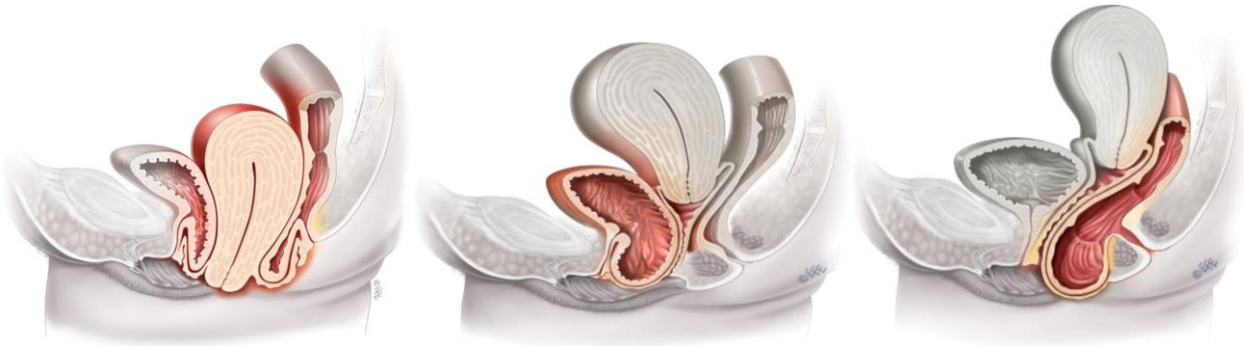

Figure 5. *Cross-sectional image of the female pelvis. From the left: Apical compartment prolapse (uterine prolapse), anterior compartment prolapse (cystocele) and posterior compartment prolapse (rectocele). Reprinted from Haylen et al[66] with permission from John Wiley and Sons.*

Anatomical POP is graded according to the POP quantification (POP-Q) system[66] into five stages (0-IV) depending on the location of the most distal part of the prolapse in each compartment (Figure 6).

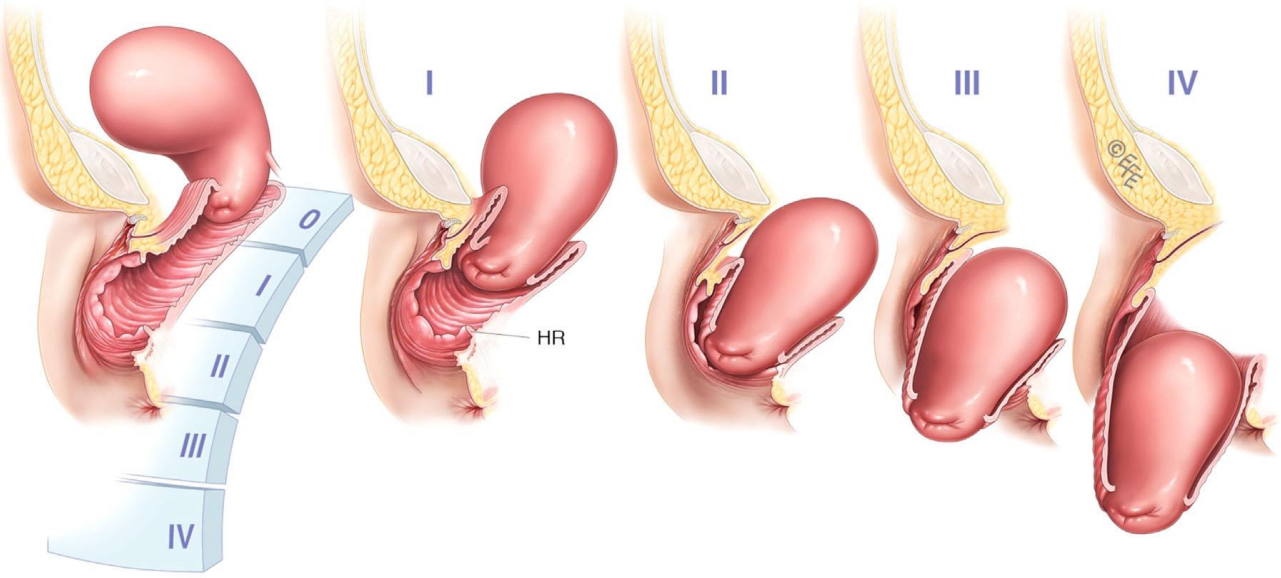

Figure 6. *Staging of a uterine prolapse according to the Pelvic Organ Prolapse Quantification system. HR: Hymenal Remnant. Reprinted from Haylen et al[66] with permission from John Wiley and Sons.*

A simplified technique of the POP-Q staging has also been introduced with good validity.[67] Usually, only POP stage ≥ 2 is considered anatomical POP, which refers to POP descending greater than 1 cm above the hymnal remnant.[68,69] Studies have shown that anatomical POP stage ≥ 2 is found in up to 50% of all women.[68,69] However, as women with POP does often not experience any symptoms, only 10-20% of these women will seek medical help.[68] In clinical practice, it is therefore important that the diagnosis of POP is based on the presence of both anatomical findings and symptoms.[66] As POP is a benign condition, the severity of symptoms and their impact on the woman's quality of life should be considered before deciding on a treatment. Pregnancies, vaginal deliveries, advancing age and obesity are well-established risk factors of POP.[34,69]

2.4.1 Pelvic organ prolapse and gynecological considerations after a spinal cord injury

The story of a 37-year old woman with SCI and no other known risk factors of POP, who had a stage 3 uterine prolapse, was presented in a case-report by Wan and Liu.[14] In the case-report and in a separate editorial it has been suggested that weakness of the PFMs, peripheral nerve damage and possible use of increased abdominal pressure during bladder and bowel emptying are conditions associated with SCI that increases the risk of POP.[13,14] In neurologically intact women, POP is considered a benign diagnosis but in women with SCI, POP could be associated with more complications. Theoretically, the SCI-associated bladder emptying problems could be aggravated by an obstructing prolapse, that may be overlooked due to reduced sensation in the pelvic area.

However, until now, no studies have investigated POP in women with SCI. In fact, there is a knowledge-gap on gynecological considerations and conditions after SCI in general. In a study by Terbizan and Schneeweiss from 1983, 102 women with complete SCI were examined gynecologically. The authors concluded that although gynecological disorders were not more common in women with SCI compared with neurologically intact women, the loss of sensibility increases the risk of disregarding gynecological disorders.[70] In addition, it has previously been demonstrated that women with mobility impairments are less likely to receive adequate gynecological screening and care.[12]

Women with SCI living in the eastern part of Denmark are required to consult their private practitioner or a specialized gynecologist on their own initiative if they want a gynecological health examination, but this may cause difficulties as many clinics do not have the adequate facilities for examining women with mobility impairments. In addition, it is likely that they encounter a physician without previous experience in treating women with SCI. Hence, it could be hypothesized that women with SCI would benefit from being offered urogynecological consultations via the Clinic for Spinal Cord Injuries at a single gynecological clinic specialized in the field of urogynecology.

3. Hypothesis and objectives

The overall aim of this thesis was to increase the knowledge on urogynecological conditions in women with SCI.

We hypothesize that women with SCI have a higher occurrence of POP compared with neurologically intact women, as SCI is often associated with weakened PFMs, potential use of increased abdominal pressure during bladder/bowel emptying and reduced sensibility, which may increase the risk of POP.

Another cornerstone in the urogynecological field is UI. UI is a more complex condition in women with SCI compared with neurologically intact women, as it can be influenced by the neurological disorder in multiple ways. As women comprise a minority of a SCI population, it is possible that some well-known urogynecological treatments are not always considered in this population, and there is a need for more specialized urogynecological follow-up.

For generations, electrical stimulation has been successfully used in the rehabilitation and treatment of various complications following SCI, including muscular spasticity and bladder emptying problems. Therefore, the rationale of using electrical stimulation in the treatment of UI after SCI seems reasonable. Many women with SCI experience reduced sensibility, which might challenge them in identifying their PFMs and performing optimal PFMT, hence, IVES as an add-on treatment to PFMT could be useful. Due to the triple effect of IVES including inhibition of detrusor overactivity, contraction of the PFMs and indirect sensory stimulation of the PFMs aiding to a better awareness of the PFMs, we hypothesize that women with incomplete SCI is treated more effectively with PFMT combined with IVES compared with PFMT alone.

Specifically, the objectives of this thesis were to investigate:

- the prevalence of symptomatic UI and conditions associated with UI in women with SCI (Study I).
- the occurrence of POP and risk factors associated with POP after SCI and to evaluate the need for urogynecological assessments and treatments in women with SCI (Study II).
- the effect of PFMT and PFMT combined with IVES on UI in women with incomplete SCI (Study III).

4. Materials and methods

4.1. Study designs

To answer the study objectives of this thesis, we conducted three separate studies with different study designs. All studies were conducted in women with SCI who were registered in the Clinic for Spinal Cord Injuries at Rigshospitalet. With the aim of investigating the prevalence of UI and conditions associated with UI, study I was designed as a retrospective, cross-sectional study based on data from the clinic's electronic Spinal Cord Injury database (SCIBase), which contain data on all women diagnosed with a SCI in the Eastern part of Denmark. To investigate the occurrence of POP and to evaluate the need for urogynecological consultations offered to women with SCI, study II was designed as an observational, cross-sectional study where women with SCI were prospectively invited to attend a urogynecological consultation and examination. The 'cross-sectional study'-design, used in study I and II, is an optimal design to investigate the prevalence of a specific symptom and has the advantage of being relatively fast and inexpensive to conduct. However, as all data are collected at the same time, it can be difficult to derive a causal relationship between potential risk factors and a given outcome.

To examine the treatment-effect of IVES combined with PFMT and PFMT alone on UI, an investigator-blinded, parallel-group, randomized clinical trial was chosen for in study III. A 'randomized controlled trial'-design ranks high in the evidence hierarchy due to elimination of the so called "placebo-effect" of a treatment. Further, the randomized allocation of intervention diminishes the risk of selection bias, as the participants are comparable at baseline in regard to known and unknown confounders.[71]

4.2. Study I

Study population

The inclusion criteria were: 1) women registered in the Clinic for Spinal Cord Injuries with a traumatic or non-traumatic SCI sustained during September 1999−August 2016, 2) attendance of a follow-up consultation or a primary visit in the clinic during August 2010–August 2016, and 3) a filled-out answer to the question regarding UI in the SCIBase.

SCIBase

The SCIBase is a multidisciplinary electronic medical record database that was established in the Clinic for Spinal Cord Injuries in September 1999 and covers all patients diagnosed with a SCI in the Clinic for SCI, Rigshospitalet after 1999 or has sustained a SCI before 1999 but attended a follow-up consultation after September 1999. The SCIBase contains internationally standardized SCI-specific questionnaires,[72] e.g. the International Standards for Neurological and Functional Classification of SCI,[20] International SCI Core Data Set,[73] International SCI Data Sets for Non-traumatic SCI,[74] International Lower Urinary Tract Function Basic SCI Data Set,[42] and International SCI QoL Basic Data Set.[75] As new international questionnaires have been developed or updated, they were added in the SCIBase. Whenever a patient attended a consultation in the clinic, the physician would fill out the relevant questionnaires in the database. The International Lower Urinary Tract Function Basic SCI Data Set was filled out routinely during every follow-up in the clinic after it was added to the SCIBase in 2010. In this study, the answers to the question "use of condom catheter/sheath" were evaluated to test the accuracy of the answers in the database.

Data collection

The most recent information regarding time, etiology and classification of the SCI,[20,73,74] lower urinary tract function,[42] QoL[75] and mobility, spousal/cohabitation and smoking status were obtained from the database. UI was defined by the question from the standardized International SCI Lower Urinary Tract Function Basic Data Set[42]: "Any involuntary urine leakage (incontinence) within the last three months" with the possible answers: "Yes, average daily", "Yes, average weekly", "Yes, average monthly", "No" and "Not relevant". The included women were divided in a "UI-group" and a "No UI-group" based on the answers. The UI-group included women with daily to monthly UI, and the no UI-group included women with the answers "No" or "Not relevant". In addition, the questionnaire contained questions regarding the primary

bladder emptying method and treatment of lower urinary tract problems, including use of medication for the lower urinary tract within the last year and any previous treatment with intravesical botulinum toxin injections. The latter information was supplemented and verified with data from the Department of Urology, Rigshospitalet, where the treatments were primarily conducted.

Information on QoL was obtained from the standardized SCI-specific questionnaire International SCI Quality of Life Basic Data Set, that was added to the SCIBase in 2014.[75] It is comprised by three questions regarding satisfaction with 1) life as a whole, 2) physical health and 3) psychological health, emotions and mood in the past four weeks. Each question is answered with a number from 0 to 10, where 0 is completely dissatisfied and 10 is completely satisfied.

4.3. Study II

Study population

During January 2013−January 2018, spinal cord injured women who were admitted or attended a routine follow-up consultation in the Clinic for Spinal Cord Injuries were offered to attend a gynecological consultation and examination at a specialized urogynecological department at Herlev Gentofte Hospital by their treating clinician. While attending the urogynecological consultation, the women were asked if they wanted to participate in the study. The number of women who declined to participate was unfortunately not registered.

The consultation

The consultation was set to last approximately one hour, and there was a nurse present during the examination. The consultation consisted of an interview, a pelvic examination and ultimately a discussion of potential treatments. During the interview, information on parity, delivery, menstrual status, previous surgery, medication, latest cytological cervical cancer screening and current symptoms were obtained. This information was supplemented with data from the national pathological database for the women who could not recall the date of the latest cytological cervical sample. In addition, data on the date, etiology, NLI and AIS score of the SCI was obtained from the Clinic for Spinal Cord Injuries.

During the interview, the woman was specifically asked if she experienced a bulge, lump or something ‘coming down’ or ‘falling out’ through her vagina. If so, she was registered with

symptomatic POP.[66] Secondly, the woman was asked if she experienced any UI (involuntary loss of urine). If UI occurred during effort or physical activity or on sneezing or coughing, she was diagnosed with symptomatic SUI.[31] During the interview, it was also registered if the woman experienced any urgency (sudden compelling desire to pass urine that is difficult to defer), any fecal incontinence (involuntary loss of feces), any bladder emptying problems defined as difficulties with voiding and/or use of other bladder emptying methods than normal according to the International SCI lower urinary tract function basic data set,[42] or bowel emptying problems if the woman expressed any difficulties with bowel emptying.

The pelvic examination

The pelvic examination was carried out with the woman placed in a supine position. The vulva, vagina and cervix were inspected, and the pelvic organs were examined using bimanual palpation and transvaginal ultrasound. The strength of the PFMs was assessed by vaginal palpation, while the woman conducted a voluntary pelvic floor muscle contraction, and categorized as either strong, normal, weak or absent.[31] Anatomical POP was evaluated under maximal abdominal straining and staged using a previously described simplified technique of the POP quantification system.[67] Each vaginal compartment was evaluated, and the largest stage of POP was used to classify the women with either POP stage ≥2 or POP stage 0-1.

When considered relevant, urogynecological and gynecological diagnostic examinations (e.g. cystometry and pressure-flow study, residual urine measurement, urine analysis, cervical cytology sample, colposcopy, biopsy etc.) were carried out, and relevant treatments were offered. Some women were also invited to attend a 2nd or 3rd consultation.

4.4. Study III

Study population

During April 2015−January 2017 participants were recruited from the Clinic for Spinal Cord Injuries, Rigshospitalet, where potential participants were contacted primarily by phone. Eligibility criteria are shown in Figure 7.

Inclusion criteria	Exclusion criteria
• Age 18−75 years • Motor incomplete SCI (AIS C, D or E) • ≥ 8 in total score on ICIQ-UI-SF • Cystometry and pressure-flow study conducted * • Being able to read Danish adequately to understand the patient information and provide an informed consent to participate * Results from a cystometry and pressure-flow study were usually available in the medical records. If not, the investigation was conducted at the urogynecological department.	• Motor complete SCI (AIS A or B) • Objective lack of ability to contract the PFMs • Treatment with vesical botulinum toxin injection within the last year • Pregnancy • Contraindication for IVES (pacemaker or other implanted electrical devices) • Considered unfit to participate based on results from the bladder diary

Figure 7. *Eligibility criteria.*
SCI, spinal cord injury; AIS, American Spinal Injury Association impairment scale; ICIQ-UI-SF, International Consultation on Incontinence Questionnaire – Urinary Incontinence – Short Form; PFMs, pelvic floor muscles; IVES, intravaginal electrical stimulation.

A sample size calculation was conducted based on a previously published study that used ICIQ-UI-SF as primary outcome.[76] With a significance level of 5% and a power of 80%, a sample of 10 participants in each group was necessary to detect a change of 5 (standard deviation, SD 4) in the total score on the ICIQ-UI-SF. To account for dropouts, we aimed at including 20 participants in each group.

The study took place at Herlev Gentofte Hospital and involved six visits for each participant during a 6-month period (Figure 8).

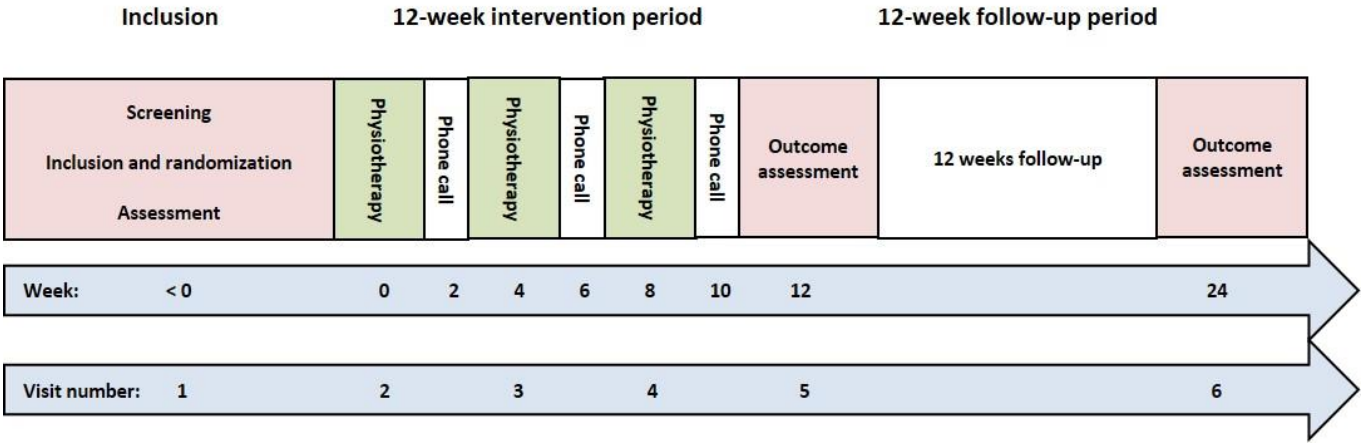

Figure 8. *Study flow for each participant.*

Screening, inclusion and randomization

During visit number 1, recruited women were screened for eligibility. The objective ability to perform a voluntary contraction of the PFMs was evaluated by a digital vaginal and/or rectal examination conducted by the primary investigator. Bladder relaxant drugs were allowed if the dose or type of medication was not changed during the study participation.

If eligible, the informed consent was signed, and participants were randomized to either Group 1 (PFMT) or Group 2 (PFMT combined with IVES). The allocation was conducted by a research-assistant, using a computer-generated randomization list with a ratio of 1:1 in block sizes of four. The primary investigator who assessed the outcomes and analyzed the data was blinded, but the research-assistant, physiotherapists and study participants were aware of the given treatment.

Interventions

The 12-week active intervention period began after visit number 2, where the woman attended an individual consultation with a specialized pelvic floor physiotherapist who instructed the women on how to perform PFMT and, for the women in Group 2, IVES. The consultation included a standardized assessment of the PFMs, including inspection, digital palpation and use of electromyography biofeedback as visual and auditory guidance while contracting the PFMs.[77] The women in the PFMT-group were instructed to conduct a daily training program consisting of approximately 30 contractions lasting 5−10 s followed by 10 s of pause. The PFMT+IVES-group received instruction on how to conduct IVES concurrent with PFMT, using the stimulation-

device Cefar Peristim Pro® (NMKimport, Værløse, Denmark) and a vaginal probe as shown in Figure 4. The women were instructed to use two different stimulation programs. Firstly, a 40 Hz intermittent stimulation-program was set to give 30 stimulation-cycles of 5−10-s active stimulation followed by 10-s pauses. During each stimulation, the women were instructed to contract the PFMs voluntarily, using the electrical stimulation as sensory guidance to when and how to perform the contraction. Secondly, a 10 Hz continuous stimulation program was used for 10-20 min during relaxation of the PFMs. Both stimulation-programs were to be conducted daily at a maximum tolerated intensity.

Women in both groups were asked to keep a daily training diary. The women attended additionally two consultations with the physiotherapist after 4 and 8 weeks where the diary was evaluated, the pelvic floor muscle function was assessed, and the training-instructions were adjusted. Motivating telephone-consultations with the physiotherapist were offered in between the consultations during the 12-week intervention period. The intervention ended after 12 weeks of training (visit 5). To evaluate a potential long-term effect of the IVES, the PFMT+IVES-group was asked to hand in the IVES-device at visit 5, and all participants were recommended to continue with PFMT lifelong.

Outcomes

All assessments are listed in Table 1. Assessments were measured at baseline (visit 1), after the 12-week intervention period (visit 5) and after additionally 12 weeks of follow-up (visit 6), except for the questionnaire Patient Global Impression of Improvement (PGI-I), which was only measured at visit 5 and 6.

Questionnaires

A Danish translation of the internationally validated and standardized ICIQ-UI-SF[78] was used as primary outcome. The questionnaire consists of three questions concerning the frequency and severity of UI and its impact on the woman's QoL. It was chosen as primary outcome in this study because of its simplicity and the fact that it is a widely used assessment tool, recommended by the International Consultation on Incontinence and International Urogynecological Association.[79] The inclusion criteria of ≥8 points on the ICIQ-UI-SF was selected to make sure that all participants experienced at least mild/moderate symptoms of UI.[80]

The questionnaire ICIQ-OAB was developed by the International Consultation of Incontinence and consists of eight questions regarding symptoms of urgency and overactive bladder and their impact on QoL.[81]

The SCI-QoL is a condition specific QoL questionnaire.[75] It consists of three questions describing satisfaction with life as a whole, physical health and psychological health, emotions and mood in the past four weeks.

The patient global impression of improvement (PGI-I) is a widely used validated questionnaire to assess a patient's subjective satisfaction with a given treatment.[82] It consists of one question, as specified in Table 1.

Table 1. Assessments performed

Assessments	Specified assessments
Questionnaires	
ICIQ-UI-SF[83] *(Primary)*	Change in total score of urinary incontinence symptoms ranging from 0−21, with a higher score indicating worse symptoms
ICIQ-OAB[81]	Change in total score on overactive bladder symptoms ranging from 0−56, with a higher score indicating worse symptoms
SCI-QoL[75]	Change in total score on quality of life ranging from 0−30, with a higher score indicating greater satisfaction
PGI-I[82]	Patient impression of improvement: 1=very much better, 2=much better, 3=a little better, 4=no change, 5=a little worse, 6=much worse, 7=very much worse
Reflectometry	
OUP-squeezing (cmH_2O)	Change in opening urethral pressure during pelvic floor muscle contraction
OUP-resting (cmH_2O)	Change in opening urethral pressure during pelvic floor muscle relaxation
3-Day bladder diary	
Daily incontinence episodes	Change in daily urinary incontinence episodes
Mean bladder capacity (ml)	Change in mean bladder capacity
Max bladder capacity (ml)	Change in maximal functional bladder capacity
Daily voiding episodes	Change in number of daily voiding episodes
24-h pad test (g)	Change in 24-hour pad test

ICIQ-UI-SF, International Consultation on Incontinence Questionnaire - Urinary Incontinence - Short Form; ICIQ-OAB, International Consultation on Incontinence Questionnaire - Overactive bladder; SCI-QoL, International Spinal Cord Injury Quality of Life Basic Data Set; PGI-I, Patient Global Impression of Improvement; OUP, opening urethral pressure.

Urethral pressure reflectometry

As a secondary outcome, the opening urethral pressure (OUP) during pelvic floor muscle contraction and relaxation was measured with urethral pressure reflectometry – a highly accurate and reproducible method that has been used to describe the urethral conditions in our research group for more than a decade.[84,85] A thin and flexible polyurethane bag connected to a catheter is placed in the urethra and inflated with air, which allows for the pressure and cross sectional area in the urethra to be measured simultaneously by use of acoustic reflectometry (Figure 9).

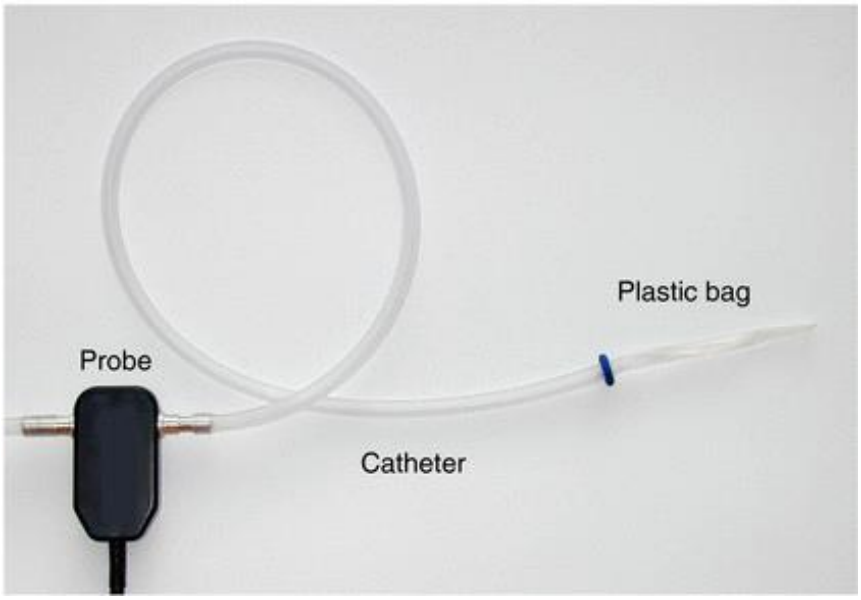

Figure 9. *In urethral pressure reflectometry, a catheter is connected to a polyurethane plastic bag that is placed in the urethra. Reprinted from Klarskov et al.[86]*

With this method, the OUP can be measured during rest and contraction of the PFMs. The method has proven to be highly sensitive in detecting pharmacologically induced changes in OUP in women with SUI.[87]

All women were given prophylactic antibiotic treatment with 400 mg Pivmecillinam and 500 mg Amoxicillin-clavulanic acid one hour prior to the urethral pressure reflectometry and in the evening after the examination to prevent urinary tract infections.

4.5. Statistical analyses

All statistical analyses were conducted using SAS software (Version 7.1; SAS Institute Inc, Cary, NC, USA). Two-sided p-values < 0.05 were considered statistically significant. Distributions of data were evaluated using histograms and quantile-quantile plots.

Demographic characteristics are presented in numbers (%), in means (SD) if data are normally distributed or in medians (Q1−Q3) if data are non-normally distributed. Comparisons between groups for categorical variables were performed with Fisher's exact test. Comparisons between groups for continuous variables were performed with Student's t-test when data were normally distributed, and with Mann-Whitney U test when data were non-normally distributed. When results are reported, data are presented as mean values (95% confidence interval), median values (Q1−Q3) or total numbers (%).

In study I, bivariate logistic regression analyses were used to investigate the age-adjusted effect of a variable on UI. Subsequently, a multivariate logistic regression analysis, including all the variables from the bivariate analyses with significance levels of $p < 0.2$, was conducted. In study II, a bivariate logistic regression analysis investigating the age-adjusted effect of time after injury on POP in a subgroup of women with a history of vaginal delivery was conducted. In both study I and study II, model assumptions of linearity of the continuous variables (e.g. age) were evaluated by testing the effects of the quadratic value of the continuous variable in the logistic regression model.

In study III, per protocol analyses were conducted on the participants who had completed the study at week 12 and week 24. For normally distributed data, analysis of covariance (ANCOVA) was used to analyze if there was a difference between the groups in change of outcome measure from baseline to follow-up at 12 and 24 weeks, adjusting for the baseline value of the outcome measure. If data were not normally distributed, a Mann-Whitney U test was used instead and adjustments for the baseline values were not conducted. Within each group, change from baseline for each outcome measure was investigated with paired t-test for normally distributed data and Wilcoxon signed-rank test for non-normally distributed data. The statistical analyses were repeated in two post-hoc analyses including only 1) participants who had trained $\geq 50\%$ of the intervention period and 2) participants with predefined urgency or mixed UI according to the ICIQ-UI-SF.

4.6. Ethics

The collection of data in the retrospective study I was approved by the Danish Health Authorities (3-3013-1745). In the prospective study II and III, all participants provided a written informed consent. Additionally, study III was approved by the Ethics Committee of the Capital Region of Denmark (H-2-2014-113) and the study was registered at clinicaltrials.gov, NCT02427230.

All three studies were approved by the Danish Data Protection Agency with the following registration number for study I (RH-2016-302), study II (HEH-2014-110) and study III (HEH-2015-056).

5. Results

The women participating in the three studies are characterized in Table 2.

Table 2. Baseline characteristics of the study populations.

Characteristics	STUDY I Participants N = 609 *	STUDY II Participants N = 98 **	STUDY III Participants N = 27
Age (y)	54 (±20)	54 (40−67)	55 (47−61)
Age at injury (y)	42 (±24)	47 (24−64)	34 (23−55)
Follow-up after injury (y)	7 (3−16)	2 (1−10)	11 (3−21)
NLI [a]			
Cervical	193 (46%)	34 (37%)	6 (23%)
Thoracic	152 (36%)	29 (32%)	8 (31%)
Lumbar	69 (16%)	26 (29%)	12 (46%)
Sacral	10 (2%)	2 (2%)	0
Completeness (AIS)			
A	30 (7%)	9 (11%)	0
B	15 (4%)	1 (1%)	0
C	39 (10%)	7 (8%)	6 (22%)
D	316 (78%)	68 (80%)	20 (74%)
E	3 (1%)	0	1 (4%)
Classification by NLI and AIS			
AIS ABC, C1-C8	26 (6%)	6 (7%)	1 (4%)
AIS ABC, Th1-S5	58 (14%)	11 (13%)	5 (19%)
AIS D, any NLI	316 (78%)	68 (80%)	20 (74%)
AIS E	3 (1%)	0	1 (4%)
Etiology			
Spinal cord injury	197 (87%)	87 (89%)	24 (89%)
Myelomeningocele	29 (13%)	11 (11%)	3 (11%)
BMI (kg/m^2)	NA	26.3 (±5.9)	24.5 (20.8−31.4)
Parity	NA	2 (0−2)	2 (1−2)
IC as primary bladder emptying method	67 (22%)	31 (32%)	16 (59%)

NLI, neurological level of injury; AIS, American Spinal Injury Association (ASIA) impairement scale; BMI, body mass index; IC, intermittent catheterization.

Results are presented in mean (±SD), median (Q1−Q3) or in total numbers (%).

* Data are missing regarding age at injury (n=80), follow-up after injury (n=80), NLI (n=185), AIS (n=206), classification of injury (n=206), etiology of injury (n=169) and use of IC (n=21).

** Data are missing regarding NLI (n=7), AIS (n=13), classification of injury (n=13) and BMI (n=19).

[a] One participant in study III had no level of injury because of AIS E (normal sensory and motor function according to the International Standards for Neurological Classification of SCI).

There was an overlap of participants in the three studies as demonstrated in Figure 10.

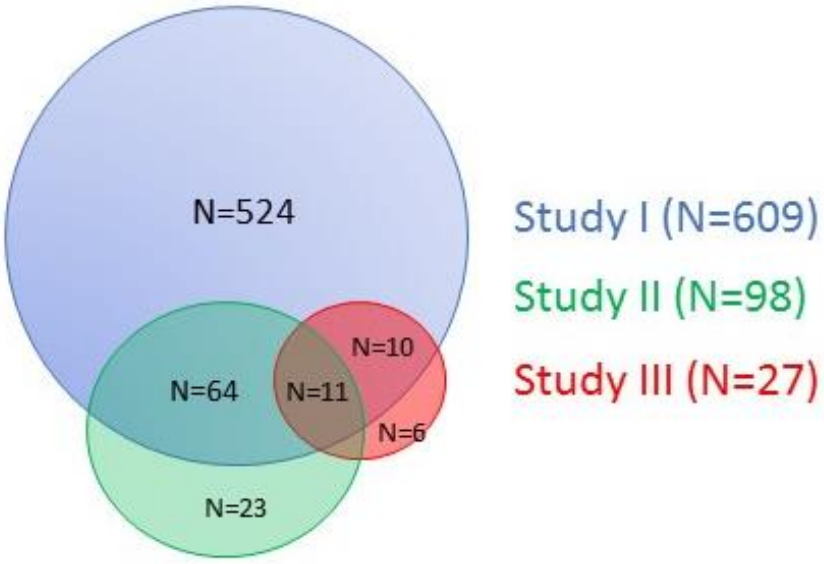

Figure 10. *Overlap of included participants in the three studies*

5.1. Study I

Of the 733 eligible participants, 124 were excluded as the standardized routine question regarding UI had never been answered in the SCIBase. Consequently, 609 participants were included. The included and excluded women were comparable on neurological level, completeness, type and etiology of SCI but the excluded women were significantly older (mean age 60 vs 54 years), older at the time of SCI (mean age 52 vs 42 years) and had a shorter follow-up period (median follow-up 4 vs. 7 years). A total of 15% of the included women had received treatment for NDO including bladder relaxant drugs within the last year (n=56, 9%) and/or intravesical botulinum toxin injections at any timepoint (n=46, 8%). Within the last year, seven had received sphincter relaxant drugs (1%) and 233 had received antibiotics as prophylactic (n=36) or therapeutic (n=197) treatment of urinary tract infection (38%).

Prevalence of UI and variables associated with UI

Symptomatic UI was reported by 299 women (49%) of whom 166 (56%) were incontinent daily, 79 (26%) were incontinent weekly and 54 (18%) were incontinent monthly. Of the 310 women without UI, 12 (4%) had answered not relevant to the UI question. When stratified by severity of UI, less severe UI (weekly/monthly UI) was significantly associated with younger age, longer follow-up after injury and myelomeningocele compared with more severe UI (daily UI).

In the following analyses, women with daily, weekly or monthly UI were pooled in one group and compared with the continent women. The QoL-questionnaire[75] was answered by 246 women (40%). In this subgroup, women with UI had a significantly lower QoL score over the last four weeks on all three QoL-domains compared with the continent women (Table 3).

Table 3. Quality of life and urinary incontinence.

QoL domain	UI (n=118)	No UI (n=128)	p
Life in general	7 (5−8)	8 (6−9)	**0.012**
Physical health	5 (3−7)	6 (4−8)	**<0.001**
Psychological health, emotions and mood	7 (5−8)	8 (5−9)	**0.039**

QoL, quality of life; UI, urinary incontinence. Results are presented in median score (Q1−Q3) where 0 is completely dissatisfied and 10 is completely satisfied. Significant results are presented in bold.

The results from the age-adjusted and multivariate logistic regression analyses investigating parameters associated with UI are shown in Table 4.

Table 4. Parameters associated with urinary incontinence in logistic regression analyses.

Parameter	n	OR (95% CI) *Age-adjusted*	p	OR (95% CI) *Multivariate* [a]	p
Age (per year)	609	1.01 (1.00−1.02)	**0.023**†	1.01 (1.00−1.02)	0.06
Type of injury	599				
Traumatic		1.0 (ref)		1.0 (ref)	
Non-traumatic		1.27 (0.89−1.82)	0.19	1.46 (0.97−2.19)	0.07
Primary bladder emptying method	588				
Normal		1.0 (ref)		1.0 (ref)	
IC [b]		1.26 (0.83−1.90)	0.28	0.90 (0.56−1.46)	0.7
Indwelling catheter [c]		0.49 (0.29−0.83)	**0.008**	0.35 (0.18−0.67)	**0.002**
Other method(s) [d]		1.81 (1.00−1.02)	0.05	1.99 (1.02−3.87)	**0.044**
Mobility	578				
Walks without aids		1.0 (ref)		1.0 (ref)	
Walks with aids		1.64 (1.07−2.52)	**0.022**	1.73 (1.08−2.76)	**0.022**
Wheelchair user		1.43 (0.92−2.24)	0.11	2.16 (1.24−3.77)	**0.007**
Spousal/living status	583				
Married/partner		1.0 (ref)		1.0 (ref)	
Unmarried/no partner		1.44 (1.04−2.00)	**0.030**	1.60 (1.11−2.32)	**0.012**
Smoking status	579				
Never		1.0 (ref)		1.0 (ref)	
Former smoker		0.76 (0.51−1.14)	0.18	0.71 (0.45−1.11)	0.13
Current smoker		0.99 (0.65−1.52)	1.0	0.96 (0.60−1.55)	0.9
Classification of injury by AIS and NLI	403				
AIS DE, any NLI		1.0 (ref)			
AIS ABC, Th1-S5		1.08 (0.61−1.91)	0.8		
AIS ABC, C1-C8		0.66 (0.29−1.51)	0.3		
Etiology	440				
Spinal cord injury		1.0 (ref)			
Myelomeningocele		1.34 (0.72−2.48)	0.4		
Follow-up	609				
< 1 year		1.0 (ref)			
1-9 years		0.89 (0.58−1.35)	0.6		
≥ 10 years		1.09 (0.70−1.70)	0.7		
Age at injury (per year)	529	1.00 (0.98−1.01)	0.5		

Modified from original article.[1] OR, odds ratio; CI, confidence interval; IC, intermittent catheterization; AIS, American Spinal Injury Association (ASIA) impairment scale; NLI, neurological level of injury.
†Univariate analysis. [a] Multivariate analysis including 521 women. [b] Including self IC and IC by attendant.
[c] Including urethral and suprapubic indwelling catheter. [d] Including bladder expression, bladder reflex triggering, Bricker conduit, ≥2 primary emptying methods and other methods. Significant results are presented in bold.

Mobility impairments, unmarried status/not living with a partner and use of normal bladder emptying method compared with indwelling catheter were significantly associated with UI.

5.2. Study II

A total of 99 women attended the consultation at the urogynecological clinic at Herlev Hospital between January 2013−January 2018. One woman did not authorize the use of her information in this study, hence, 98 women were included. The same two senior doctors specialized in the field of urogynecology consulted 91 of the women. Two women were consulted by a medical doctor under gynecological training, while the remaining seven women were seen by other specialized senior urogynecological doctors. In 41 women, this was the first gynecological examination after the injury. Twenty-five of the included women were nullipara. Nine had undergone at least one parity after injury of whom five had delivered by caesarean section and four by vaginal delivery. Four women had previously undergone POP repair surgery and 22 had received treatment for UI within the last year (19 with bladder relaxant drugs and five with vesical botulinum toxin injections). Regarding primary bladder emptying method, eight used suprapubic catheter, five used urethral cathether and 31 used IC.

Patient-reported urogynecological symptoms are presented in Figure 11.

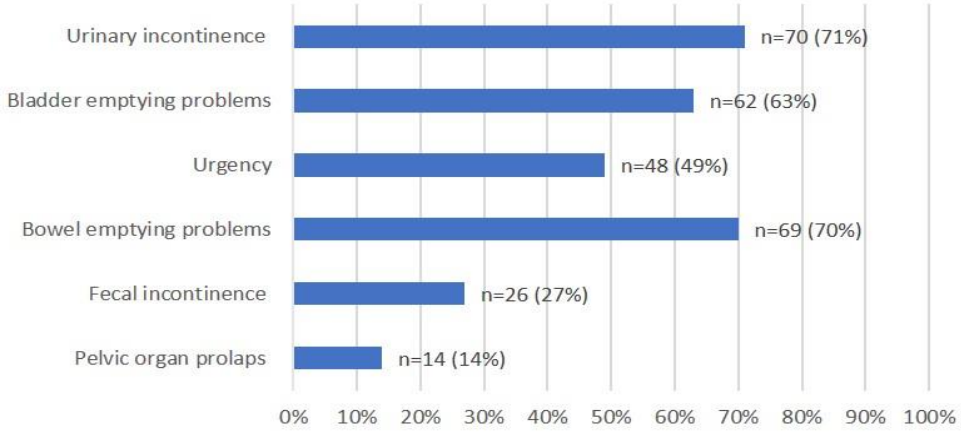

Figure 11. *Patient-reported urogynecological symptoms*

When asked about the onset of symptoms, 3% experienced UI before the SCI, 4% experienced urgency before the SCI and 8% had symptoms of POP before the SCI.

Symptoms of SUI were present in 44 of the 70 women with UI (63%), where 14 (20%) had pure SUI and 30 (43%) had mixed UI.

Anatomical POP stage ≥ 2 was found in 21 women (21%) of whom 12 had symptoms of POP (57%). Five women had POP stage 3 and 16 women had POP stage 2. POP stage ≥ 2 was described in the anterior compartment in 11 women, in the apical compartment in three women

and in the posterior compartment in 15 women. Characteristics associated with anatomical POP are shown in Table 5.

Table 5. Characteristics associated with anatomical POP

Characteristics	POP stage 0-1 (n = 77)	POP stage ≥2 (n = 21)	p
Mean age (y)	50.0 (45.8−54.1)	61.5 (56.4−45.8)	**0.0007**
Mean age at injury (y)	40.9 (35.6−46.2)	50.3 (38.2−62.4)	0.11
Median follow-up after injury (y)	2.7 (0.8−9.6)	1.0 (0.4−5.7)	0.3
Mean body mass index (kg/m^2)	25.9 (24.4−27.4)	27.3 (24.4−30.3)	0.4
Mean parity	1.4 (1.1−1.6)	2.0 (1.5−2.6)	**0.014**
History of vaginal delivery			**0.011**
Yes	42 (54%)	18 (86%)	
No	35 (45%)	3 (14%)	
Menopause			**0.025**
Yes	41 (53%)	17 (81%)	
No	36 (47%)	4 (19%)	
Hysterectomy			0.20
Yes	8 (10%)	0 (0%)	
No	69 (90%)	21 (100%)	
Classification of injury by NLI and AIS			0.25
C1-C8, AIS ABC	6 (9%)	0 (0%)	
Th1-S5, AIS ABC	7 (10%)	4 (24%)	
Any NLI, AIS D	55 (81%)	13 (76%)	
Etiology of injury			1.0
Spinal cord injury	68 (88%)	19 (90%)	
Myelomeningocele	9 (12%)	2 (10%)	
Mobility			0.6
Walks without walking aids	22 (29%)	4 (19%)	
Walks with walking aids	41 (53%)	14 (67%)	
Permanent wheelchair user	14 (18%)	3 (14%)	
Primary bladder emptying method			0.4
Bladder expression / Valsalva's maneuver	7 (9%)	3 (14%)	
Other method(s)	70 (91%)	18 (86%)	
Pelvic floor muscle strength			0.20
Absent or weak	41 (59%)	15 (75%)	
Normal or strong	29 (41%)	5 (25%)	
Bowel emptying problem	55 (71%)	14 (67%)	0.8
Symptomatic urinary incontinence	54 (70%)	16 (76%)	0.8
Symptomatic fecal incontinence	18 (23%)	8 (38%)	0.26

Modified from original article.[2] POP, Pelvic organ prolapse; NLI, Neurological level of injury; AIS, American Spinal Injury Association impairement scale. Results are presented in mean (95% confidence interval), median (Q1−Q3) or in total numbers (%). Significant results are presented in bold.

Women with POP stage ≥ 2 were significantly older, had a higher parity, more had delivered vaginally, and more were post-menopausal. To investigate the effect of time after injury on the development of POP, a bivariate logistic analysis was conducted. Because the number of women with POP was limited, a multivariate analysis including several covariates were not feasible, thus, the analysis was carried out in a subgroup of women who had delivered vaginally (Table 6). In this group, no association between time after injury and POP stage ≥ 2 was found.

Table 6. Age-adjusted bivariate logistic regression analysis on the risk of POP stage ≥ 2 in a subgroup of women with a history of vaginal delivery.

Follow-up after injury	OR (95% CI) adjusted to age	p
< 1 year (n=42)	1.00 (ref)	-
1–5 years (n=6)	0.47 (0.05−4.77)	0.5
> **5 years** (n=12)	0.71 (0.16−3.08)	0.6
OR, odds ratio; CI, confidence interval. Sixty women were included, of whom 18 had POP stage ≥ 2.		

Diagnostics and treatment

The date of the latest cervical cytology sample was evaluated in women aged 23−64 years (n=60). In 18 of the 60 women (30%), the nationally recommended cervical cancer screenings program[88] had not been followed. Among the 98 included women in this study, 48 cervical cytology samples, four biopsies, one colposcopy and one antigen CA-125 blood-sample were collected; no participants were diagnosed with dysplasia or cancer based on the results from these tests. Of the women in this study, 65% were offered treatment after the examination. Eight participants (8%) were treated with surgery of whom three underwent POP repair surgery (native tissue repair/cervical amputation), one underwent urethral injection therapy and a mid-urethral vaginal tape operation combined with a suprapubic catheter insertion, three underwent vesical botulinum toxin injections and one had labia majores reduction performed. Conservative treatment was used in 56 participants (57%) of whom 40 participants received pharmacological treatment, including vaginal estradiol (n=31) and bladder relaxant drugs (n=6), and 37 participants received non-pharmacological treatments, including PFMT (n=22), PFMs stretching therapy (n=1), pessary for UI (n=12) or pessary for POP (n=4). Consequently, only 34 participants (35%) did not receive any treatment other than life style advise and counselling. Among the 44 participants with symptoms of SUI, 33 (75%) ended up receiving urogynecological treatment for the incontinence including surgery (n=1), PFMT (n=15), pessary (n=11), tampons (n=4) and/or vaginal estradiol (n=18).

5.3. Study III

Between April 2015−September 2016, 141 women were identified as potential candidates via the Clinic for Spinal Cord Injuries and contacted by phone. Of these, 26 women were interested, but did not meet the inclusion criteria. A total of 75 women declined to participate, and it was not further investigated if the women met the inclusion criteria. The most frequently stated reasons for declining to participate were that the women were not urinary incontinent, they were not bothered by their UI, UI was not their biggest problem, participation would require too much time or the transportation time to the hospital was too long.

Of the 40 eligible women attending the screening visit, 36 women were included in the study and randomized to an intervention. One woman was excluded from the PFMT+IVES-group after randomization but prior to the active intervention-period due to polyuria. Eight women (four in each group) dropped out during the intervention-period and one woman in the PFMT+IVES-group was excluded after the 12-week assessment. Consequently, there were 13 women in the PFMT-group and 14 in the PFMT+IVES-group after 12 weeks and 13 women in each group after 24 weeks (Figure 12). The inclusion was terminated before reaching the calculated sample-size as there were no more eligible women in the Clinic for Spinal Cord Injuries available.

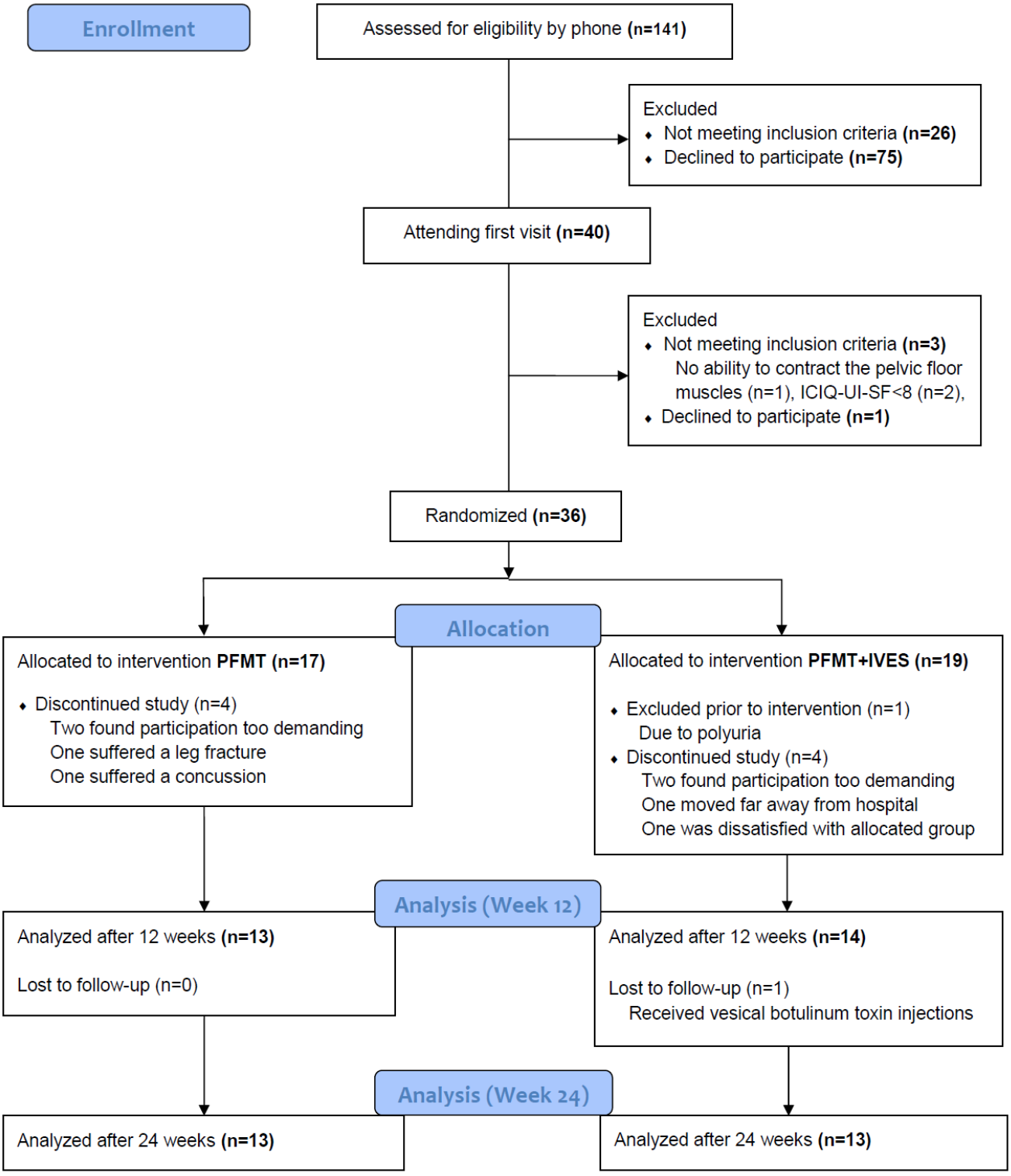

Figure 12. *Flowchart. Reprinted from Elmelund et al[3] with permission from Springer Nature. PFMT; pelvic floor muscle training, IVES; intravaginal electrical stimulation.*

Baseline characteristics and change in outcome measures are reported in Table 7 and Table 8.

Table 7. Baseline characteristics in the two groups.

Characteristics	Group 1 PFMT (n=13)	Group 2 PFMT+IVES (n=14)	*P*
Median age (y)	47 (36−56)	59 (49−67)	**0.027**
Urinary incontinence [a]			0.2
Stress	3 (23%)	1 (7%)	
Urgency	4 (31%)	4 (29%)	
Mixed	4 (31%)	9 (64%)	
Undefined	2 (15%)	0	
Detrusor function [b]			0.6
Normal	5 (38%)	3 (21%)	
Detrusor overactivity	6 (46%)	7 (50%)	
Acontractile/underactive	2 (15%)	4 (29%)	
Clean intermittent catheterization	6 (46%)	10 (71%)	0.3
Use of bladder-relaxant drugs	2 (15%)	4 (29%)	0.7
Use of muscle-relaxant drugs [c]	4 (31%)	6 (43%)	0.7
Reflectometry			
OUP-squeezing (cmH_2O)	56.5 (±16.5)	47.7 (±12.9)	0.13
OUP-resting (cmH_2O)	50.7 (±13.5)	42.9 (±14.7)	0.17
3-day bladder diary			
Daily incontinence episodes	1 (0−2)	2 (1−4)	0.07
Mean bladder capacity (mL)	313 (±58)	200 (±72)	**0.001**
Max bladder capacity (mL)	558 (±154)	344 (±125)	**0.001**
Daily voiding episodes	6 (±2)	7 (±2)	0.19
Daily used pads	1 (0−3)	2 (2−4)	**0.022**
Daily fluid intake (mL)	1901 (±345)	1492 (±376)	**0.008**
Daily diuresis (mL)	1976 (±506)	1493 (±413)	**0.013**
24-hour pad test (g)	34 (7−70)	32 (13−174)	0.6
Questionnaires			
ICIQ-UI-SF	11 (10−16)	13.5 (12−16)	0.2
ICIQ-OAB	18 (16−30)	36.5 (29−43)	**0.018**
SCI-QoL	18 (17−20)	20 (15−24)	0.5

Modified from original article.[3] PFMT, pelvic floor muscle training; IVES, intravaginal electrical stimulation; OUP, opening urethral pressure; ICIQ-UI-SF, International Consultation on Incontinence Questionnaire - Urinary Incontinence - Short Form, ICIQ-OAB, International Consultation on Incontinence Questionnaire - Overactive Bladder; SCI-QoL, International Spinal Cord Injury Quality of Life Basic Data Set. Data are presented as number (%), mean (±SD) or median (Q1−Q3). [a] Urinary incontinence is classified according to ICIQ-UI-SF: Urgency if yes to 'leaks before you can get to the toilet', Stress if yes to 'leaks when you cough or sneeze' or 'leaks when you are physically active/exercising', Mixed if yes in both categories and Undefined if no in both categories. [b] Detrusor function on the most recent cystometry and pressure-flow study. [c] Including benzodiazepine (n=1), per oral baclofen (n=3), baclofen pump (n=1) and gabapentin (n=7), which, besides treating neuropathic pain, also has a spasmolytic effect.

Table 8. Change in outcome measures after intervention at 12 and 24 weeks follow-up.

Outcome measures	12 weeks follow-up				24 weeks follow-up			
	Group 1 (PFMT) N=13	**Group 2** (PFMT+IVES) N=14	**Group 2 – Group 1** (adjusted) †	**P**	**Group 1** (PFMT) N=13	**Group 2** (PFMT+IVES) N=13	**Group 2 – Group 1** (adjusted) †	**P**
ICIQ-UI-SF	-2.4 (-4.3−-0.5)*	-2.2 (-4.8−-0.4)	0.4 (-2.8−3.6)	0.8	-2.5 (-4.5−-0.6)*	-2.5 (-5.5−0.4)	0.3 (-3.1−3.7)	0.8
ICIQ-OAB	1.6 (-6.9−10.1)	-3 (-10.3−4.3)	2.4 (-8.6−13.3)	0.7	1.2 (-5.8−8.1)	-5.8 (-9.0−-2.7)*	-4.2 (-12.4−4.1)	0.3
Reflectometry								
OUP-squeezing (cmH_2O)	7.7 (1.7−13.8)*	1.4 (-2.4−5.2)	-5.2 (-12.3−1.8)	0.14	6.4 (-0.2−13.0)	1.5 (-2.5−5.4)	-3.9 (-11.8−3.9)	0.3
OUP-resting (cmH_2O)	3.9 (0.5−7.3)*	-1.3 (-4.6−1.9)	-5.7 (-10.4−-1.1)	**0.018**	1.9 (-2.7−6.4)	0.1 (-3.3−3.4)	-1.0 (-6.9−4.9)	0.7
3-day bladder diary								
Daily incontinence episodes	-0.4 (-0.8−-0.1)*	0.1 (-0.6−0.8)	0.6 (-0.2−1.4)	0.14	-0.6 (-1.0−-0.2)*	-0.1 (-1.1−0.9)	-0.6 (-0.6−1.7)	0.3
Mean bladder capacity (mL)	22 (-43−87)	-3 (-20−15)	-23 (-117−70)	0.6	-25 (-71−21)	12 (-17−42)	12 (-55−79)	0.7
Max bladder capacity (mL)	-67 (-175−41)	-9 (-56−38)	-46 (-172−80)	0.5	-120 (-227−-13)*	-3 (-50−44)	17 (-101−135)	0.8
Daily voiding episodes	-0.6 (-1.8−0.7)	-0.5 (-1.6−0.7)	0.9 (-0.5−2.2)	0.18	0 (-1.4−1.4)	-0.4 (-1.3−0.5)	0.2 (-1.0−1.4)	0.7
24-hour pad test (g)	-6.0 (IQR -54−5)	-32.5 (IQR -112−3)**	-	0.6	-11.0 (IQR -84−-2)**	-13.5 (IQR -101−17)	-	0.7
SCI-QoL	2 (IQR 0−6)	1 (IQR -3−6)	-	0.7	3 (IQR 0−6)	1 (IQR -2−3)	-	0.3
PGI-I	3 (IQR 2−3)	3 (IQR 3−4)	-	0.7	3 (IQR 3−4)	3 (IQR 3−4)	-	0.9

Modified from original article.[3] PFMT, pelvic floor muscle training; IVES, intravaginal electrical stimulation; ICIQ-UI-SF, International Consultation on Incontinence Questionnaire - Urinary Incontinence - Short Form; ICIQ-OAB, International Consultation on Incontinence Questionnaire - Overactive Bladder; OUP, opening urethral pressure; SCI-QoL, International Spinal Cord Injury Quality of Life Basic Data Set; PGI-I, Patient Global Impression of Improvement, where 1= very much better, 2= much better, 3= a little better, 4= no change, 5= a little worse, 6= much worse, 7= very much worse. Results are calculated by subtracting outcomes at week 12 or 24 from pre-treatment outcomes at week 0 and presented as mean (95% confidence interval) or median (interquartile range, IQR, by Q1−Q3). Missing data occurred in the 3-day bladder diary variables and the 24-hour pad test in both groups as specified in the original article.[3]

†Analysis of Covariance (ANCOVA) was adjusted for the baseline value. *Significant change by paired t-test. **Significant change by paired Wilcoxon signed rank test.

The changes in outcome measures did not differ significantly between the groups at 12 and 24 weeks, except for the OUP during rest which had improved significantly by 5.7 cmH_2O in the PFMT-group compared with the PFMT+IVES-group at week 12. The primary outcome measure, mean ICIQ-UI-SF total score, and the secondary outcome measures, daily episodes of UI and OUP during squeeze and rest measured with urethral pressure reflectometry are visualized in Figure 13.

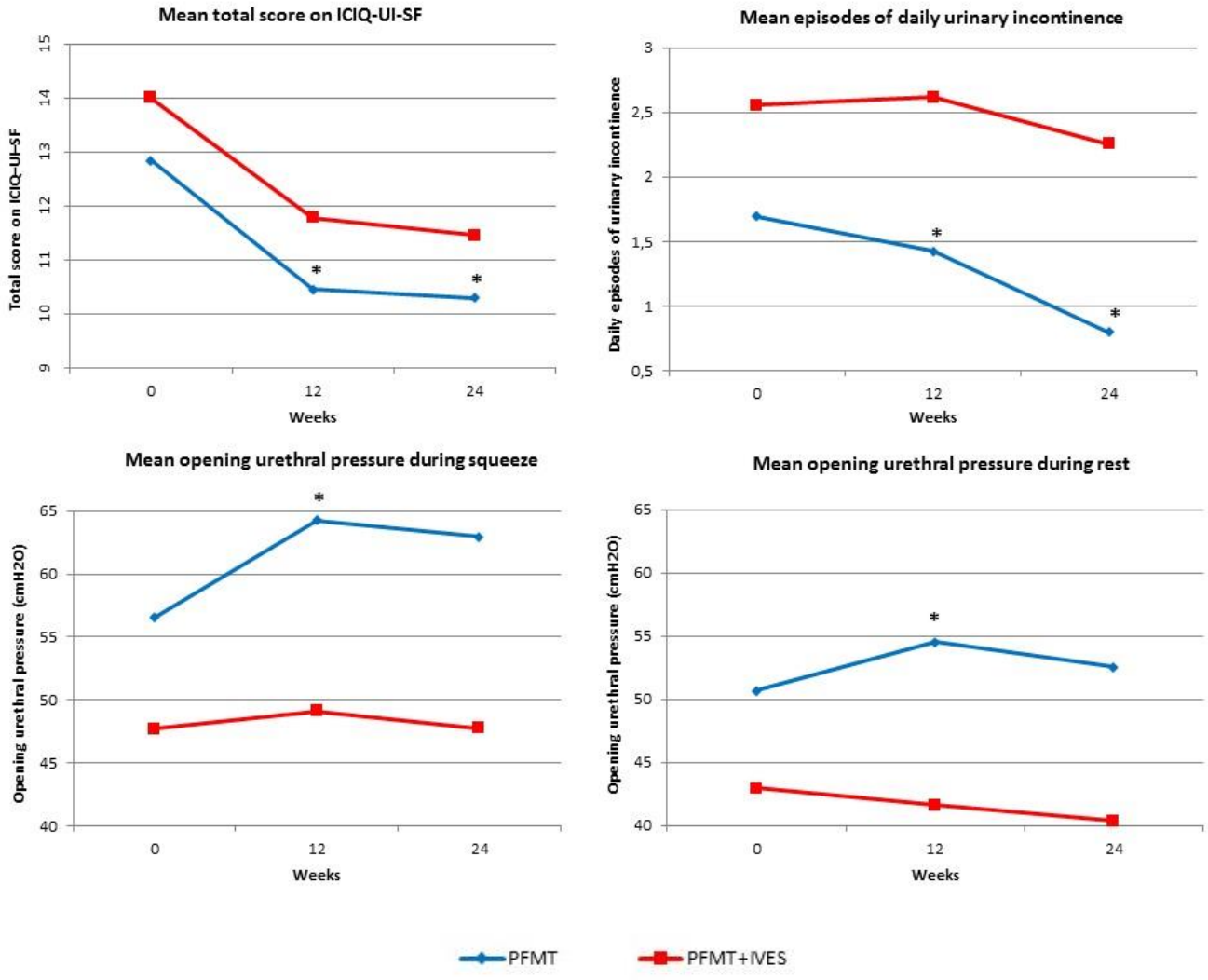

Figure 13. *Mean outcome measures at week 0, 12 and 24.*
** p < 0.05 by paired t-test comparing measures at baseline with week 12 and 24 in each intervention-group. ICIQ-UI-SF; International Consultation on Incontinence Questionnaire - Urinary Incontinence - Short Form, PFMT; pelvic floor muscle training, IVES; intravaginal electrical stimulation. Modified from Elmelund et al.*[3]

The within-group analyses demonstrated a significant improvement from baseline at 12 weeks in the PFMT-group on the primary outcome, ICIQ-UI-SF, the OUP during rest, the OUP during squeeze and the mean daily episodes of UI. In the PFMT+IVES-group, only the 24-h pad test had improved. At 24 weeks follow-up, there was a significant within-group improvement from baseline in the PFMT-group for the ICIQ-UI-SF score, the mean episodes of UI and the 24-h pad test, whereas only the ICIQ-OAB score had improved in the PFMT+IVES-group.

Compliance and side effects

Compliance with training according to the training diary was generally good in both groups. The intervention was performed in a median of 76 days in the PFMT-group and 67 days in the PFMT+IVES-group (p=0.2). The mean number of daily contractions was 28 with a duration of 8 s in the PFMT-group. In the PFMT+IVES-group, the mean stimulation time with the high-frequency and low-frequency IVES-programs were 9 and 15 min, respectively. Soreness of the PFMs was the only reported side effect which was experienced by one woman in the PFMT-group.

Post hoc analyses

In accordance with the results from the per-protocol analyses, the treatment effect did not differ between the groups in the two post-hoc analyses, excluding the women who trained less than 50% of the active intervention-period (n=4) (Table 9) and the women with SUI or undefined UI according to the baseline ICIQ-UI-SF (n=6) (Table 10).

Table 9. Change in outcome measures in a subgroup of women who trained minimum 50% of the days during the intervention period (n=23)

Outcome measures	12 weeks follow-up				24 weeks follow-up			
	Group 1 (PFMT) N=13	**Group 2** (PFMT+IVES) N=14	**Group 2 – Group 1** (adjusted) †	**P**	**Group 1** (PFMT) N=13	**Group 2** (PFMT+IVES) N=13	**Group 2 – Group 1** (adjusted) †	**P**
ICIQ-UI-SF	-2.7 (-4.6−-0.7)*	-2.6 (-6−0.7)	0.8 (-3.0−4.5)	0.7	-2.8 (-4.9−-0.6)*	-3.2 (-6.3−0.0)*	0.3 (-3.3−4.0)	0.9
ICIQ-OAB	0 (-8.5−8.5)	-5.6 (-14.1−2.8)	2.7 (-8.8−14.3)	0.6	-0.4 (-7.1−6.2)	-6.7 (-9.9−-3.5)*	-1.8 (-9.6−6.0)	0.6
Reflectometry								
OUP-squeezing (cmH_2O)	8.1 (1.5−14.7)*	1.4 (-3.3−6.1)	-4.4 (-4.4−13)	0.3	6.2 (-1.1−13.4)	1.0 (-3.5−5.6)	-3.0 (-12.3−6.4)	0.5
OUP-resting (cmH_2O)	4.1 (0.4−7.8)*	-0.8 (-4.0−2.4)	-4.5 (-9.9−1.0)	0.10	1.2 (-3.6−6.0)	0.2 (-3.8−4.2)	0.9 (-5.8−7.6)	0.8
3-day bladder diary								
Daily incontinence episodes	-0.4 (-0.8−0.1)*	0.0 (-0.8−0.9)	0.5 (-0.3−1.3)	0.19	-0.6 (-1.0−0.2)*	-0.6 (-1.4−0.3)	0.2 (-0.7−1.0)	0.7
Mean bladder capacity (mL)	22 (-43−87)	-6 (-26−14)	-30 (-148−88)	0.6	-25 (-71−21)	14 (-12−39)	21 (-51−94)	0.5
Max bladder capacity (mL)	-67 (-175−41)	17 (-29−63)	-32 (-187−123)	0.7	-120 (-227−-13)*	13 (-37−62)	19 (-121−159)	0.8
Daily voiding episodes	-0.6 (-1.8−0.7)	-0.6 (-2.2−1.0)	1.2 (-0.4−2.7)	0.13	0 (-1.4−1.4)	-0.5 (-1.6−0.5)	0.3 (-1.1−1.7)	0.6
24-hour pad test (g)	-6 (IQR -54−5)	-82 (IQR -139−-14)**	-	0.13	-11 (IQR -84−-2)**	-31 (IQR -149−-2)	-	0.9
SCI-QoL	2 (IQR -1−6)	1 (IQR -10−4)	-	0.5	2.5 (IQR -2−7)	2 (IQR -1−5)	-	0.5
PGI-I	3 (IQR 2−3)	3 (IQR 3−4)	-	0.5	3 (IQR 3−4)	3 (IQR 3−4)	-	1.0

Modified from original article.[3] PFMT, pelvic floor muscle training; IVES, intravaginal electrical stimulation; ICIQ-UI-SF, International Consultation on Incontinence Questionnaire - Urinary Incontinence - Short Form; ICIQ-OAB, International Consultation on Incontinence Questionnaire - Overactive Bladder; OUP, opening urethral pressure; SCI-QoL, International Spinal Cord Injury Quality of Life Basic Data Set; PGI-I, Patient Global Impression of Improvement, where 1= very much better, 2= much better, 3= a little better, 4= no change, 5= a little worse, 6= much worse, 7= very much worse. Results are calculated by subtracting outcomes at week 12 or 24 from pre-treatment outcomes at week 0 and presented as mean (95% confidence interval) or median (interquartile range, IQR, by Q1−Q3). Missing data occurred in the 3-day bladder diary variables and the 24-hour pad test in both groups as specified in the original article.[3]

†Analysis of Covariance (ANCOVA) was adjusted for the baseline value. *Significant change by paired t-test. **Significant change by paired Wilcoxon signed rank test.

Table 10. Change in outcome measures in a subgroup of women with urgency or mixed urinary incontinence on ICIQ-UI-SF (n=21)

Outcome measures	12 weeks follow-up				24 weeks follow-up			
	Group 1 (PFMT) N=13	**Group 2** (PFMT+IVES) N=14	**Group 2 – Group 1** (adjusted) †	**P**	**Group 1** (PFMT) N=13	**Group 2** (PFMT+IVES) N=13	**Group 2 – Group 1** (adjusted) †	**P**
ICIQ-UI-SF	-2.5 (-5.5−0.5)	-1.7 (-4.2−0.9)	1.3 (-2.5−5.0)	0.5	-1.9 (-5.0−1.3)	-2 (-4.9−0.9)	0.4 (-3.7−4.5)	0.9
ICIQ-OAB	4.0 (-5.0−13.0)	-2.8 (-10.7−5.0)	0.2 (-11.6−12.0)	1.0	2.1 (-7.9−12.1)	-5.3 (-8.4−-2.1)*	-4.1 (-13.2−5.1)	0.4
Reflectometry								
OUP-squeezing (cmH_2O)	5.8 (-1.8−13.4)	0.6 (-3.0−4.2)	-4.9 (-2.2−12.1)	0.16	7.1 (-3.8−18.1)	1.1 (-3.1−5.3)	-5.2 (-14.9−4.5)	0.3
OUP-resting (cmH_2O)	2.5 (-2.2−7.2)	-1.6 (-5.1−1.9)	-4.6 (-9.9−0.6)	0.08	3.2 (-3.7−10.2)	0.2 (-3.4−3.8)	-2.5 (-9.5−4.6)	0.5
3-day bladder diary								
Daily incontinence episodes	-0.2 (-0.6−0.2)	0.1 (-0.6−0.8)	0.3 (-0.8−1.5)	0.5	-0.6* (-1.2−-0.1)	-0.1 (-1.1−0.9)	0.5 (-1.1−2.0)	0.5
Mean bladder capacity (mL)	-22 (-84−-20)	-3 (-20−15)	5 (-57−66)	0.9	-44 (-122−33)	12 (-20−44)	22 (-66−109)	0.6
Max bladder capacity (mL)	-124 (-262−14)	-9 (-56−38)	10 (-84−104)	0.8	-156 (-298−-15)*	-11 (-59−37)	50 (-54−154)	0.3
Daily voiding episodes	-0.3 (-2.6−2.0)	-0.5 (-1.6−0.7)	0.2 (-1.3−1.7)	0.8	0.3 (-2.4−2.9)	-0.5 (-1.4−0.4)	-0.5 (-1.8−0.9)	0.4
24-hour pad test (g)	-32 (IQR -177−-4)**	-51 (IQR -139−7)**	-	0.7	-34 (IQR -177−-10)**	-14 (IQR -149−32)	-	0.4
SCI-QoL	3 (IQR 0−5.5)	1 (IQR -3−6)	-	0.6	2.5 (IQR -3.5−3.5)	1.5 (IQR -1.5−4)	-	1.0
PGI-I	2.5 (IQR 2−3)	3 (IQR 3−4)	-	0.3	3.5 (IQR 2.5−4)	3 (IQR 3−4)	-	0.8

Modified from original article.[3] PFMT, pelvic floor muscle training; IVES, intravaginal electrical stimulation; ICIQ-UI-SF, International Consultation on Incontinence Questionnaire - Urinary Incontinence - Short Form; ICIQ-OAB, International Consultation on Incontinence Questionnaire - Overactive Bladder; OUP, opening urethral pressure; SCI-QoL, International Spinal Cord Injury Quality of Life Basic Data Set; PGI-I, Patient Global Impression of Improvement, where 1= very much better, 2= much better, 3= a little better, 4= no change, 5= a little worse, 6= much worse, 7= very much worse. Results are calculated by subtracting outcomes at week 12 or 24 from pre-treatment outcomes at week 0 and presented as mean (95% confidence interval) or median (interquartile range, IQR, by Q1−Q3). Missing data occurred in the 3-day bladder diary variables and the 24-hour pad test in both groups as specified in the original article.[3]

†Analysis of Covariance (ANCOVA) was adjusted for the baseline value. *Significant change by paired t-test. **Significant change by paired Wilcoxon signed rank test.

6. Discussion

6.1. Main findings

- Half of the women with SCI experience symptoms of UI varying from daily to monthly with the majority experiencing daily UI.
- Symptomatic UI is associated with reduced QoL, unmarried/non-cohabiting status, impaired mobility and normal bladder emptying method compared with indwelling catheter use.
- During routine urogynecological assessments, any UI symptoms and bladder and bowel emptying problems occurred in more than 60% of women with SCI, and 75% of the women presenting with symptoms of SUI received urogynecological treatment for their incontinence.
- POP is not a prevalent anatomical condition in women with SCI. It is associated with increasing age, parity, vaginal delivery and menopause but not with time after injury.
- PFMT combined with IVES is not superior to PFMT alone in the treatment of UI in women with SCI.
- PFMT improves the symptoms of UI with a persistent effect after 3 months of follow-up.

6.2. Urinary incontinence

The prevalence of symptomatic UI was 49% in study I, while 71% experienced UI in study II. This difference is most likely due to the use of different definitions of UI, as UI varying from daily to monthly on average over the last three months was registered in study I and any UI, including UI only during specific occasions like a urinary tract infection was registered in study II. Further, it is possible that the different study designs contributed to these findings; questions asked by a urogynecologist during a urogynecological consultation could result in more women reporting UI than questions asked by an SCI-specialized physician during a routine follow-up consultation. The two study populations were comparable on injury, demographics and age, but the women in study II had a shorter follow-up period after injury (median 2 years) than the women in study I (median 7 years).

Nonetheless, a prevalence of UI between 49%−71% in women with SCI is strikingly high. The reported prevalence of UI in neurologically intact women varies from 25%−46%.[32-34] Even though a 49% prevalence of UI after SCI seems comparable to the highest reported prevalence of UI of 46% found in neurologically intact women in a Danish study,[34] there is an important difference between the characteristic of UI found in the two populations: Only one fourth of the incontinent neurologically intact women had previously consulted a physician with their UI.[89] In comparison, all the women with SCI were already followed at the Clinic for Spinal Cord Injuries, where their bladder and urinary symptoms were routinely evaluated by SCI-specialists and urologists and treated with medication, change of bladder emptying method, vesical botulinum toxin injections etc.

A prevalence of UI on 49-71% in women with SCI could indicate that the management of UI after SCI is not optimal. When managing a patient with UI, it is important to firstly identify the problem, it's impact on the patient's QoL and ultimately discuss potential treatment options with the patient. This should be done repeatedly and if the desired effect of a treatment is not obtained, alternate treatment-options should be presented to the patient. Preferably, this should be managed in collaboration with SCI-clinicians, urologists and/or urogynecologists. Nevertheless, it is also important to remember that UI is a common condition in women in general, affecting up to 46% of whom the majority do not seek medical treatment, and that the symptoms and impact of UI varies from women to women. Other QoL-reducing complications to a SCI, e.g. pain, spasticity, bowel problems etc. may also affect a woman's wish to receive treatment. Ultimately, it is the patient's decision whether she wants treatment and what kind of treatment, but to make this decision, she needs to be informed of the treatment options, the estimated effect of the treatments and their potential complications.

To the best of our knowledge, no studies have previously investigated the prevalence of UI in a large sample of women with SCI, but UI has been examined in male SCI-populations. In a Danish questionnaire-based study, 236 individuals with SCI followed at the Clinic for Spinal Cord Injuries, Rigshospitalet, were included, of whom only 18% were women.[37] A total of 43% reported UI, and 20% had daily UI. Compared with our study findings, it appears that UI is a more prevalent and severe problem in women compared with men after SCI, which is in accordance with results from other mixed-gender SCI studies.[5,90]

In the univariate analysis in study I, the risk of UI increased with increasing age, which is in agreement with studies conducted in neurologically intact women.[32,34] However, the multivariate analysis adjusted for age revealed that unmarried/non-cohabiting status, bladder emptying method and impaired mobility were covariates associated with UI. The use of an indwelling (suprapubic or urethral) catheter decreased the risk of UI, but given the cross-sectional study design, it is difficult to establish a causal relationship. Though an indwelling catheter might reduce UI in some women, indwelling catheters should not be interpreted as an effective treatment of UI. In fact, it is likely that women with UI were recommended to use IC whereas women with voiding problems were recommended to use indwelling catheters, but these conclusions cannot be drawn from this cross-sectional study. As indwelling catheters can predispose to urinary tract infections and other long-term complications, IC is recommended over indwelling catheters. If long-term indwelling catheters have to be used, suprapubic catheters should be preferred over transurethral catheters.[25,41]

The multivariate analysis also demonstrated an association between unmarried/non-cohabiting status and UI. Though a causal relationship cannot be established in this study, it seems reasonable that UI has a negative influence on partnerships after SCI. In support of this, UI has previously been associated with loneliness and depression[91] and reduced satisfaction with sexual activity after SCI.[39] In addition, UI was significantly associated with decreased QoL in our study, according to a questionnaire that was established to evaluate the overall QoL in persons with SCI who experience many complications after SCI.[75] This is in agreement with previously published results demonstrating that incontinent individuals with SCI were more limited in the physical, social, personal and emotional domains compared with continent persons with SCI.[38] The fact that UI was associated with reduced QoL regarding life in general, physical health and psychological health, emphasizes that UI has a great impact on the overall QoL after SCI.

The most prominent risk indicator of UI in study I was impaired mobility, especially permanent wheelchair use (OR 2.16). In a recently published report from the International Continence Society, this phenomena was defined as ‘impaired mobility urinary incontinence’ which is UI caused by an inability to reach the toilet in time for voiding because of physical or medical disability.[26] Especially symptoms of NDO incontinence or overflow incontinence are enhanced by mobility impairments that makes it difficult for the woman to remove clothes and to reach the toilet in time.

Among the women with UI in study II, 63% had symptoms of SUI, where 20% had pure SUI and 43% had mixed UI. In neurologically intact women, this proportion was 70%-86%, and pure SUI was the largest subtype of UI.[32,34,92] Different aspects of the neurogenic bladder dysfunction can contribute to the development of UI after SCI, including NDO, acontractile detrusor function, insufficient urethral sphincter and weakened PFMs. This explains the larger proportion of women with symptoms of mixed UI found in this study. However, the general classification of UI in SUI, UUI and mixed UI based on the woman's symptoms does not apply well for women with complicated UI due to neurogenic bladder dysfunction. Therefore, urodynamic evaluations rather than clinical symptoms are recommended to distinguish between the subtypes of UI,[25] especially regarding UI other than SUI.

In a recent study, the prevalence of SUI demonstrated with urodynamic investigations or supine stress tests was surprisingly low (16%) in women with multiple sclerosis compared with neurologically intact women,[93] but to our knowledge, this has not been investigated in women with SCI. Following the urogynecological consultation, 75% of the 44 women presenting with symptoms of SUI received treatment, primarily conservative, for their UI including PFMT, pessary and/or vaginal estradiol. Only one woman underwent surgical treatment for SUI with urethral injection therapy, but due to an insufficient effect, the woman received a tension-free vaginal tape combined with a suprapubic catheter as the woman had an acontractile bladder and were not able to carry out IC. The mid-urethral vaginal tape operations that have revolutionized the treatment of SUI in neurologically intact women, have also demonstrated good long-term results on neurogenic SUI, although results from randomized studies are lacking.[48,94] However, the fact that only one woman received a tension-free vaginal tape, witnesses of some reluctance among urogynecologists to perform this treatment in women with SCI, presumably due to a concern of postoperative voiding difficulties.

The large proportion of women who received treatment for SUI in study II, combined with the fact that all the included women were offered regular urological and SCI-specific follow-up visits, suggest that urogynecological treatments, especially for SUI, may be underused in women with SCI. As high-pressure bladders are considered a risk indicator of renal deterioration after SCI,[40,95] the management of especially NDO is a priority in this population. Thus, 22% of the included women were already treated with vesical botulinum toxin injections or bladder relaxant drugs and 45% used IC or indwelling catheter as bladder emptying method before attending the urogynecological consultation. Though the effect of the prescribed urogynecological treatments

was not the scope of this article, the results suggest that urogynecological consultations and treatments are valuable in the management of UI in women with SCI.

6.3. Pelvic organ prolapse

In study II, the occurrence of anatomical POP stage ≥ 2 was 21%. In comparison, 50% had anatomical POP in a study by Swift conducted in 497 neurologically intact women.[69] In this study, women seen for routine gynecological health care were included, and POP was classified according to the POP quantification system. The women in the study were on average 10 years younger than the women with SCI in our study, suggesting that the actual difference in the occurrence of POP between the two populations may be larger.

In a study including 280 women with multiple sclerosis, the occurrence of anatomical POP stage ≥ 2 was only 9%,[93] supporting the theory that a neurological injury does not increase the risk of POP. We found that POP was significantly associated with age, parity, vaginal delivery and menopause which corresponds to the risk indicators found in the neurologically intact population.[69] On the other hand, POP was not associated with the level or severity of the SCI, and after adjusting for age in a subgroup of women with a history of vaginal delivery, the risk of POP did not increase with increasing time after injury. It has been proposed that the risk of POP may increase after SCI due to weakness of the PFMs and use of bladder emptying methods that increase the abdominal pressure.[13,14] In this study, anatomical POP was not associated with absent/weak pelvic floor muscle-strength compared with normal/strong pelvic floor muscle-strength, nor was there an association between use of bladder expression or Valsalva's manoeuvre as primary bladder emptying methods and POP. Based on this study, the concern that SCI increases the risk of POP can be disregarded. In fact, an SCI may even have a protective effect on the development of POP as less stress is applied on the pelvic organs and the PFMs in women with mobility impairments compared with physically active, neurologically intact women. Though a protective effect of SCI on the development of POP is not clinically relevant, our findings can be used to eliminate the concern that the risk of POP increases after SCI. Furthermore, the concern of an increased risk of POP after SCI should not affect the mode of delivery in a pregnant woman with SCI.

In the 21 women with POP stage ≥ 2, prolapse in the posterior compartment was the most common (n=15) followed by the anterior compartment (n=11) and lastly the apical compartment

(n=3). In neurologically intact women, prolapse in the anterior compartment is most common, detected twice as often as in the posterior compartment and three times as often as in the middle compartment.[68] Due to the limited number of women with POP in this study, this difference is most likely coincidental. However, it is also possible that posterior compartment POP occur more commonly in women with SCI who often experience bowel emptying problems and constipation, but larger studies are required to explore this hypothesis. In the general population, treatment of POP is symptomatic and should only be carried out if the woman's QoL is affected. As more women with SCI may not be bothered by their prolapse due to reduced sensitivity, fewer patients might be candidates for treatment. In the few cases where POP obstructs voiding or cause sub-optimal bladder emptying, treatment should be considered. The International Urogynecological Association recommends conservative treatment with e.g. vaginal pessaries or surgery.[66]

6.4. Intravaginal electrical stimulation and pelvic floor muscle training

The fact that IVES and PFMT were not superior to PFMT alone in treating UI after SCI was surprising. Our results differed from the findings of a similar study conducted in persons with multiple sclerosis where 9 weeks of daily PFMT and intravaginal/anal electrical stimulation by 10 and 40 Hz was superior to PFMT and sham electrical stimulation.[64] In this study, the daily UI episodes were reduced by 85% in the electrical stimulation-group compared with 3% in our study, and with 47% in the PFMT-group compared with 25% in our study. However, these study-results may be biased by the fact that 34% of the included participants were continent at baseline, but change in daily UI episodes was used as primary outcome. Further, adjustments of baseline values were not included in the final analyses. In a recent study including 25 women with multiple sclerosis,[65] no difference was found between PFMT and PFMT combined with 10 Hz-IVES on the 24-h pad test, urgency and urgency UI episodes, much in line with our study results.

Though not significant, our results were in favour of PFMT alone compared with PFMT+IVES in almost all outcome measures, and PFMT was significantly superior according to the OUP during rest. The OUP in particular, is an objective measure of improved pelvic floor muscle strength that is known to reduce SUI. These results are in agreement with studies showing that

the effect of IVES is inferior[96] or comparable[97] to PFMT in neurologically intact women with SUI.

There were no changes in the ICIQ-OAB score, the daily voiding episodes and the bladder capacity after 12 weeks in our PFMT+IVES-group. Additionally, there was no difference between the groups or changes in the urgency-associated outcomes after 12 weeks in the subgroup of women with urgency or mixed UI according to the ICIQ-UI-SF, underlining that potential beneficial effects of IVES on urgency and overactive bladder symptoms were not overlooked in this study.

In comparison with PFMT, IVES is a more lengthy, expensive and inconvenient treatment that requires good hand-function, a private setting and up to 30 min of daily commitment compared with 10 min of daily PFMT. This, combined with the lack of additional effect, supports that IVES as add-on to PFMT cannot be recommended in the treatment of UI in women with incomplete SCI. In fact, our results suggest that PFMT may be carried out less effectively while handling an IVES-device at the same time. Theoretically, PFMT conducted separately from the IVES could have been more effective, but the use of a realistic daily training program is also an important consideration.

PFMT alone significantly improved the ICIQ-UI-SF, the OUP during squeeze and rest and the daily UI episodes after 12 weeks compared with baseline. Though a 2.5-point reduction on the ICIQ-UI-SF is a relatively limited effect, this effect-size corresponds to the anticipated clinical relevant difference after conservative treatment with PFMT,[98] especially considering that these women suffer from complex and often refractory UI.

6.5. Methodological considerations / Strengths and limitations

6.5.1 Study I

This study has several strengths: To the best of our knowledge, it is the largest study describing UI after SCI and the first to investigate the prevalence of UI specifically in women with SCI. In addition, data were registered according to an internationally standardized SCI-specific questionnaire. Nonetheless, the study also has some limitations. To be included in this study, women should have attended a consultation between 2010-2016. Though all patients in the Clinic for Spinal Cord Injuries are invited to attend follow-up visit every 2nd year after the diagnosis of the SCI, it is possible that some of the women with an injury before 2010 did not attend a consultation in this period, which could have biased the results if they differed systematically from the included women. Further, 17% of the identified study population had no answer to the UI-question and were excluded. Though comparable on injury parameters, the excluded women were older than the included women, which could have led to an underestimation of the prevalence of UI in this study. Information on body mass index and parity, which are known risk factors of UI, were also not available in the database. Finally, this was a retrospective study based on information from the SCIBase, thus, the quality and validity of the answers provided in the database are crucial. After 1999, the SCIBase functioned as an electronic medical record database where all information on patients would be registered, thus, the database covered information on all patients diagnosed with a SCI in the clinic after September 1999. Unfortunately, a relatively large percentage (30-34%) of the participants had no NLI or AIS score in the SCIBase, and it is unknown why no classification of the SCI had been performed in these patients. Regrettably, missing data is a frequent limitation in a study collecting data retrospectively. Conversely, the response rate on the questions regarding UI were fairly high (87%).

As the questionnaires in this study were answered by the treating physician during each patient consultation, there is a risk that some answers could have been typed in incorrectly. To test the accuracy of the answers in the database, the question “use of condom catheter/sheat” as collecting appliances for UI was evaluated. There were no positive answers to the question, suggesting a good accuracy of the database.

6.5.2 Study II

The primary strength of study II is its novelty as it is the first study to investigate POP after SCI and to evaluate the need for urogynecological assessments in women with SCI. The urogynecological consultations were predominantly conducted by the same two specialized urogynecological senior doctors, facilitating consistency in obtaining data and managing the treatment of the patients. However, the study also has some flaws. No age-matched cohort of women was included in the study, making the comparison with neurologically intact women somewhat theoretical. Furthermore, the median follow-up period was not very long and when analysing risk factors of POP, multivariate risk analyses could not be carried out due to the limited number of participants. Additionally, the diagnosis of SUI was based primarily on reported symptoms but was not confirmed urodynamically in this study. As urodynamic evaluations were already included in the standardized urological follow-up program, and urodynamic investigations are relatively comprehensive in this population, requiring prophylactic antibiotic treatment due to an increased risk of urinary tract infections, these examinations were only carried out when there was a clinical indication, e.g. prior to surgical treatment of UI.

It could be questioned if the included women were representative of the complete population of women with SCI, given that individuals with urogynecological symptoms might be more prone to accept the invitation of a urogynecological consultation, thus, causing selection bias. If true, this would have resulted in an overestimation of the occurrence of POP in this study, which only strengthens the conclusion that the risk of POP does not increase after SCI. However, the occurrence of other urogynecological symptoms including UI would be overestimated. To explore this postulate, the included women in study II were cross-checked with the women in study I. Among the 98 women included in study II, 75 were also included in study I. In this group of women, 56% experienced UI according to the data from study I compared with 71% according to the data from study II. This suggests that study II was not affected by selection bias but underlines the impact of using different definitions of UI and different study designs.

6.5.3 Study III

The strengths of study III include the randomized investigator-blinded design, the use of the internationally standardized and validated questionnaire ICIQ-UI-SF as primary outcome, and the fact that this is the first randomized study investigating PFMT and IVES in women with SCI. Nevertheless, it also has some limitations. Firstly, a third placebo-group was not included in the study; hence, the effect of PFMT was not adjusted to the effect of placebo. To account for this, objective outcome measures were included in the study e.g. the 24-h pad test and the OUP. In particular the OUP, that was analyzed by a blinded investigator, has proven to be a highly sensitive measure not influenced by the effect of placebo.[87] Secondly, there were significant differences between the two intervention-groups at baseline. To compensate for any differences between the groups, statistical analyses adjusting for the outcome measures at baseline were selected for the parametric outcomes. Thirdly, only 13 women in each group completed the study protocol. According to the initial sample size calculation, 10 women in each group were considered necessary but in a renewed calculation of the sample size, based on a more appropriate minimal important difference of 2.5 points (SD 2.6) from a recently published PFMT-study,[98] at least 17 women should be included in each group to detect a difference on the ICIQ-UI-SF. Thus, it could be questioned if a superior effect of PFMT+IVES was overlooked in this study due to a small sample size. However, as the outcome measures were predominantly in favour of PFMT rather than PFMT+IVES, it is very unlikely that the inclusion of additionally four women in each group would lead to significant results in the reverse direction. Thus, we believe that a true superior effect of PFMT+IVES compared with PFMT was not overseen in this study.

The varying severity of injury in a SCI population is often a challenge when conducting research in this group of patients. In this study, women with an AIS score C, D and E participated, which included both women unable to walk and women without any mobility disabilities. However, the distribution of AIS scores were similar in the two intervention-groups, and therefore, potential differences in severity of injury were not likely to influence the results.

7. Conclusion

In conclusion, we have found that UI is a prevalent condition in women with SCI, affecting half to three-quarters of the population, and that almost one-third of women with SCI experience daily UI. We have also found that UI is associated with impaired mobility, unmarried/non-cohabiting status and decreased QoL.

Our studies suggest that there is a need for specialized urogynecological follow-up, especially in women with symptoms of SUI. Women with SCI who experience UI should be offered a consultation at a specialized urogynecological clinic with adequate facilities and experience in managing women with SCI.

Moreover, we have demonstrated that IVES combined with PFMT is not superior to PFMT in the treatment of UI. However, PFMT improves the symptoms of UI with a persistent effect after 3 months of follow-up and we recommend it as first-line conservative treatment of UI after SCI.

Finally, we established that anatomical POP is rare in women with SCI compared with neurologically intact women and that the risk of POP does not increase with increasing time after injury.

7.1. Perspectives

This thesis brings new insights into UI and other urogynecological conditions in women with SCI. Given that UI can be a sensitive topic for many women, it may be an underreported problem. High quality studies investigating the prevalence of UI are essential for clinicians and the health authorities to offer appropriate management of the condition. In clinical practice, it is important that clinicians repeatedly remember to ask questions about the occurrence, severity and impact of UI on QoL, including the woman's motivation for receiving treatment at different time-points after the SCI.

This thesis showed that IVES as an add-on treatment to PFMT is not effective in reducing UI after SCI. Publications of negative results that demonstrate a lack of effect of a given treatment are especially important, given that positive results are more likely to be published and cited, which may falsely distort the conclusions drawn from meta-analyses.

However, intensive PFMT was found to be an effective conservative treatment of UI after SCI, but PFMT may also have other advantages than those evaluated in study III. Many of the

included women expressed satisfaction with the intervention as they felt they increased their knowledge on UI, bladder function and pelvic floor function, and they felt empowered by managing their own condition with training. It is important to recognize the motivating and empowering effects of PFMT in addition to the effect on UI.

Although urogynecological consultations and treatments, including PFMT-programs, are offered to the women followed at the Clinic for Spinal Cord Injuries, Rigshospitalet, urogynecological conditions after SCI are still not gaining enough attention nationally as well as internationally. It is our hope that information on UI, bladder function and treatment options of UI after a neurological disorder are made more accessible to women with SCI in the future, e.g. by use of the web, social medias or pamphlets. The results of this thesis have shed light upon an underreported issue, and may contribute to the development of guidelines on the management of UI and other urogynecological conditions in women with SCI.

7.2. Future studies

This thesis has revealed several areas of interest that should be explored further in future studies:

- Randomized controlled studies investigating the effect of PFMT compared with placebo in women with incomplete SCI would be warranted to confirm the results of this thesis.
- Randomized controlled studies investigating the effect of urogynecological treatments of UI including pessaries, intraurethral injection therapy and mid-urethral sling operations in women with SCI.
- Explorative studies examining the prevalence and risk factors of different subtypes of UI diagnosed with urodynamic investigations in women with SCI.
- Longitudinal studies exploring the causal relationship between UI and the bladder emptying method, adjusted for the effect of parity, body mass index, mobility and SCI demographics in women with SCI.
- Studies exploring the impact of education in pelvic floor muscle function, bladder function, life style advice and PFMT on women's QoL and satisfaction with their sexual lives.

8. Summary

Spinal cord injury (SCI) is associated with multiple complications, including urinary incontinence (UI). However, there is a knowledge-gap on the prevalence and treatment of UI in women with SCI. Furthermore, it has been questioned if pelvic organ prolapse (POP) occurs more frequently in women with SCI, primarily because of the weakened pelvic floor muscles (PFMs), but this has never been investigated.

Hence, the overall aim of this thesis was to increase our knowledge on urogynecological conditions in women with SCI. Specifically, we aimed at investigating the prevalence of UI, factors associated with UI and the effect of pelvic floor muscle training (PFMT) with and without intravaginal electrical stimulation (IVES) on UI in women with SCI. An additional aim was to examine the occurrence of POP after SCI and to evaluate the need for specialized urogynecological assessments offered to women with SCI.

Study I was a cross-sectional study. It included 609 women and was based on standardized questionnaires that had been filled out and registered in a database by the clinician during each consultation at the SCI-clinic. We found a 49% prevalence of daily to monthly UI, and UI was associated with reduced quality of life, unmarried/non-cohabiting status and impaired mobility. In the cross-sectional **Study II**, 98 women with SCI underwent a urogynecological assessment. Information on urogynecological symptoms was obtained, and the occurrence of POP was investigated during a pelvic examination. We found that 21% had anatomical POP and that POP was associated with increasing age, vaginal delivery, parity and menopause but not with time after injury or severity of injury. Nonetheless, UI and bladder/bowel emptying problems were highly prevalent, affecting 63-71% of the women. **Study III** was a randomized trial, investigating the effect of 12-weeks daily PFMT or PFMT and IVES on UI. Outcome measures included a UI questionnaire, daily UI episodes and urethral opening pressure measured with urethral pressure reflectometry. A total of 26 women completed the study. We found that PFMT+IVES was not superior to PFMT alone. Only PFMT improved the symptoms of UI with a persistent effect after 3 months follow-up.

This thesis shows that although anatomical POP does not occur frequently after SCI, symptoms of UI are highly prevalent in this group of women. Further, it demonstrates that urogynecological consultations should be included in the standardized follow-up program, especially in women with UI after SCI. Finally, PFMT without IVES is an effective conservative treatment of UI in women with incomplete SCI.

9. Resumé

Der er ofte mange komplikationer forbundet med en rygmarvsskade (RMS), herunder urin inkontinens (UI), men prævalensen og behandlingen af UI hos kvinder med en RMS er ikke tilstrækkeligt belyst i litteraturen. I en kasuistik er der desuden stillet spørgsmål ved om risikoen for genital prolaps stiger efter en RMS pga. den svækkede bækkenbundsmuskulatur, men dette har ikke tidligere været undersøgt.

Formålet med denne afhandling var at øge vores viden om urogynækologiske problemstillinger hos kvinder med en RMS. Mere specifikt ønskede vi at undersøge prævalensen af UI og faktorer associeret med UI samt at undersøge effekten af bækkenbundstræning (BBT) med eller uden intravaginal elektrisk stimulation (IVES) på UI hos kvinder med en RMS. Desuden ønskede vi at undersøge forekomsten af genital prolaps efter en RMS og evaluere behovet for specialiserede urogynækologiske konsultationer hos disse kvinder.

Studie I var et tværsnitsstudie. Data på de 609 inkluderede kvinder blev indhentet fra standardiserede spørgeskemaer, som blev udfyldt i en database af den behandlende læge ved hvert patient-besøg i RMS-klinikken. Prævalensen af daglig til månedlig UI var 49 % og UI var forbundet med nedsat livskvalitet, ugift/ikke-samboende status og nedsat mobilitet. I tværsnits studiet, **Studie II**, fik 98 kvinder med en RMS en urogynækologisk konsultation. Urogynækologiske symptomer blev registeret og forekomsten af genital prolaps blev undersøgt ved en gynækologisk undersøgelse. Vi fandt at 21 % havde genital prolaps og at genital prolaps var associeret med stigende alder, vaginale fødsler, paritet og menopause, men ikke med sværhedsgraden af eller opfølgningstiden efter RMS. Der var en høj forekomst af andre urogynækologiske problemstillinger, herunder 63-71 % med UI, blære- eller tarmtømnings-problemer. I det randomiserede **Studie III** undersøgte vi effekten af 12 ugers daglig BBT eller BBT og IVES på UI. Effektmålene inkluderede bl.a. et spørgeskema om UI, antal daglige UI-episoder og det uretrale åbningstryk målt med uretraltryks reflektometri. I alt gennemførte 26 kvinder studiet. Vi fandt at BBT+IVES ikke var bedre end BBT alene, og kun BBT forbedrede symptomerne på UI med en vedvarende effekt efter 3 måneders opfølgning.

Denne afhandling demonstrerer at selvom genital prolaps ikke er et udbredt problem efter en RMS, er symptomer på UI meget hyppige i denne gruppe af kvinder. Desuden vises det at urogynækologiske konsultationer bør inkluderes i det standardiserede opfølgningsprogram, især hos kvinder med UI efter en RMS. Endeligt demonstreres det at BBT uden IVES er en effektiv konservativ behandling af UI hos kvinder med en inkomplet RMS.

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Appendix

Paper I

Prevalence of urinary incontinence in women with spinal cord injury.

Elmelund M, Klarskov N, Biering-Sørensen F.

Spinal Cord. [E-pub ahead of print 12 June 2018. doi: 10.1038/s41393-018-0157-0].

Paper II

Pelvic organ prolapse and urogynecological assessment in women with spinal cord injury.

Elmelund M, Biering-Sørensen F, Bing MH, Klarskov N.

Spinal Cord. [E-pub ahead of print 6 October 2018. doi: 10.1038/s41393-018-0181-0].

Paper III

The effect of pelvic floor muscle training and intravaginal electrical stimulation on urinary incontinence in women with incomplete spinal cord injury: An investigator-blinded parallel randomized clinical trial.

Elmelund M, Biering-Sørensen F, Due U, Klarskov N.

Int Urogynecol J. [E-pub ahead of print 24 March 2018. doi: 10.1007/s00192-018-3630-6].

Questionnaires:

International Consultation on Incontinence Questionnaire – Urinary Incontinence – Short Form (ICIQ-UI-SF)

International Consultation on Incontinence Questionnaire – Overactive Bladder (ICIQ-OAB)

International Spinal Cord Injury Quality of Life Basic Data Set (SCI-QoL)

Patient Global Impression of Improvement (PGI-I)

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ISCoS The International Spinal Cord Society

ARTICLE

Prevalence of urinary incontinence in women with spinal cord injury

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Abstract

Study Design Cross-sectional study.

Objectives There is a knowledge gap on urinary incontinence in women with spinal cord injury. Hence, the aim of this study was to determine the prevalence and conditions associated with urinary incontinence in this population.

Setting Clinic for Spinal Cord Injuries, Rigshospitalet, Denmark.

Methods Women with a spinal cord injury between September 1999 and August 2016, who attended a consultation in our clinic during August 2010–August 2016, were included. Data were obtained from an electronic medical record database, in which standardized questionnaires were filled out by the treating physician during the consultation. Data regarding the injury, bladder function, mobility, spousal/cohabitation status, and quality of life were obtained from the most recently filled-out questionnaires.

Results Of the 609 included women, 299 (49%) experienced urinary incontinence: 27% daily, 13% weekly, and 9% monthly. The odds of urinary incontinence increased if the woman used a wheelchair permanently (odds ratio (OR) 2.16, 95% confidence interval (CI) 1.24–3.77), needed aids to walk (OR 1.73, 95% CI 1.08–2.76), and if the woman's spousal/cohabitation status was unmarried/not living with a partner (OR 1.60, 95% CI 1.11–2.32). Conversely, the odds of urinary incontinence decreased if the woman used an indwelling catheter (OR 0.35, 95% CI 0.18–0.67) compared with normal bladder-emptying method. Finally, incontinence was associated with decreased quality of life on the general, physical, and emotional domain.

Conclusions Urinary incontinence is a prevalent problem in women with spinal cord injury, affecting half of the population, and it is associated with impaired mobility, unmarried/non-cohabiting status, and reduced quality of life.

Introduction

Urinary incontinence (UI) frequently occurs as a consequence of neurogenic bladder dysfunction following a spinal cord injury (SCI) where neurogenic detrusor overactivity can result in reflex UI, acontractile detrusor can result in overflow UI, and underactive urethral sphincter and paralysis of the pelvic floor muscles can result in neurogenic stress UI [1]. Despite the abundance of many secondary health conditions following SCI, persons living with an SCI have ranked urinary problems as the most important health problem after injury [2, 3]. The prevalence of UI in persons with SCI has been investigated in several studies with results varying from 34% in a Korean study [4] to 73% in a Turkish study [3]. However, all studies were conducted primarily in male SCI persons, with the largest female proportion being no more than 35% [2], and the majority was conducted in selected groups of persons with SCI.

The reported annual incidence rate of SCI varies from 10 to 58 per million for traumatic injuries [5, 6] and from 11 to 26 per million for non-traumatic injuries [7, 8], where women comprise 18–28% of the traumatic and approximately half of the non-traumatic SCI population [5, 8]. Given the substantial proportion of women in the SCI population and the fact that there are fundamental anatomical and functional differences between the genders with a much higher prevalence of UI in women compared with men in general, there is a need for studies investigating UI and conditions regarding UI after SCI in women alone.

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Hence, the aim of this study was to investigate the prevalence of symptomatic UI and conditions associated with UI including quality of life (QoL) in women with an SCI.

Methods

Study design and participants

This cross-sectional database study was conducted in August 2016. The Clinic for Spinal Cord Injuries, Rigshospitalet is one of two national clinics where all persons with an SCI in Denmark are followed from the time of diagnosis. All patients are offered routine follow-up consultations every 2nd year lifelong. In this study, data were collected for all women registered in the Clinic for Spinal Cord Injuries, Rigshospitalet, Denmark with an SCI sustained during September 1999–August 2016, who attended a consultation in the clinic during August 2010–August 2016. During each consultation, the treating physician interviews the patient according to standardized questionnaires. If the physician had failed to fill out the standardized routine question regarding UI from the questionnaire International SCI Lower Urinary Tract Function Basic Data Set [9], the woman was excluded from the study.

Data collection

Data were obtained from the structured multidisciplinary electronic medical record database, spinal cord injury database (SCIBase) [10]. The SCIBase was established in September 1999 and contained internationally validated questionnaires and data, for example, International Standards for Neurological and Functional Classification of Spinal Cord Injury (ISNCSCI), 1996 [11] and Levi and Ertzgaard [12]. When updates of the ISNCSCI by Kirschblum et al. [13] and various International SCI Data Sets were developed, these were included as well. The injury was classified according to the International SCI Core Data Set after its publication in 2006 [14]. If symptoms had changed after the initial assessment, a re-evaluation of the injury was normally conducted. In 2014, questions regarding non-traumatic etiology of injury was added, according to the simultaneously published dataset for non-traumatic SCI [15], and in August 2010, the International SCI Lower Urinary Tract Function Basic Data Set [9] was added to the database. Information regarding date, etiology, level, and completeness of injury by the ISNCSCI [13], bladder function, UI, and treatment of UI were collected from the most recently filled-out questionnaires. The definition of UI was based on the questionnaire from the International SCI Lower Urinary Tract Function Basic Data Set [9]: "Any involuntary urine leakage (incontinence) within the last three months" with the following answer options: "Yes, average daily," "Yes, average weekly," "Yes, average monthly," "No," and "Not relevant". Women were divided into two groups, where the women answering yes to daily, weekly, or monthly UI were included in the UI group and the women answering no or not relevant were included in the no UI group. The primary bladder emptying methods were reported in the study in accordance with the International SCI Lower Urinary Tract Function Basic Data Set [9]. Normal bladder emptying method was defined as voluntary initiation of micturition without reflex stimulation or compression of the bladder, which does not presume entirely normal function. In addition to the data obtained from the SCIBase, information regarding treatments with vesical botulinum toxin injections was obtained from the Department of Urology, Rigshospitalet, where the treatments were carried out.

In April 2014, the International SCI Quality of Life Basic Data Set was added to the SCIBase [16]. The questionnaire was developed specifically to persons with an SCI and contains three questions regarding the satisfaction with (1) life as a whole, (2) physical health, and (3) psychological health, emotions, and mood in the past 4 weeks. Answers are given as numbers ranging from 0 to 10, where 0 is completely dissatisfied and 10 is completely satisfied. The most recently filled-out questionnaire was obtained in this study.

Finally, the number of urinary tract infections within the last 12 months, smoking status, alcohol consumption, spousal/cohabitation status, and mobility were obtained from the most recently filled-out questionnaires. Spousal/cohabitation status was defined as "Married/cohabiting partner" if the woman was married or living together with a partner and "Unmarried/no cohabiting partner" if the woman was unmarried, separated, or widowed and did not live with a partner. Mobility was defined as "Walks without walking aids" if the woman never used devices to walk, "Walks with walking aids" if the woman was able to walk with a walking frame, crutches, canes, or occasional used a wheelchair, and "Permanent wheelchair user" if the woman used a manual or electric wheelchair permanently.

To test the accuracy of the provided answers in the database, the answer "use of condom catheter/sheath" as collecting appliances for UI was evaluated.

Statistical analysis

Comparisons between groups in Tables 3 and 4 were conducted using Fisher's exact test for categorical variables. Student's *t* tests were used for normally distributed

continuous variables, and Mann–Whitney *U* tests were used for non-normally distributed continuous variables. In Fig. 2, the differences in QoL scores according to UI frequencies were investigated using the non-parametric Kruskal–Wallis test. As age is known to increase the risk of UI in women [17], each covariate was adjusted for age in a bivariate logistic regression (Table 5). Second, a multivariate logistic regression analysis was conducted including the variables with $p < 0.2$ in the bivariate logistic regression analyses. Model assumptions of linearity were tested for the quantitative variables by including a quadratic value of the variable in each model. All analyses were conducted using SAS version 7.1 (SAS Institute Inc., Cary, NC, USA), and a p value <0.05 was considered statistically significant.

Results

Study population

Of the 733 eligible women identified, a total of 124 women were excluded due to missing data on the question

Table 1 Baseline characteristics

Characteristics	Number	Included women ($n = 609$)	Number	Excluded women ($n = 124$)
Mean age (years)	609	53.9 (±19.7)*	80	60.1 (±20.3)*
Mean age at injury (years)	529	42.2 (±23.8)*	88	52.1 (±23.9)*
Median follow-up (years)	529	7.2 (2.7–16.4)*	70	3.5 (0.4–7.9)*
Etiology of injury	440		77	
Traumatic, sports		14 (3%)		0
Traumatic, assault		2 (0.5%)		1 (1%)
Traumatic, transport		35 (8%)		8 (10%)
Traumatic, fall		53 (12%)		9 (12%)
Traumatic, other cause		9 (2%)		1 (1%)
Non-traumatic, congenital		57 (13%)		6 (8%)
Non-traumatic, degenerative		97 (22%)		24 (31%)
Non-traumatic, benign tumor		47 (11%)		12 (16%)
Non-traumatic, malign. tumor		7 (2%)		0
Non-traumatic, vascular		36 (8%)		6 (8%)
Non-traumatic, infection		12 (3%)		2 (3%)
Non-traumatic, other cause		71 (16%)		8 (10%)
Neurological level of injury	424		86	
Cervical		193 (46%)		42 (49%)
Thoracic		152 (36%)		32 (37%)
Lumbar		69 (16%)		10 (12%)
Sacral		10 (2%)		2 (2%)
Completeness (AIS)	403		73	
A		30 (7%)		4 (6%)
B		15 (4%)		4 (6%)
C		39 (10%)		13 (18%)
D		316 (78%)		52 (71%)
E		3 (1%)		0
Classification of injury by AIS and NLI	403		73	
AIS ABC, C1–C8		26 (6%)		9 (12%)
AIS ABC, Th1–S5		58 (14%)		12 (16%)
AIS D, any NLI		316 (78%)		52 (71%)
AIS E		3 (1%)		0

AIS American Spinal Injury Association (ASIA) impairement scale, *NLI* neurological level of injury

Results are presented in mean (±SD), median (interquartile range), or in total numbers (%)

* $p < 0.05$

Table 2 Missing data and time interval between answering of the urinary incontinence question and other questions

Question	*N* with missing data	*N* with deviation in time from the UI answer	Median (range) time deviation in years
Spinal cord injury characteristics			
Neurological level of injury[a]	185 (30%)	—	—
Completeness of injury[a]	206 (34%)	—	—
Traumatic vs. non-traumatic etiology of injury[a]	10 (2%)	—	—
Specified etiology of injury[b]	169 (28%)	—	—
Lower urinary tract			
Any involuntary urine leakage (UI)[c]	NA	NA	NA
Bladder emptying method[c]	21 (3%)	0	NA
Self-supporting bladder empty	29 (5%)	0	NA
Awareness of the need to empty the bladder[c]	92 (15%)	0	NA
Daily voluntary bladder emptyings[c]	175 (29%)	0	NA
Collecting appliances for UI[c]	156 (26%)	0	NA
Drugs for urinary tract in the last year[c]	74 (12%)	0	NA
Quality of life[d]	361 (59%)	41 (17%)	−0.9 (−2.0 to 2.9)
Treated urinary tract infections in the last year	164 (27%)	125 (28%)	−2.2 (−9.8 to 1.9)
Mobility	31 (5%)	58 (10%)	−1.0 (−5.1 to 2.9)
Smoking status	30 (5%)	102 (18%)	−1.3 (−6.5 to 2.9)
Alcohol consumption	28 (5%)	92 (16%)	−1.2 (−6.5 to 2.9)
Spousal/cohabitation status	26 (4%)	77 (13%)	−1.1 (−5.1 to 2.9)

UI urinary incontinence, *SCI* spinal cord injury, *NA* not applicable

[a]According to International standards for neurological classification of spinal cord injury (revised 2011) [13], and International spinal cord injury core data Set [14]

[b]According to International spinal cord injury data sets for non-traumatic spinal cord injury [15]

[c]According to International spinal cord injury lower urinary tract function basic data set [9]

[d]According to International spinal cord injury quality of life basic data set [16]

regarding UI. Hence, 609 women were included in the study. The excluded women did not differ in level, completeness, type, and etiology of injury compared with the included women. However, compared with the included women, the excluded women were significantly older at the last follow-up visit and at time of injury, and they had a significantly shorter median follow-up period (Table 1). The degree of missing data and the timeframe according to when the questionnaires were filled out are shown in Table 2.

Prevalence of UI

A total of 299 women (49%) reported of symptomatic UI varying from daily to monthly. When divided by frequency, 166 (27%) experienced UI daily, 79 (13%) experienced UI weekly, and 54 (9%) experienced UI monthly (Fig. 1). The answer "Not relevant" was applied in 12 women (2%), of whom 9 used an indwelling catheter (5 suprapubic and 4 transurethral), 2 used clean intermittent catheterization, and 1 used an unknown bladder emptying method. To the question regarding collecting appliances of UI, 11 of the 12 women did not use diapers/pads, and the 12 women were included in the continent group in the following analysis.

There were no positive answers to the question "use of condom catheter/sheath" as collecting appliances for UI among the included women.

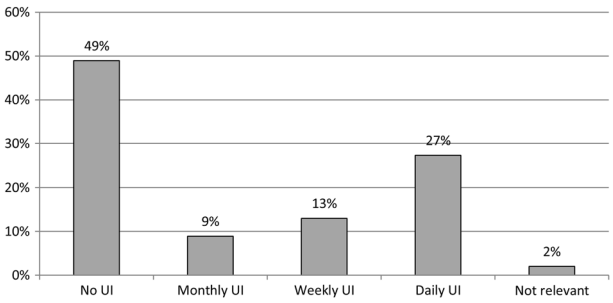

Fig. 1 Urinary incontinence within the last 3 months among the included women ($n = 609$). *UI* urinary incontinence

Table 3 Characteristics associated with frequency of urinary incontinence

Characteristics	Number	No UI	Weekly/monthly UI	Daily UI
Mean age (years)	609	52.1 (50.0–54.3)	50.6 (47.3–53.9)	59.9 (56.9–62.8)*
Mean age at injury (years)	529	40.7 (37.9–43.4)	36.1 (31.8–40.4)	49.6 (45.8–53.5)*, **
Median follow-up (years)	529	6.5 (2.7–14.7)	9.6 (5.0–21.6)***	6.6 (2.1–13.8)*
Type of injury	599			
Traumatic		94 (31%)	34 (26%)	41 (25%)
Non-traumatic		213 (69%)	97 (74%)	120 (75%)
Etiology of injury	440			
Spinal cord injury		197 (87%)	80 (79%)	106 (94%)*
Myelomeningocele		29 (13%)	21 (21%)	7 (6%)*
Classification of injury by AIS and NLI	403			
AIS ABC, C1–C8		16 (8%)	3 (4%)	7 (7%)
AIS ABC, Th1–S5		30 (14%)	15 (18%)	13 (12%)
AIS DE, any NLI		167 (78%)	67 (79%)	85 (81%)
Level of Injury	424			
Tetraplegia		109 (49%)	34 (39%)	50 (44%)
Paraplegia		115 (51%)	53 (61%)	63 (56%)
Primary bladder emptying method	588			
Normal		163 (54%)	61 (48%)	93 (58%)**
IC[a]		67 (22%)	37 (29%)	33 (21%)**
Indwelling catheter[b]		51 (17%)	15 (12%)	12 (8%)**
Other method(s)[c]		20 (7%)	15 (12%)	21 (13%)**
Mobility	578			
Walks without aids		99 (34%)	34 (26%)	31 (20%)**
Walks with aids		104 (35%)	51 (40%)	73 (47%)**
Wheelchair user		91 (31%)	44 (34%)	51 (33%)**
Spousal/cohabitation status	583			
Married/cohabiting partner		163 (55%)	60 (46%)	71 (46%)
Unmarried/no cohabiting partner		136 (45%)	70 (54%)	83 (54%)
Smoking status	579			
Never		157 (53%)	71 (56%)	83 (54%)
Former smoker		82 (28%)	29 (23%)	40 (26%)
Current smoker		59 (20%)	27 (21%)	31 (20%)
Alcohol consumption	581			
≥5 units per day		1 (0.3%)	0	1 (1%)
1–4 units per day		23 (8%)	12 (9%)	17 (11%)
Not daily		240 (80%)	102 (80%)	107 (70%)
Never		36 (12%)	14 (11%)	28 (18%)

Results are presented in mean (±SD), median (interquartile range), and numbers (%)

UI urinary incontinence, *IC* intermittent catheterization, *AIS* American Spinal Injury Association (ASIA) impairement scale, *NLI* neurological level of injury

*Significant difference between the daily UI group and the weekly/monthly UI group; **significant difference between the no UI group and the daily UI group; ***significant difference between the no UI group and the weekly/monthly group

[a]Including self IC and IC by attendant

[b]Including urethral and suprapubic indwelling catheter

[c]Including bladder expression, bladder reflex triggering, Bricker conduit, ≥2 primary emptying methods, and other methods

Table 4 Bladder characteristics according to urinary incontinence

Characteristics	Number	UI	Number	No UI	*p* value
Primary bladder emptying method	287		301		—
Normal voiding		154 (54%)		163 (54%)	
Self IC		61 (21%)		64 (21%)	
IC by attendant		9 (3%)		3 (1%)	
Indwelling transurethral catheter		12 (4%)		23 (8%)	
Indwelling suprapubic catheter		15 (5%)		28 (9%)	
Voluntary reflex triggering		6 (2%)		0	
Involuntary reflex triggering		4 (1%)		0	
Bladder expression[a]		7 (2%)		5 (2%)	
Other method		3 (1%)		4 (1%)	
≥2 primary emptying methods		16 (5%)		11 (4%)	
Self-supporting bladder emptying	285		295		0.7
Yes		233 (82%)		246 (83%)	
No		52 (18%)		49 (17%)	
Awareness of the need to empty the bladder[b]	251		266		**0.021**
Yes, directly		180 (72%)		189 (71%)	
Yes, indirectly		43 (17%)		29 (11%)	
No		28 (11%)		48 (18%)	
Median daily voluntary bladder emptyings	221	7 (6–8)	213	6 (5–7)	**<0.001**
Collecting appliances[c]	279		174		
Yes, diaper/pads		169 (61%)		17 (10%)	**<0.001**
Yes, ostomy bag		0		7 (4%)	**0.015**
Yes, other methods		60 (22%)		12 (7%)	—
No		54 (19%)		141 (81%)	**<0.001**
Drugs for urinary tract in last year[c]	269		266		
Yes, bladder relaxant drugs		37 (14%)		19 (7%)	**0.011**
Yes, sphincter relaxant drugs		5 (2%)		2 (1%)	0.3
Yes, antibiotics unspecified		107 (40%)		90 (34%)	0.08
Prophylactic		17 (6%)		19 (7%)	0.9
Treatment of urinary tract infection		91 (34%)		76 (29%)	0.10
Yes, other		10 (4%)		8 (3%)	—
No		130 (48%)		157 (59%)	0.08
Vesical botulinum toxin injections[d]		28 (10%)		18 (7%)	0.12
Treated urinary tract infections in last year	229	1 (0–3)	216	1 (0–2)	0.7

UI urinary incontinence, *IC* intermittent catheterization

[a]Including Valsalvas manouvre and Credé

[b]"Yes, directly" refers to any kind of bladder sensation, "Yes, indirectly" refers to a nonspecific bladder sensation, for example, by abdominal fullness, sweating, or spasticity, and "No" refers to absent bladder sensation

[c]Each person can have more than one answer

[d]Treatment with vesical botulinum toxin injections at any time

Covariates associated with UI

Differences between the groups of women with daily UI, weekly or monthly UI, and no UI are shown in Table 3. The women with daily UI were significantly older at follow-up, at the time of injury, and had a shorter follow-up period compared with the women with weekly/monthly UI. In addition, a larger proportion of women with myelomeningocele as etiology of injury experienced weekly/monthly UI instead of daily UI. When comparing the continent group with the weekly/monthly UI group, the groups only differed on median follow-up period, whereas the continent group and the daily UI group differed on mean age at injury, bladder emptying method, and mobility.

Table 5 Risk of urinary incontinence in logistic regression analysis

Parameter	Number	Bivariate[a]		Multivariate[b]	
		OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (per year)	609	1.01 (1.00–1.02)	**0.023***	1.01 (1.00–1.02)	0.06
Type of injury	599				
Traumatic		1.0 (ref.)		1.0 (ref.)	
Non-traumatic		1.27 (0.89–1.82)	0.19	1.46 (0.97–2.19)	0.07
Primary bladder emptying method	588				
Normal		1.0 (ref.)		1.0 (ref.)	
IC[c]		1.26 (0.83–1.90)	0.28	0.90 (0.56–1.46)	0.7
Indwelling catheter[d]		0.49 (0.29–0.83)	**0.008**	0.35 (0.18–0.67)	**0.002**
Other method(s)[e]		1.81 (1.00–1.02)	0.05	1.99 (1.02–3.87)	**0.044**
Mobility	578				
Walks without aids		1.0 (ref.)		1.0 (ref.)	
Walks with aids		1.64 (1.07–2.52)	**0.022**	1.73 (1.08–2.76)	**0.022**
Wheelchair user		1.43 (0.92–2.24)	0.11	2.16 (1.24–3.77)	**0.007**
Spousal/cohabitation status	583				
Married/cohabiting partner		1.0 (ref.)		1.0 (ref.)	
Unmarried/no cohabiting partner		1.44 (1.04–2.00)	**0.030**	1.60 (1.11–2.32)	**0.012**
Smoking status	579				
Never		1.0 (ref.)		1.0 (ref.)	
Former smoker		0.76 (0.51–1.14)	0.18	0.71 (0.45–1.11)	0.13
Current smoker		0.99 (0.65–1.52)	1.0	0.96 (0.60–1.55)	0.9
Alcohol consumption	581				
Not daily/never		1.0 (ref.)			
≥1 unit per day		1.22 (0.69–2.17)	0.5		
Classification of injury by AIS and NLI	403				
AIS DE, any NLI		1.0 (ref.)			
AIS ABC, Th1–S5		1.08 (0.61–1.91)	0.8		
AIS ABC, C1–C8		0.66 (0.29–1.51)	0.3		
Etiology	440				
Spinal cord injury		1.0 (ref.)			
Myelomeningocele		1.34 (0.72–2.48)	0.4		
Follow-up	609				
<1 year		1.0 (ref.)			
1–9 years		0.89 (0.58–1.35)	0.6		
≥10 years		1.09 (0.70–1.70)	0.7		
Age at injury (per year)	529	1.00 (0.98–1.01)	0.5		

OR odds ratio, *IC* intermittent catheterization, *AIS* American Spinal Injury Association (ASIA) impairment scale, *NLI* neurological level of injury

*Univariate analysis

[a]Adjusted for age

[b]Multivariate analysis including 521 women

[c]Including self IC and IC by attendant

[d]Including urethral and suprapubic indwelling catheter

[e]Including bladder expression, bladder reflex triggering, Bricker conduit, ≥2 primary emptying methods, and other methods

The UI groups were pooled and compared with the continent group in Tables 4 and 5. A larger proportion of women in the UI group had indirect bladder sensation and a smaller proportion had no bladder sensation, the number of daily voluntary bladder emptyings was higher and more women used diapers/pads and bladder relaxant

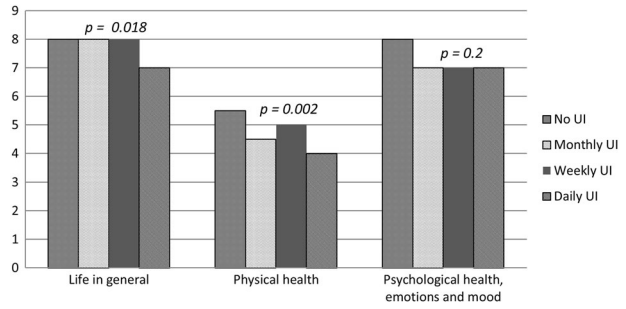

Fig. 2 Quality of life and frequency of urinary incontinence ($n = 246$). Women's satisfaction in the past 4 weeks, where 0 is completely dissatisfied and 10 is completely satisfied. *UI* urinary incontinence

drugs compared with the women in the no UI group (Table 4).

In the multivariate logistic regression analysis, the bladder emptying method, mobility, and spousal/cohabitation status were associated with UI (Table 5). Women were less likely to be incontinent if they used indwelling urethral or suprapubic catheter compared with women using normal bladder emptying method (OR 0.35, 95% CI 0.18–0.67) and more likely to be incontinent if they used another method (reflex triggering/bladder expression/other methods) compared with women using normal bladder emptying method (OR 1.99, 95% CI 1.02–3.87). Compared with women walking without devices, UI was more likely in women walking with aids (OR 1.73, 95% CI 1.08–2.76) or women using a wheelchair (OR 2.16, 95% CI 1.24–3.77). Finally, UI was associated with unmarried, separated, or widowed status compared with married women or women living together with a partner (OR 1.60, 95% CI 1.11–2.32).

QoL and UI

The International SCI QoL Basic Data Set [16] was filled out by 246 women (40%). Compared with the group of continent women ($n = 128$), the women with UI ($n = 118$) reported a lower median satisfaction score over the last 4 weeks with their life in general (7 (interquartile range (IQR) 5–8) vs. 8 (IQR 6–9), $p = 0.012$), with their physical health (5 (IQR 3–7) vs. 5.5 (IQR 4–8), $p = 0.001$) and with their psychological health, emotions, and mood (7 (IQR 5–8) vs. 8 (IQR 5–9), $p = 0.039$).

The median scores of the questionnaire according to the frequency of UI are shown in Fig. 2.

Discussion

In this large cross-sectional database study, we found that approximately half of the female SCI population experience symptomatic UI with the majority experiencing daily UI. UI was associated with impaired mobility, unmarried/non-cohabiting status, use of non-indwelling catheter, and reduced QoL. A prevalence of 49% of whom the majority experience daily UI is surprisingly high given the fact that the included female population are already followed at a highly specialized SCI clinic offering regular follow-up visits every second year.

The prevalence of symptomatic UI in able-bodied westernized populations shows a vide variability with results varying from 25% to 46% [17–19], mainly due to differences in the definitions of UI, design of the study, and included study populations. Though the 49% prevalence of UI in women with SCI is not much higher than the reported prevalence of 46% in able-bodied women found in one study [19], the severity of UI in women with SCI differs from the general female population. In a Norwegian questionnaire-based study defining UI as "any" UI with no time limits, only 20% of the incontinent women experienced daily UI compared with 56% in our study [17]. In addition, the able-bodied populations in the questionnaire-based prevalence studies are community-dwelling women who have not necessarily consulted a medical doctor with their UI problems, whereas the SCI women in this study were already followed at a highly specialized clinic that offers treatment of UI and bladder emptying problems.

To date, the prevalence of UI in SCI persons has only been investigated in studies including both men and women, where women comprise a minority of the population. Hansen et al. [20] investigated the prevalence of UI using the same definition of UI as in the present study. In 236 traumatic SCI individuals, of whom 18% were women, the overall self-reported prevalence of UI was 43% and the prevalence of daily UI was 20%, which is a little lower than in the present study [20]. Two other studies investigating UI in mixed-gender SCI populations found that women had the highest prevalence of UI [3, 21].

We found no association between UI and level or completeness of injury, type of injury, age at injury, and follow-up period after injury in the logistic regression analysis, which is in accordance with most other studies [2, 3]. Though no association was found between the American Spinal Injury Association (ASIA) impairement scale (AIS) score and UI in our study, the odds of UI increased significantly with impaired mobility in the multivariate analysis. It has previously been proposed that functional impairment can lead to UI due to difficulties in getting to the bathroom and removing clothes [22]. In terms of etiology of injury, myelomeningocele was associated with weekly/monthly UI compared with daily UI, which could be explained by the fact that the women with myelomeningocele were younger at follow-up than the women with

non-myelomeningocele in this study (median age 26 years vs. 61 years, respectively).

Further, UI was less likely to occur if the woman used an indwelling catheter compared with normal bladder emptying method, but due to the cross-sectional design of this study, the causality cannot be established. The association between UI and unmarried/non-cohabitation status and reduced QoL on the general, physical, and emotional domain underlines the impact of UI on the woman's general life situation and well-being. The QoL questionnaire was not specific to the symptoms of UI, but was developed as a tool to measure the general QoL in persons with SCI, who face a large variability of complications following an SCI. The fact that UI is significantly associated with reduced QoL on this general QoL questionnaire underlines the impact of UI in this population. The results are in agreement with the study by Liu et al. [23], showing a reduced QoL on the mental, emotional, and social domain in incontinent SCI persons. In addition, UI has been reported as a major physical problem associated with sexual activity in SCI persons [24] and it is associated with depression and loneliness in neurologically intact persons [25], which could explain the association between UI and unmarried/non-cohabitation status found in this study.

Fifteen percent of the study population had received treatment for neurogenic detrusor overactivity (9% used bladder relaxant drugs and 8% had received vesical botulinum toxin injection previously). The limited use could be explained by the fact that a large proportion of the female incontinence is caused by stress UI, which would require other treatment options that were not registered in this study.

To date, this is the largest study investigating the prevalence of UI in SCI persons, and the first to investigate UI in women alone. It is a strength that data were obtained from a database including only internationally standardized SCI-specific questionnaires, which makes the study results robust and comparable to future studies. Second, data were extracted from a database that contained information on all women with an SCI followed in the Clinic for SCI, Rigshospitalet, which covers nearly half of the female SCI population living in Denmark. This design is unique as most other SCI studies were conducted in selected groups of SCI persons who were referred to or treated at tertiary clinics. Nonetheless, the study also has some limitations. First, if a woman with SCI had not visited a clinic between 2010 and 2016, she was not included in this study. As all persons with SCI in the eastern part of Denmark are invited to attend follow-up visits in the clinic every second year, it is assumed that most of the population was seen in the clinic in this period; however, it is a limitation that the complete list of women with SCI living in the eastern part of Denmark was not obtainable. Second, 17% of the identified population had missing data on the UI question and were excluded. The excluded women were comparable to the included women regarding the type of injury, but were of older age. As age is known to increase the risk of UI in women [17], the prevalence of UI could be underestimated in this study. Second, the study was conducted on data from a database where mistakes could occur during several processes, for example, when the information was entered in the database or during extraction of the data. To investigate the magnitude of this problem, the authors evaluated the answers to the condom-catheter question, but the lack of positive answers suggests a good accuracy of the database. Third, there were no information on UI prior to injury or body mass index and parity, which are known risk indicators of UI, nor were we able to distinguish between the types of UI based on urodynamic investigations.

As the majority of the included women had an incomplete injury, and 78% were classified with an AIS D, it could be argued that there is an overrepresentation of incomplete injuries in this study. On the other hand, as this study included all women with an SCI during 1999–2016, who attended a regular follow-up visit in our clinic during 2010–2016, the study population merely reflects the group of women with a newly sustained SCI living in Denmark. This is in accordance with studies demonstrating a tendency towards an increase in incomplete injuries over time, with the highest proportion of incomplete injuries among the non-traumatic injuries [26, 27].

In conclusion, half of the women with an SCI are urinary incontinent, of whom the majority experience UI daily, and UI is associated with impaired mobility, unmarried/non-cohabitation status, and reduced QoL. Clinicians should bear in mind that UI is a prevalent and severe problem in women with SCI that can potentially be treated at a specialized urogynecological or urological department in collaboration with SCI-specialized clinicians. It would be interesting for future studies to evaluate urogynecological treatments of UI in women with SCI.

Author contributions ME was responsible for designing and planning of the study, data acquisition, data analysis and interpretation, and writing the report. NK contributed to the design and planning of the study, interpretation of the results, and providing feedback on the report. FB-S contributed to the design and planning of the study, data acquisition, interpretation of the results, and proving feedback on the report.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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ARTICLE

Pelvic organ prolapse and urogynecological assessment in women with spinal cord injury

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Abstract

Study design Observational cross-sectional study.

Objectives Due to weakened pelvic floor muscles, the risk of pelvic organ prolapse (POP) may increase after a spinal cord injury (SCI); hence, the aim of this study was to investigate the occurrence of POP after SCI and to evaluate the need for urogynecological consultations offered to women with SCI.

Setting Clinic for Spinal Cord Injuries, Rigshospitalet, Denmark.

Methods Women with SCI who visited our SCI-clinic during January 2013−January 2018 were offered a specialized urogynecological consultation. Any symptoms of POP, urinary/fecal incontinence, or bladder/bowel emptying problems were registered, and POP was classified according to the POP quantification system during a pelvic examination. Differences in baseline characteristics between women with POP stage 0−1 and POP stage ≥2 were investigated.

Results A total of 98 women were included in the study. Fourteen women (14%) reported POP symptoms and 21 women (21%) had anatomical POP stage ≥2. The group with POP stage ≥2 had a significantly higher age, higher parity, more with vaginal delivery, and more postmenopausal women, but the groups did not differ on median time after injury, neurological level, and completeness of injury. A total of 71% experienced urinary incontinence, 27% experienced fecal incontinence, 63% experienced bladder emptying problems, and 70% experienced bowel emptying problems. Consequently, 65% received treatment.

Conclusions Women with SCI are not in increased risk of developing anatomical POP. Nonetheless, the high occurrence of other urogynecological issues and the high treatment-rate supports the need for specialized urogynecological consultations offered to women with SCI.

Introduction

It is well-known that women with mobility impairments are less likely to receive adequate gynecological screening and care [1]. This, combined with a changed sensibility after injury, raises a concern if women with spinal cord injury (SCI) are in higher risk of having undiagnosed gynecological disorders than able-bodied women.

Pelvic organ prolapse (POP) is a common anatomical condition, affecting up to 50% of an adult female population, and it is well-documented that the risk of POP increases with advancing age, parity, and vaginal births [2]. In a case report by Wan and Liu [3], the story of a 37-year old nulliparous spinal cord injured woman with a stage 3 uterine prolapse was brought to attention, and it has been questioned if the risk of POP increases after a SCI due to weakness of the pelvic floor muscles, peripheral nerve damage and potential use of increased abdominal pressure during bladder and bowel emptying [3, 4]. Though POP is a benign condition in able-bodied women, the complications of POP in women with SCI may be more comprehensive as the SCI-associated bladder emptying problems and potential urinary retention may be aggravated by an obstructing POP, that can go unnoticed due to reduces sensibility. Nonetheless, there is a complete knowledge-gap regarding POP in women with SCI [5].

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The Clinic for Spinal Cord Injuries, Rigshospitalet is one of two clinics in Denmark where all persons with SCI are followed every second year from the time of diagnosis. Besides regular consultations with SCI-specialized physicians, the follow-up program includes standardized urological evaluation and treatment of lower urinary tract complications. However, urogynecological assessments in the women with SCI is not a part of the follow-up program. Hence, the aim of this study was to evaluate if specialized urogynecological consultations and treatments should be offered to women with SCI in addition to the standardized urological and SCI-specialized follow-up program. A secondary aim was to investigate the occurrence of POP and other urogynecological issues in women with SCI and to examine risk factors associated with anatomical POP.

Methods

Study design and participants

While attending a routine follow-up consultation or during the primary admission after the injury in the Clinic for Spinal Cord Injuries, Rigshospitalet between January 2013 and January 2018, women with SCI were offered a gynecological consultation and examination by their treating physician. The gynecological consultation and examination would take place at a specialized urogynecological department, where the woman was asked if she wanted to participate in the study. This observational cross-sectional study was approved by the Danish Health Authorities and all participant provided written informed consent. Some of the women participating in this study were also included in a recently published study, investigating the prevalence UI in women with SCI from the Clinic for Spinal Cord Injuries, Rigshospitalet by use of information from the clinic's database [6].

The consultation and examination

The consultation was conducted primarily by a senior doctor specialized in the field of urogynecology. A nurse was present during the examination, and equipment facilitating transfer to and from the examination table was available. During the consultation, a medical history was obtained including parity, mode of delivery, menstrual status, previous urogynecological surgery, and current medication. In addition, the woman was asked if she ever experienced a bulge, lump, or something coming down or falling out through the vagina. If she answered yes, she was registered with symptoms of POP [7]. In addition, she was asked if she ever experienced any involuntary loss of urine (registered as symptoms of UI), any sudden compelling desire to pass urine which is difficult to defer (registered as symptoms of urgency) or any involuntary loss of feces (registered as fecal incontinence) [7]. Prior to the consultation, the woman was also asked to fill out a Danish translation of the validated International Consultation on Incontinence questionnaire, urinary incontinence, short form (ICIQ-UI-SF) [8], and a questionnaire regarding the severity of POP symptoms, originating from the internationally validated International Consultation on Incontinence questionnaire, vaginal symptoms (ICIQ-VS) [9]. Both questionnaires contain three sub-questions regarding the frequency, severity and impact of UI, or POP on quality of life, resulting in a total score ranging from 0–21 for the UI-questionnaire and 0–17 for the POP questionnaire with a higher score indicating more severe symptoms. In addition, the situations in which UI occurred were registered in the ICIQ-UI-SF questionnaire. If the woman reported of UI during effort or physical activity or on sneezing or coughing, she was diagnosed with symptomatic stress UI. Further, bladder emptying problems were registered if the woman answered yes when asked if she experienced any difficulties with voiding and/or if she used a primary bladder emptying method other than normal according to the International SCI lower urinary tract function basic data set [10]. Bowel emptying problems were registered if the woman answered yes when asked if she experienced any difficulties with bowel emptying. Finally, the woman was asked if she had a partner and if she was currently sexually active.

A pelvic examination was conducted with the woman in a supine position and included inspection of the vulva, vagina, and cervix, bimanual palpation, and an intravaginal ultrasound examination of the internal pelvic organs. The pelvic floor muscle strength was evaluated by vaginal palpation during voluntary pelvic floor muscle contraction. The muscle strength was classified as strong, normal, weak, or absent [7]. The anatomical definition of the sign of POP was evaluated during abdominal straining, and POP was classified in each vaginal compartment according to the simplified technique of the POP quantification system as described by Swift et al. [11]. The compartment with the largest stage of POP was reported in the results.

Information was obtained from medical records regarding the date, etiology, neurological level, and completeness of injury according to the American Spinal Injury Association Impairment Scale (AIS) [12–14]. Information from the most recent cytological cervical cancer screenings test was obtained. If the woman could not recall the date, this was obtained from a national pathological database. If a cervical cytology sample had not been collected within the last three years for women aged 23–49 years or within the last five years for women aged 50–64 years, as recommended in the Danish cercival cancer screenings program [15], the sample was collected during the examination.

When indicated, additional diagnostic tests were conducted and relevant treatments were offered.

Statistical analyses

The distribution of patient-reported urogynecological issues according to completeness of injury was tested using Fisher's exact test, and differences in characteristics between women with POP stage 0–1 and POP stage ≥2 were investigated using Student's *t*-test, Mann–Whitney *U*-test or Fisher's exact test. A bivariate logistic regression analysis was conducted in a subgroup of women with a history of vaginal delivery. The outcome was risk of POP stage ≥2, and the included parameters were age and follow-up period divided by <1 year, 1–5 years, and >5 years after injury. The assumption of linearity was tested for the variable age by including a quadratic value of age in the model. All analyses were conducted using SAS version 7.1 (SAS Institute Inc, Cary, NC, USA), and a p-value <0.05 was considered statistically significant.

Results

Study population

Between January 2013 and January 2018, 99 women with SCI attended the urogynecological consultation. One woman declined to participate during the consultation, and 98 women were included in the study. Demographics on the included women are shown in Table 1. During this period, ~700 women with SCI were listed as patients in the Clinic. The women included in this study were comparable with the complete group of women in terms of classification of injury (catagorized by neurological level and completeness of injury) and median age at injury (44 years vs 47 years in this study).

Senior medical doctors specialized in the field of urogynecology consulted 96 of the 98 women of whom 91 women were consulted by the same two senior doctors. Two women attended a consultation with a medical doctor in gynecological training. Among the included women, 41 had not been gynecologically examined after the onset of injury. The follow-up period ranged between 2 months and 61 years after SCI.

Patient-reported symptoms

Patient-reported urogynecological symptoms are shown in Fig. 1. The most frequently reported symptoms were bowel emptying problems (70%), bladder emptying problems (63%), UI (71%), and urgency (49%). Of the 70 urinary incontinent women, 44 presented with symptoms of stress UI. Urgency was significantly more frequent among the women with a less complete injury (AIS D), and bladder

Table 1 Demographic information on the 98 included women

Median age (years)	54 (40–67)
Median age at injury (years)	47 (24–64)
Median follow-up after injury (years)	2.3 (0.6–9.6)
Mean body mass index (kg/m^2)	26.3 (±5.9)
Median parity	2 (0–2)
Nullipara	25 (26%)
History of vaginal delivery	60 (61%)
Women with parity after injury [a]	9 (9%)
Menopause	58 (59%)
Hysterectomy	8 (8%)
Previous prolapse surgery	4 (4%)
Receiving treatment for UI [b]	22 (22%)
Receiving HRT	2 (2%)
Neurological level of injury	
Cervical	34 (37%)
Thoracic	29 (32%)
Lumbar	26 (29%)
Sacral	2 (2%)
Completeness (AIS)	
A	9 (11%)
B	1 (1%)
C	7 (8%)
D	68 (80%)
Classification of injury by NLI and AIS	
C1-C8, AIS ABC	6 (7%)
Th1-S5, AIS ABC	11 (13%)
Any NLI, AIS D	68 (80%)
Etiology of injury	
Traumatic, sports	2 (2%)
Traumatic, assault	0
Traumatic, transport	9 (9%)
Traumatic, fall	11 (11%)
Traumatic, other cause	7 (7%)
Non-traumatic, congenital	11 (11%)
Non-traumatic, degenerative	14 (14%)
Non-traumatic, benign tumor	13 (13%)
Non-traumatic, malignant tumor	3 (3%)
Non-traumatic, vascular	11 (11%)
Non-traumatic, infection	7 (7%)
Non-traumatic, other cause	10 (10%)
Mobility	
Walks without walking aids	26 (27%)
Walks with walking aids	55 (56%)
Permanent wheelchair user	17 (17%)

Results are presented in mean (±sd), median (q25–q75) or in total numbers (%). Data is incomplete regarding NLI ($n = 7$), AIS ($n = 13$), classification of injury by AIS and NLI ($n = 13$) and body mass index ($n = 19$)

AIS American Spinal Injury Association impairment scale, *NLI* neurological level of injury, *UI* urinary incontinence, *HRT* hormone replacement therapy

[a]Including five vaginal deliveries and eight cesarean sections.

[b]Including bladder relaxant drugs ($n = 19$) or vesical botulinum toxin injections within the last year ($n = 5$)

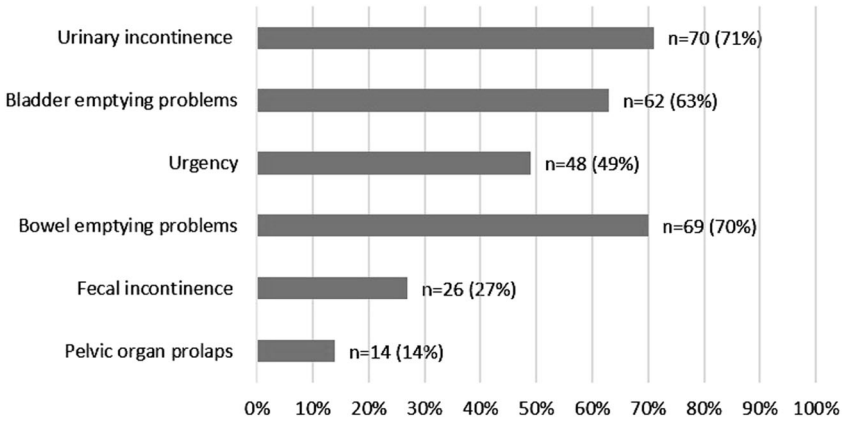

Fig. 1 Patient-reported urogynecological symptoms

emptying problems were significantly more frequent among the women with a more complete injury (AIS ABC). When the women were asked about the debut of the symptom, 3% reported of UI prior to the SCI, 4% had urgency prior to the SCI, 8% had POP symptoms prior to the SCI and no women had fecal incontinence prior to the SCI. Of the 70 incontinent women, 59 had filled out the ICIQ-UI-SF questionnaire. The mean (±SD) total score was 12.1 (±4.5). A total of 14 women reported of symptomatic POP of whom 12 had filled out the POP questionnaire. The median (interquartile range) total score was 10 (8.5–13). When asked about their bladder emptying methods as described in the International SCI lower urinary tract function basic data set [10], 39 (40%) used normal bladder emptying, 31 (32%) used clean intermittent catheterization, 10 (10%) used abdominal expression, 5 (5%) used reflex triggering, 8 (8%) had a suprapubic catheter, and 5 (5%) had a urethral cathether. In this case, normal bladder emptying method refers to voluntary initiation of micturition without reflex stimulation or compression, but does not presume entirely normal bladder function. A total of 54 women (55%) had a partner and 38 women (39%) were sexually active.

Objective findings, diagnostics, and treatments

Objective gynecological findings, diagnostics, and treatments are presented in Table 2 and Table 3. The pelvic floor muscle strength was evaluated in 90 of the 98 women and was absent in 21%, weak in 41%, normal in 24%, and strong in 13%. Among the women aged 23–64 years ($n = 60$), 18 (30%) had not followed the recommended cervical cancer screening program. A total of 48 cervical cytology samples, four biopsies, one colcoscopy, and one ovarian cancer screening with antigen CA-125 were carried out; none led to further diagnostics and treatments.

Overall, 34 women (35%) received no treatment or only counseling, 56 women (57%) received conservative treatment including medication or other conservative treatments as described in Table 3, and eight women (8%) received a surgical treatment, of whom three women underwent POP-repair surgery (one combined anterior and posterior colporrhaphy and two amputations of the cervix). POP-repair surgery was only conducted in those women who had a strong wish of surgical treatment and where pessary treatment of the POP was insufficient. Two women were bothered by pain and pelvic pressure due to an elongated collum and one woman experienced complications with conducting intermittent catheterization due to the prolapse. All three women expressed satisfaction with the post-operative result. Of the

Table 2 Objective gynecological findings

Pelvic examination	
Pelvic organ prolapse stage ≥2	21 (21%)
Anterior compartment	11 (11%)
Apical compartment	3 (3%)
Posterior compartment	15 (15%)
Abnormality of external genitals [a]	4 (4%)
Vulvar or vaginal ulcers	4 (4%)
Vaginal atrophic mucosa	26 (27%)
Other vaginal pathology [b]	6 (6%)
Cervical pathology [c]	3 (3%)
Cervical or vaginal polyp	4 (4%)
Rectal prolaps	1 (1%)
No pathology	45 (46%)
Ultrasound examination	
No pathology	81 (83%)
Ovarian cyst >30 mm	1 (1%)
Uterin fibroids	16 (16%)

[a]Including labial agglutination ($n = 1$), lichen sclerosus ($n = 1$), changes after circumsition ($n = 1$), and labia majores hypertrophy ($n = 1$)

[b]Including vaginal erythema ($n = 5$), abnormal vaginal discharge ($n = 1$), and vaginal cyst ($n = 1$)

[c]Including cervical hyperkeratosis ($n = 1$), erythroplakia ($n = 1$), and erosion ($n = 1$)

Table 3 Diagnostics and treatments

Diagnostics	
Biopsy [a]	4 (4%)
Ovarian cancer antigen CA-125 test	1 (1%)
Cervical cytology test	48 (49%)
Colposcopy	1 (1%)
Urine test strip	8 (8%)
Urine or urethral culture	2 (2%)
Residual urine measurement	12 (12%)
Free uroflowmetry	8 (8%)
Cystometry and pressure-flow study	2 (2%)
Treatments	
No treatment [b]	34 (35%)
Surgery	8 (8%)
Prolapse surgery	3 (3%)
Mid-urethral tape operation	1 (1%)
Urethral injection therapy	1 (1%)
Botulinum toxin injections	3 (3%)
Labia majores reduction [c]	1 (1%)
Medication	40 (41%)
Bladder relaxant drugs	6 (6%)
Drugs improving bowel emptying	2 (2%)
Oral antibiotic treatment	2 (2%)
Cutan antibiotics or hormone treatment	7 (7%)
Vaginal estradiol treatment	31 (32%)
Other conservative treatment	37 (38%)
Pessary for vaginal prolapse	4 (4%)
Pessary for urinary incontinence	12 (12%)
Tampons for urinary incontinence	5 (5%)
Pelvic floor muscle training [d]	22 (22%)
Intrauterin device insertion/removal	2 (2%)
Counseling on fluid intake, bladder emptying method, contraception or pregnancy	17 (17%)

[a]Biopsy from cervix ($n = 2$), labia majores ($n = 1$), and endometrium ($n = 1$)

[b]Including women who received counseling

[c]Due to labia majora hypertrophy causing bladder emptying problems with clean intermittent catheterization

[d]Excluding one woman receiving pelvic floor stretching therapy

44 women with symptomatic stress UI, 33 (75%) received treatment of stress UI including referral to a group or individual pelvic floor muscle training-program with a physiotherapist either at the hospital or locally ($n = 15$), pessary for UI ($n = 11$), tampons for UI ($n = 4$), vaginal estradiol treatment ($n = 18$), and surgery ($n = 1$). The surgical treatment of SUI included intraurethral injection therapy with Bulkamid® in a woman with urodynamically confirmed SUI, acontractile bladder and paresis of the pelvic floor muscles, but the treatment was not effective. As the woman could not carry out intermittent catheterization, she was treated with a tight mid-urethral tape combined with a suprapubic catheter which resulted in complete continence.

Pelvic organ prolapse

At examination, 21 women (21%) had POP stage ≥2; 16 had POP stage 2 and 5 had POP stage 3. Among the women with a history of vaginal delivery, 70% had POP stage 0–1, 22% had POP stage 2, and 8% had POP stage 3 compared with 92% with POP stage 0–1, 8% with POP stage 2 and none with POP stage 3 among the women with no history of vaginal delivery. Of the 21 women with POP stage ≥ 2, 12 experienced symptoms of POP (57%).

Mean age and parity were significantly higher in women with POP stage ≥2, and more women with POP stage ≥2 were menopausal and had a history of vaginal delivery than women with POP stage 0–1 (Table 4). In addition, a logistic regression analysis was conducted in a subgroup of women with a history of vaginal delivery ($n = 60$), which included no women with myelomeningocele as etiology of injury. When adjusting to age, the odds of having POP stage ≥2 was 0.47 (95% CI 0.05–4.77, $p = 0.5$) after 1–5 years follow up and 0.71 (95% CI 0.16–3.08, $p = 0.6$) after >5 years follow up compared with <1 year follow up after injury, hence, the risk of having POP stage ≥2 did not increase with increasing time after injury. There was no difference in primary bladder emptying methods between the two groups, where the majority of women used normal bladder emptying or intermittent catheterization in both groups (Fig. 2).

Discussion

In this observational study, 21% of women with SCI had anatomical POP stage 2 or more, and POP was associated with the known risk factors age, parity, vaginal delivery, and menopause [2], but not with completeness and level of injury or follow-up period after injury.

Swift investigated the prevalence of anatomical POP according to the POP quantification system in neurologically intact women with a mean age of 44 years and found that 50% had anatomical POP stage ≥2 [2]. It could be argued that parity and mode of delivery may differ in women with and without a SCI, but even among the women with a history of vaginal delivery, 58% had POP stage ≥2 in the study by Swift compared with 30% in the present study. In a group of Brazilian women comparable with this study population on parity, body mass index and mode of delivery but younger of age (mean age 41 years), POP stage ≥2 occurred in 24.5% [16]. In comparison, anatomical POP is not more prevalent in women with SCI compared with

Table 4 Characteristics associated with POP stage ≥2

Characteristics	POP stage 0–1 ($n = 77$)	POP stage ≥2 ($n = 21$)	p
Mean age (years)	50.0 (45.8–54.1)	61.5 (56.4–45.8)	**0.0007**
Mean age at injury (years)	40.9 (35.6–46.2)	50.3 (38.2–62.4)	0.11
Median follow-up after injury (years)	2.7 (0.8–9.6)	1.0 (0.4–5.7)	0.3
Mean body mass index (kg/m^2)	25.9 (24.4–27.4)	27.3 (24.4–30.3)	0.4
Mean parity	1.4 (1.1–1.6)	2.0 (1.5–2.6)	**0.014**
History of vaginal delivery			**0.011**
Yes	42 (54%)	18 (86%)	
No	35 (45%)	3 (14%)	
Menopause			**0.025**
Yes	41 (53%)	17 (81%)	
No	36 (47%)	4 (19%)	
Hysterectomy			0.20
Yes	8 (10%)	0 (0%)	
No	69 (90%)	21 (100%)	
Classification of injury by NLI and AIS			0.25
C1-C8, AIS ABC	6 (9%)	0 (0%)	
Th1-S5, AIS ABC	7 (10%)	4 (24%)	
Any NLI, AIS D	55 (81%)	13 (76%)	
Etiology of injury			1.0
Spinal cord injury	68 (88%)	19 (90%)	
Myelomeningocele	9 (12%)	2 (10%)	
Mobility			0.6
Walks without walking aids	22 (29%)	4 (19%)	
Walks with walking aids	41 (53%)	14 (67%)	
Permanent wheelchair user	14 (18%)	3 (14%)	
Primary bladder emptying method			0.4
Bladder expression/ Valsalva's maneuver	7 (9%)	3 (14%)	
Other method(s)	70 (91%)	18 (86%)	
Pelvic floor muscle strength			0.20
Absent or weak	41 (59%)	15 (75%)	
Normal or strong	29 (41%)	5 (25%)	
Bowel emptying problem	55 (71%)	14 (67%)	0.8
Urinary incontinence	54 (70%)	16 (76%)	0.8
Fecal incontinence	18 (23%)	8 (38%)	0.26

Results are presented in mean (95% confidence interval), median (q25-q75) or in total numbers (%)

POP Pelvic organ prolapse, *NLI* Neurological level of injury, *AIS* American Spinal Injury Association impairment scale

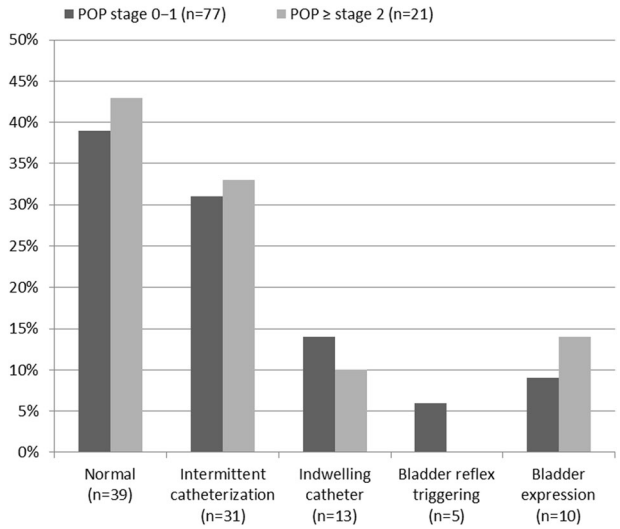

Fig. 2 Anatomical pelvic organ prolapse according to primary bladder emptying method

neurologically intact women. Additionally, the risk of POP does not increase with increasing time after injury in this study. Even among the women with the longest follow-up period due to a congenital myelomeningocele as etiology of the spinal cord lesion (median follow-up was 40 years, range 18–61), only 18% had POP, suggesting that a SCI is not a risk indicator of POP.

POP has not previously been investigated in women with SCI, but Dillon et al. investigated the prevalence of POP in 280 women with multiple sclerosis (MS) [17], and found that only 9% had anatomical POP stage ≥2. Though the evolving symptoms in persons with MS differs fundamentally from the more chronic complications after a SCI, the findings of both studies indicate that women with a neurological disorder have a lower occurrence of POP compared with able-bodied women. We hypothesize that this is due primarily to impaired mobility, where less stress is applied on the pelvic organs, connective tissue, and pelvic floor muscles compared with neurologically intact women. Clinically, these findings are relevant when considering mode of delivery in a pregnant woman with SCI, as the concern of an increased risk of POP after a SCI may be disregarded.

Overall, 70% of the study population had followed the age-specific cervical cancer screening program. During 2009–2015, the coverage of cervical cancer screening was 75–76% in Danish women, which is comparable to the coverage found in our study [18]. Previous studies have shown that among women with disabilities, non-ambulatory status and major lower extremity mobility difficulties were associated with an increased risk of non-participation in the cervical cancer screening program [19, 20]. Given that the majority of the spinal cord injured women in this study were ambulatory with a less complete injury, the coverage of the cancer screening program might be lower in completely paralyzed women. No women were diagnosed with dysplasia or gynecological cancer as a consequence of this study, which is not surprising considering the limited size of the study. Nonetheless, physicians should consider women with SCI as a vulnerable population for receipt of cervical cytology tests and regular gynecological health examinations.

The high occurrences of symptomatic UI (71%), fecal incontinence (27%), bladder- (63%), and bowel emptying problems (70%) show that the majority of the included women deal with several urogynecological complications

following the injury. All the included women were followed at the highly specialized Clinic for SCI prior to the consultation, where the bladder function is regularly evaluated using urodynamic investigations. Due to the risk of renal deterioration following a SCI, treatment of neurogenic bladder dysfunction and especially high-pressure detrusor overactivity is highly prioritized in this population [21, 22]. Among the included women, 22% were already receiving treatment with intravesical botulinum toxin injections or antimuscarinic/beta-3 adrenoceptor agonistic therapy and 45% used either intermittent catheterization or permanent catheter prior to the consultation. Despite of this, 75% of the women with symptomatic stress UI received treatment of their incontinence as a consequence of this study, which underlines the value of specialized urogynecological consultations offered to urinary incontinent women with a SCI.

The strength of this study is primarily its novelty as it is the first study to investigate the occurrence of POP in women with SCI. The limitations of the study include the small size, which prevents the use of multivariate analyses, and the relatively short follow-up period. Secondly, there was no age-matched cohort of women undergoing pelvic examination in the study, making the comparisons with able-bodied women somewhat conjectural. Thirdly, the diagnosis of SUI was based on the woman's reported symptoms and not on urodynamic evaluations. With the purpose of identifying detrusor overactivity, urodynamic investigations were already a part of the standardized urological follow-up program in the Clinic for Spinal Cord Injuries, thus, urodynamic evaluations were only conducted in this study when it was clinically relevant, e.g., prior to surgical treatment of UI. Unfortunately, the results from the urodynamic evaluations conducted in the standardized follow-up program were not available in this study. Finally, the number of eligible women who were offered to attend the gynecological consultation but declined or did not show up was not registered. However, ~700 women were listed as patients in the Clinic for Spinal Cord Injuries, of whom a seventh was included in this study. It could be questioned if the study population is a representable sample of women with SCI or if the women with urogynecological issues are overrepresented in this study. The same authors conducted a study including the majority of women ($n = 609$) followed at the Clinic for Spinal Cord Injuries [6], and data were collected from a SCI database containing standardized SCI-specific questionnaires, including a validated bladder function questionnaire [10]. In this study, the prevalence of daily to monthly UI within the last three months was 49%, which is lower than the 71% occurrence of any UI without time-limits found in the present study. However, of the 98 included women in this study 75 were also included in the database study, and in this sample 56% experienced UI compared with 71% in the present study. This suggests that the descrepancy between the study-findings is caused primarily by use of different definitions of UI rather than selection bias. Further, the two study populations did not differ on neurological level of injury, completeness of injury, age, and age at injury, but the women in the present study had a shorter median follow-up period after injury (2.3 years) compared with the women in the database study (7.2 years).

In conclusion, the occurrence of anatomical POP in women with SCI is not higher than in neurologically intact women, and the risk of POP does not increase with increasing time after injury. Though anatomical POP does not occur more frequently in women with SCI, other urogynecological issues like UI are highly prevalent, supporting the value of urogynecological consultations and treatments offered to women with SCI. It would be interesting for future studies to investigate the effect of urogynecological interventions on UI and other urogynecological issues, including an evaluation of conservative as well as surgical treatments of in particular stress UI in women with a neurological disorder.

Author contributions ME was responsible for designing and planning the study, data analysis and interpretation, and writing the report. FB-S contributed to the design and planning of the study, interpretation of the results, and provided feedback on the report. MHB was responsible for data acquisition, contributed to interpretation of the results, and provided feedback on the report. NK contributed to the design and planning of the study, data analysis, interpretation of the results, and provided feedback on the report.

Compliance with ethical standards

Conflict of interest ME and NK have received paid travel expenses from Contura travel expenses from Contura and MB has received paid travel expenses from Normedi. FB-S has no conflicts of interest to disclose.

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ORIGINAL ARTICLE

The effect of pelvic floor muscle training and intravaginal electrical stimulation on urinary incontinence in women with incomplete spinal cord injury: an investigator-blinded parallel randomized clinical trial

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Abstract

Introduction and hypothesis Urinary incontinence is a prevalent problem in women with spinal cord injury. The aim of this study was to examine the effect of pelvic floor muscle training (PFMT) alone and combined with intravaginal electrical stimulation (IVES) on urinary incontinence in women with incomplete spinal cord injury.

Methods In this investigator-blinded randomized clinical trial, we recruited women aged 18–75 with incomplete spinal cord injury and urinary incontinence from a single spinal cord injury clinic in Denmark. Women were randomly assigned to either PFMT or PFMT combined with IVES daily at home for 12 weeks. All women were trained by a physiotherapist using vaginal palpation and electromyography biofeedback. Outcome measures were recorded at baseline (week 0), post-intervention (week 12) and follow-up (week 24) and included change in the total score on the International Consultation on Incontinence Questionnaire urinary incontinence short form (ICIQ-UI-SF) and daily episodes of urinary incontinence.

Results From 27 April 2015−9 September 2016, we randomly assigned 36 women (17 in the PFMT group and 19 in the PFMT+IVES group); 27 completed the interventions (13 in the PFMT group and 14 in the PFMT+IVES group). The results showed no difference between the groups on ICIQ-UI-SF or episodes of urinary incontinence at 12 and 24 weeks. Only the PFMT group had a significant change from baseline on ICIQ-UI-SF [−2.4 (95% CI -4.3−−0.5), $p = 0.018$] and daily episodes of urinary incontinence [−0.4 (95% CI -0.8−−0.1), $p = 0.026$] at 12 weeks.

Conclusions PFMT+IVES is not superior to PFMT alone in reducing urinary incontinence in women with incomplete spinal cord injury.

Keywords Urinary incontinence · Spinal cord injury · Pelvic floor muscle training · Electrical stimulation · Neurogenic bladder

Introduction

Urinary incontinence (UI) is a prevalent problem in persons with spinal cord injury (SCI), affecting approximately 52% [1]. The characteristics of UI in persons with SCI vary according to the type of neurogenic bladder dysfunction: neurogenic detrusor overactivity (NDO) can result in urgency UI, acontractile bladder can result in overflow UI, and underactive urethral sphincter as well as weakness of the pelvic floor muscles (PFMs) can result in neurogenic stress UI [2]. Studies have shown that urinary incontinent SCI persons experience reduced quality of life (QoL) compared with their urinary continent counterparts. In addition, UI has been reported to be one of the primary physical problems affecting the sexuality of SCI women [3].

Pelvic floor muscle training (PFMT) is a well-established first-line conservative treatment of stress UI in able-bodied women [4]. Moreover, studies have shown that PFMT can decrease urgency UI because of inhibition of bladder contractions [5, 6]. Another conservative treatment of UI is electrical stimulation (ES). The mechanism of action is unclear; however, it has been suggested that ES at high frequencies (40–

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50 Hz) stimulates the efferent motor fibers of the pudendal nerve, facilitating PFM contraction. This may lead to muscle hypertrophy and increased urethral pressure. Conversely, ES at low frequencies (5–10 Hz) stimulates the afferent fibers of the pudendal nerve, promoting bladder relaxation by inhibiting the parasympathetic vesical motor neurons [7]. The evidence of using high-frequency ES to reduce stress UI in able-bodied women is contradictory, and most studies find no additional effect of high-frequency intravaginal ES compared with PFMT alone [8–10]. Nevertheless, there is a lack of studies investigating high-frequency ES in persons with neurologic disorders. On the other hand, low-frequency ES applied intravaginally has shown good results on urgency UI comparable or superior to anticholinergic medication [11, 12]. It could be hypothesized that a combination of high- and low-frequency ES is beneficial particularly in SCI persons with NDO and reduced strength and sensibility of the PFMs given the threefold effect of the stimulation: relaxation of the bladder, strengthening of the PFMs and increased awareness of the PFMs. However, the effect of non-invasive ES in persons with UI due to neurologic disorder has been sparsely examined, and the literature includes only two randomized clinical trial studies [13]. These studies showed promising results on UI in persons with stroke or multiple sclerosis [14, 15]. To our knowledge, no studies have investigated the effect of PFMT alone or combined with intravaginal electrical stimulation (IVES) on UI in women with SCI. Hence, the aim of this investigator-blinded parallel randomized clinical trial was to examine the effect of PFMT and PFMT combined with IVES on UI in women with incomplete SCI.

Materials and methods

Study participants

This was an investigator-blinded parallel-group randomized clinical trial. Eligible participants were women aged 18–75 years with incomplete SCI and UI with a total score of ≥ 8 on the International Consultation on Incontinence Questionnaire UI short form (ICIQ-UI-SF). Exclusion criteria were motor completeness of injury (A or B on the American Spinal Injury Association Impairment Scale) [16], lack of ability to contract the PFMs examined by the investigator, vesical botulinum toxin injection within the last year, pregnancy and use of a pacemaker. The use of bladder-relaxant drugs was allowed if the dose was not changed during the study. To describe the urodynamic detrusor function, the most recent cystometry and pressure-flow study was searched for in the medical records. If not available, a cystometry and pressure-flow study was to be performed in our department. As the occurrence of stress UI was not investigated in the cystometry and pressure-flow studies conducted prior to this study, the type of UI was defined by the ICIQ-UI-SF questionnaire. Participants were recruited from a single SCI center in Denmark during April 2015–January 2017.

Study design

Recruited women attended a screening visit where a digital vaginal and rectal examination was conducted by the primary investigator to examine if the women were able to perform a voluntary PFM contraction. In addition, the ICIQ-UI-SF questionnaire was filled out and evaluated according to the exclusion criteria.

If eligible, participants were randomized 1:1 to one of two groups: (1) PFMT or (2) PFMT combined with IVES. We used a computer-generated randomization list in a block size of four. Allocation was conducted by a research-assistant according to the order of inclusion. Whereas the research assistant, physiotherapists and study participants were aware of the allocated arm, the primary investigator who assessed the outcomes and analyzed data was blinded. The study was approved by the National Committee on Health Research in Denmark, and the study was registered at clinicaltrials.gov, NCT02427230.

Shortly after enrollment, the participants attended a second visit during which all women received an individual physiotherapeutic standardized consultation [17]. With the woman in a supine position, the examination included visual inspection, digital vaginal and rectal palpation and electromyography biofeedback (U-Control EMG Biofeedback®, NMKimport, Værløse, DK) with a vaginal or anal sensor as visual and auditory guidance tools. All physiotherapists had been trained in PFMT and IVES during a 5-day course held by a specialized pelvic floor physiotherapist. Instructions for PFMT included approximately 30 near-maximal contractions of 5–10-s duration followed by 10 s of pause, adjusted to the woman's pelvic floor muscle function. In addition to the PFMT instructions, the PFMT+IVES group received instructions on how to use an electrical stimulation device, Cefar Peristim Pro® (NMKimport, Værløse, DK), with a vaginal probe. Instructions included the daily use of two stimulation programs. First, an intermittent stimulation (frequency 40 Hz, pulse width 250 μs) was applied for 7.5–10 min, during which 30 stimulation cycles were given, each including 5–10 s of stimulation followed by 10-s breaks. The women were instructed to perform the active PFMT program concurrent with the IVES, using the electrical device as guidance on how and when to contract the muscles. Second, a continuous stimulation (frequency 10 Hz, pulse width 250 μs) was applied for 10–20 min, during which the women were instructed to relax their PFMs. Both stimulation programs should be delivered at the women's maximum tolerated intensity. Women in both groups were asked to train daily for 12 weeks and to keep a daily training diary. During the active training period, the women attended two additional consultations with

the physiotherapist at week 4 and 8 where the training diary was evaluated, the PFMT was assessed using vaginal palpation and electromyography biofeedback, and the training instructions were adjusted according to the patient's improvements. To enhance motivation, participants were also offered a phone consultation with the physiotherapist at week 2, 6 and 10. At the 12-week visit, the IVES device was handed in, and all participants were encouraged to continue PFMT.

Outcomes

Outcomes were measured during the first visit after enrollment (week 0) after the 12-week intervention period (week 12) and after 12 additional weeks of follow-up (week 24). The primary outcome measure was change in total score on the validated questionnaire, ICIQ-UI-SF, developed by the International Consultation on Incontinence [18], which was translated into Danish and tested for content validity and test-retest reliability in a study investigating urinary incontinence during and after pregnancy [19]. The questionnaire contains questions regarding the frequency, severity and the impact of UI on QoL, providing a total score ranging from 0 to 21 with a higher score indicating worse symptoms and greater impact on QoL.

Secondary outcomes included change in opening urethral pressure (OUP) during PFM contraction and at rest measured with urethral pressure reflectometry (UPR) [20]. UPR measures the pressure and cross-sectional area in the urethra simultaneously using a thin polyurethane bag placed in the urethra. The bag is inflated with air, and the cross-sectional area is measured with acoustic reflectometry. The method has proven to be highly sensitive in detecting changes in the OUP caused by drugs reducing stress UI [21]. To prevent urinary tract infection caused by the UPR, all women were given a prophylactic antibiotic treatment (400 mg pivmecillinam and 500 mg amoxicillin-clavulanic acid), which was administered 1 h prior to the investigation and in the evening.

Other secondary outcomes included change in 3-day bladder diary parameters (daily episodes of UI, mean bladder capacity, maximal functional bladder capacity and number of daily voiding episodes), a 24-h pad test, total score on the International Consultation on Incontinence Questionnaire overactive bladder (ICIQ-OAB), in which the total score range is 0–56, with a higher score indicating worse symptoms [22], and total score on the International SCI QoL Basic Data Set (SCI-QoL) in which the total score range is 0–30, with a higher number meaning greater satisfaction [23]. At week 12 and 24, the Patient Global Impression of Improvement scale (PGI-I) was applied [24].

Sample size and statistical methods

To detect a change in total score on ICIQ-UI-SF of 5 (SD 4), which is in accordance with the study of Sirls et al. [25], with a two-sided 5% significance level and a power of 80%, a sample of ten women per group was necessary. To compensate for possible dropouts, we aimed at including 20 women in each group.

We analyzed data only for those women who completed the study (per protocol). Parametric, nonparametric and categorical baseline parameters were presented as mean (± SD), median (interquartile range) or numbers (%) and analyzed using Student's t-test, Mann-Whitney-U test or Fisher's exact test, respectively. Changes from baseline at 12 and 24 weeks were analyzed using analysis of covariance (ANCOVA) in parametric data, presenting results as mean (95% confidence interval), and Mann-Whitney-U test in nonparametric data, presenting results as median (interquartile range). The ANCOVA analysis included the baseline value of the parameter as a fixed effect, when the effect of intervention group was examined. In each group, change from baseline was analyzed using a paired t-test in the parametric data or Wilcoxon signed rank test in nonparametric data. The statistical analyses were repeated in two subgroups as post-hoc analyses after excluding: (1) participants who trained < 50% of the days in the intervention period or (2) participants with stress or undefined UI. All statistical analyses were performed in SAS version 7.1, and $p < 0.05$ was considered statistically significant.

Results

The Consolidated Standards of Reporting Trials flow diagram is presented in Fig. 1. From 27 April 2015−9 September 2016, we included and randomized 36 women. One woman in the PFMT+IVES group was excluded after enrollment but prior to the first session with the physiotherapist as the investigators found that polyuria and excessive daily fluid intake (> 4 l) were the main causes of the woman's frequency and UI symptoms. Four women in each group discontinued the study. The time of dropout during the study was the same in the two groups: One dropped out prior to the active intervention period, two dropped out after 0–4 weeks of the active intervention period and one dropped out after 4–8 weeks of the active intervention period in both groups. One woman in the PFMT+IVES group was excluded after 12 weeks because of vesical botulinum toxin injections.

Table 1 lists baseline characteristics of the study groups. The women in the PFMT+IVES group were significantly older, had a lower mean and maximum functional bladder capacity, used more pads, had a lower daily fluid intake and daily diuresis, and had a higher score on the ICIQ-OAB compared with the women in the PFMT group. Three women (one in the PFMT and two in the PFMT+IVES group) reported UI symptoms prior to the SCI. Only four women (two in the PFMT and two in the PFMT-IVES group) had a normal

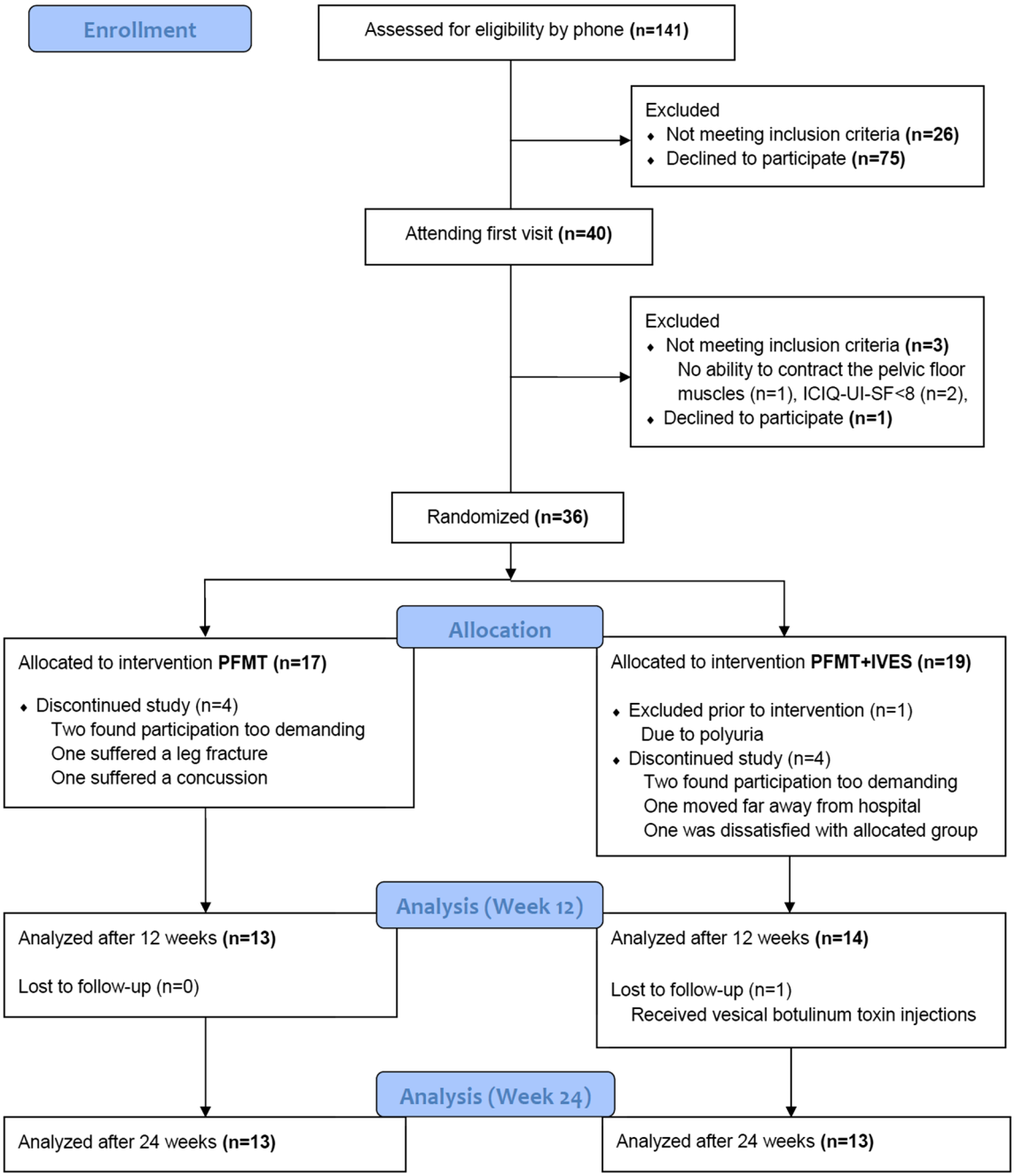

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram

sensation by pin prick and light touch in the S3 and S4-S5 dermatomes.

The changes from baseline in outcome measures after intervention at week 12 or 24 are shown in Tables 2 and 3 and Fig. 2. There were no significant between-group differences at week 12, except for the change in OUP-resting, which showed a 5.7 cmH2O larger increase in pressure in the PFMT group compared with the PFMT+IVES group. The within-group analyses showed a significant change from baseline at 12 weeks (marked with an *) in the PFMT group regarding the total score on ICIQ-UI-SF [−2.4 (95% CI -4.3−−0.5), p = 0.018], OUP-squeezing [7.7 cmH2O (95% CI 1.7–13.8), p = 0.017], OUP-resting [3.9 cmH2O (95% CI 0.5–7.3), p = 0.030] and daily incontinence episodes [−0.4 (95% CI -0.8−−0.1), p = 0.030]. The PFMT+IVES group only improved significantly on the 24-h pad test [median − 32.5 g (IQR −112–3), p = 0.045].

At week 24 (Table 3), there were no significant between-group differences in change in outcome measures from baseline. The within-group analysis showed a significant change from baseline in the PFMT group on the ICIQ-UI-SF [−2.5 (95% CI -4.5−−0.6), p = 0.016], number

Table 1 Baseline characteristics and outcome measures

Characteristics	All ($n = 27$)	PFMT ($n = 13$)	PFMT+IVES ($n = 14$)	*P*
Age, years	55 (47–61)	47 (36–56)	59 (49–67)	**0.027**
Parity	2 (1–2)	2 (0–2)	2 (1–2)	0.4
Body mass index, kg/m^2	24.5 (20.8–31.4)	24.7 (21.6–27.7)	22.5 (18.4–32.0)	0.8
Etiology of injury				1.0
Spinal cord injury	24 (89%)	11 (85%)	13 (93%)	
Myelomeningocele	3 (11%)	2 (15%)	1 (7%)	
Level of injury[a]				0.4
Cervical	6 (23%)	4 (31%)	2 (14%)	
Thoracic	8 (31%)	5 (38%)	3 (21%)	
Lumbar	12 (46%)	4 (31%)	8 (57%)	
Completeness[b]				1.0
C	6 (22%)	3 (23%)	3 (21.5%)	
D	20 (74%)	10 (77%)	10 (71.5%)	
E	1 (4%)	0	1 (7%)	
Follow-up after injury, years	11 (3–21)	13 (4–26)	10 (3–19)	0.7
Urinary incontinence[c]				0.2
Stress	4 (15%)	3 (23%)	1 (7%)	
Urgency	8 (30%)	4 (31%)	4 (29%)	
Mixed	13 (48%)	4 (31%)	9 (64%)	
Undefined	2 (7%)	2 (15%)	0	
Detrusor function[d]				0.6
Normal	8 (30%)	5 (38%)	3 (21%)	
Detrusor overactivity	13 (48%)	6 (46%)	7 (50%)	
Acontractile/underactive	6 (22%)	2 (15%)	4 (29%)	
Clean intermittent catheterization	16 (59%)	6 (46%)	10 (71%)	0.3
Use of bladder-relaxant drugs	6 (22%)	2 (15%)	4 (29%)	0.7
Use of muscle-relaxant drugs[e]	10 (37%)	4 (31%)	6 (43%)	0.7
Reflectometry				
OUP-squeezing, cmH_2O	51.9 (± 15.1)	56.5 (± 16.5)	47.7 (± 12.9)	0.13
OUP-resting, cmH_2O	46.7 (± 14.4)	50.7 (± 13.5)	42.9 (± 14.7)	0.17
3-Day bladder diary				
Daily incontinence episodes	1.5 (0.5–3)	1 (0–2)	2 (1–4)	0.07
Mean bladder capacity, ml	252 (± 87)	313 (± 58)	200 (± 72)	**0.001**
Max bladder capacity, ml	443 (± 174)	558 (± 154)	344 (± 125)	**0.001**
Daily voiding episodes	7 (± 2)	6 (± 2)	7 (± 2)	0.19
Daily used pads	2 (1–4)	1 (0–3)	2 (2–4)	**0.022**
Daily fluid intake, ml	1681 (± 412)	1901 (± 345)	1492 (± 376)	**0.008**
Daily diuresis, ml	1716 (± 511)	1976 (± 506)	1493 (± 413)	**0.013**
24-h pad test, g	33 (11–164)	34 (7–70)	32 (13–174)	0.6
Questionnaires				
ICIQ-UI-SF	13 (11–16)	11 (10–16)	13.5 (12–16)	0.2
ICIQ-OAB	30 (16–39)	18 (16–30)	36.5 (29–43)	**0.018**
SCI-QoL	19 (15–24)	18 (17–20)	20 (15–24)	0.5

PFMT, pelvic floor muscle training; IVES, intravaginal electrical stimulation; OUP, opening urethral pressure; ICIQ-UI-SF, International Consultation on Incontinence Questionnaire Urinary Incontinence Short Form, ICIQ-OAB, International Consultation on Incontinence Questionnaire Overactive bladder; SCI-QoL, International Spinal Cord Injury Quality of Life Basic Data Set. Data are presented as number (%), mean (±SD) or median (interquartile range). [a] Excluding one patient with no level of injury because of completeness E. [b] Completeness is classified according to the American Spinal Injury Association Impairment Scale. [c] Urinary incontinence is classified according to ICIQ-UI-SF; urgency if yes to "leaks before you can get to the toilet." Stress if yes to "leaks when you cough or sneeze" or "leaks when you are physically active/exercising." Mixed if yes to both categories and undefined if no to both categories. [d] Detrusor function on the most recent cystometry and pressure-flow study. [e] Including benzodiazepine (n = 1), per oral baclofen ($n = 3$), baclofen pump (n = 1) and gabapentin ($n = 7$), which was used in the treatment of neurogenic pain, but also has an anti-spasmolytic effect

of daily incontinence episodes [−0.6 (95% CI -1.0−−0.2), $p = 0.010$], the maximal functional bladder capacity [−120 ml (95% CI -227−−13), $p = 0.031$] and the 24-h pad test [median − 11 g (IQR −84−−2), $p = 0.020$]. The PFMT+IVES group improved on ICIQ-OAB (−5.8, [95% CI -9.0−−2.7], $p = 0.002$).

According to the training diary, women in the PFMT group performed the intervention daily in a median of 76 days (range 31–91). Women in the PFMT+IVES group performed the intervention daily in a median of 67 days (range 14–95) (Mann-Whitney-U, $p = 0.2$). On the days when the intervention was carried out, compliance with the training instruction

was generally good. The mean number of contractions was 28 (range 22–30) with a mean duration of 8 s (range 5–10) in the PFMT group, and the mean stimulation time was 9 min (range 8–10) with the intermittent stimulation and 15 min (range 15–20) with the continuous stimulation in the IVES+PFMT group. Four women (one in the PFMT group and three in the PFMT+IVES group) did not perform the assigned intervention more than 50% of the days during the 84-day intervention period. When excluding the four women from the study population in a sub-analysis (supplementary Table A), there was no difference between the groups in any parameters, and the within-group results at week 12 did not differ from those found in the complete study population.

In a second sub-analysis (supplementary Table B), only the women with urgency or mixed UI according to the ICIQ-UI-SF answers were included ($n = 21$). The results showed no differences between the groups in any parameters.

One woman in the PFMT group reported soreness in the pelvic floor area, but no other adverse events were reported.

Discussion

This is the first randomized clinical trial investigating the effect of PFMT and IVES in women with neurogenic UI after SCI. The trial demonstrates that IVES combined with PFMT is not superior to PFMT alone in reducing UI and improving QoL. After a 12-week training period, only the PFMT group showed significant improvement of the ICIQ-UI-SF score, daily UI episodes and the OUP during contraction and at rest. A significant effect on daily UI episodes and ICIQ-UI-SF was also found at week 24, demonstrating a persistent effect 3 months after the intensive PFMT program had ended.

Given the novelty of the study, a comparison with results from other studies conducted in SCI persons is not possible. However, our findings differ from the findings in a similar study by McClurg et al. that included 74 multiple sclerosis patients [15]. The authors found that 9 weeks of daily intravaginal/intra-anal electrical stimulation (40 and 10 Hz) in addition to PFMT was more effective than PFMT alone on lower urinary tract dysfunction. The mean number of daily UI episodes was reduced

Table 2 Change in outcome measures after intervention at 12 weeks

Outcome measures	*n*	PFMT	*n*	PFMT+IVES	IVES+PFMT − PFMT *(adjusted)*[a]	*P*
ICIQ-UI-SF	*13*	−2.4 (−4.3—0.5)*	*14*	−2.2 (−4.8—0.4)	0.4 (−2.8–3.6)	0.8
ICIQ-OAB	*13*	1.6 (−6.9–10.1)	*14*	−3 (−10.3–4.3)	2.4 (−8.6–13.3)	0.7
Reflectometry						
OUP-squeezing, cmH_2O	*13*	7.7 (1.7–13.8)*	*14*	1.4 (−2.4–5.2)	−5.2 (−12.3–1.8)	0.14
OUP-resting, cmH_2O	*13*	3.9 (0.5–7.3)*	*14*	−1.3 (−4.6–1.9)	−5.7 (−10.4—1.1)	**0.018**
3-Day bladder diary						
Daily incontinence episodes	*11*	−0.4 (−0.8—0.1)*	*12*	0.1 (−0.6–0.8)	0.6 (−0.2–1.4)	0.14
Mean bladder capacity, ml	*12*	22 (−43–87)	*13*	−3 (−20–15)	−23 (−117–70)	0.6
Max bladder capacity, ml	*12*	−67 (−175–41)	*13*	−9 (−56–38)	−46 (−172–80)	0.5
Daily voiding episodes	*12*	−0.6 (−1.8–0.7)	*13*	−0.5 (−1.6–0.7)	0.9 (−0.5–2.2)	0.18
24-h pad test, g	*12*	−6.0 (IQR −54 − 5)	*12*	−32.5 (IQR −112–3) [$]	–	0.6
SCI-QoL	*13*	2 (IQR 0–6)	*14*	1 (IQR −3 − 6)	–	0.7
PGI-I	*13*	3 (IQR 2–3)	*14*	3 (IQR 3–4)	–	0.7

PFMT, pelvic floor muscle training; IVES, intravaginal electrical stimulation; ICIQ-UI-SF, International Consultation on Incontinence Questionnaire Urinary Incontinence Short Form; OUP, opening urethral pressure; ICIQ-OAB, International Consultation on Incontinence Questionnaire Overactive bladder; SCI-QoL, International Spinal Cord Injury Quality of Life Basic Data Set; PGI-I, Patient Global Impression of Improvement, where 1 = very much better, 2 = much better, 3 = a little better, 4 = no change, 5 = a little worse, 6 = much worse and 7 = very much worse

Results are calculated by subtracting post-treatment values (week 12) from pre-treatment values (week 0) and presented as mean (95% confidence interval) or median (IQR, interquartile range). [a] Analysis of covariance (ANCOVA) was adjusted for the baseline value. *Significant change by paired t-test. [$] Significant change by paired Wilcoxon signed rank test

Table 3 Change in outcome measures after follow-up at 24 weeks

Outcome measures	*n*	PFMT	n	PFMT+IVES	IVES+PFMT – PFMT *(adjusted)*[a]	*P*
ICIQ-UI-SF	*13*	−2.5 (−4.5—0.6)*	*13*	−2.5 (−5.5–0.4)	0.3 (−3.1–3.7)	0.8
ICIQ-OAB	*13*	1.2 (−5.8–8.1)	*13*	−5.8 (−9.0—2.7)*	−4.2 (−12.4–4.1)	0.3
Reflectometry						
OUP-squeezing, cmH_2O	*13*	6.4 (−0.2–13.0)	*13*	1.5 (−2.5–5.4)	−3.9 (−11.8–3.9)	0.3
OUP-resting, cmH_2O	*13*	1.9 (−2.7–6.4)	*13*	0.1 (−3.3–3.4)	−1.0 (−6.9–4.9)	0.7
3-Day bladder diary						
Daily incontinence episodes	*10*	−0.6 (−1.0—0.2)*	*11*	−0.1 (−1.1–0.9)	−0.6 (−0.6–1.7)	0.3
Mean bladder capacity, ml	*12*	−25 (−71–21)	*13*	12 (−17–42)	12 (−55–79)	0.7
Max bladder capacity, ml	*12*	−120 (−227—13)*	*13*	−3 (−50–44)	17 (−101–135)	0.8
Daily voiding episodes	*12*	0 (−1.4–1.4)	*13*	−0.4 (−1.3–0.5)	0.2 (−1.0–1.4)	0.7
24-h pad test, g	*11*	−11.0 (IQR −84—2) [$]	*12*	−13.5 (IQR −101 − 17)	–	0.7
SCI-QoL	*13*	3 (IQR 0–6)	*13*	1 (IQR −2 − 3)	–	0.3
PGI-I	*13*	3 (IQR 3–4)	*13*	3 (IQR 3–4)	–	0.9

PFMT, pelvic floor muscle training; IVES, intravaginal electrical stimulation; ICIQ-UI-SF, International Consultation on Incontinence Questionnaire Urinary Incontinence Short Form; OUP, opening urethral pressure; ICIQ-OAB, International Consultation on Incontinence Questionnaire Overactive bladder; SCI-QoL, International Spinal Cord Injury Quality of Life Basic Data Set; PGI-I, Patient Global Impression of Improvement, where 1 = very much better, 2 = much better, 3 = a little better, 4 = no change, 5 = a little worse, 6 = much worse and 7 = very much worse

Results are calculated by subtracting follow-up values (week 24) from pre-treatment values (week 0) and presented as mean (95% confidence interval) or median (IQR, interquartile range). [a] Analysis of covariance (ANCOVA) was adjusted for the baseline value. *Significant change by paired t-test. [$] Significant change by paired Wilcoxon signed rank test

by 85% in the electrical stimulation group and 47% in the PFMT group. In comparison, the reduction in UI episodes was 25% in the PFMT group and 3% in the PFMT+IVES group in our study. In fact, PFMT+IVES was less effective than PFMT in most parameters, which could be due to suboptimal performance of PFMT while handling an electrical device and holding a vaginal probe in place simultaneously. The increase in OUP after intervention represents an objective measure of improved strength of the PFMs, which is known to reduce stress UI. The superior effect of PFMT compared with PFMT+IVES on OUP is in agreement with studies showing that the effect of IVES is inferior [8] or equal to PFMT [9] in able-bodied women with stress UI.

Some studies conducted in able-bodied women with urgency UI have shown that low-frequency IVES effectively reduces urgency UI/symptoms and increases bladder capacity, comparable to the effect of anticholinergic medication [11–13]. In a study by Ozdedeli et al., IVES reduced daily UI episodes from 1.7 to 0.3, reduced the number of urgency episodes from 4.7 to 1.7 and increased the maximal cystometric bladder capacity from 329 ml to 442 ml with an effect comparable to trospium hydrochloride [12]. In our study, we found no significant changes from baseline in the number of daily voiding episodes in the mean and maximal bladder capacity or in the ICIQ-OAB score in the IVES+PFMT group, demonstrating a lack of effect of IVES on the urgency-associated outcomes. A significant reduction of the ICIQ-OAB score was found in the IVES group at the 24-week follow-up compared with baseline, but given the fact that there was no effect at the 12-week follow-up and that IVES was not applied from week 12–24, this was more likely due to effective post-intervention PFMT.

It could be argued that the effect of IVES was obscured by the heterogeneity in the study population regarding types of UI. Consequently, we conducted a sub-analysis including only the women with urgency or mixed UI, but no differences between the groups or changes from baseline at 12 weeks in urgency-associated outcomes were found in the IVES+PFMT group.

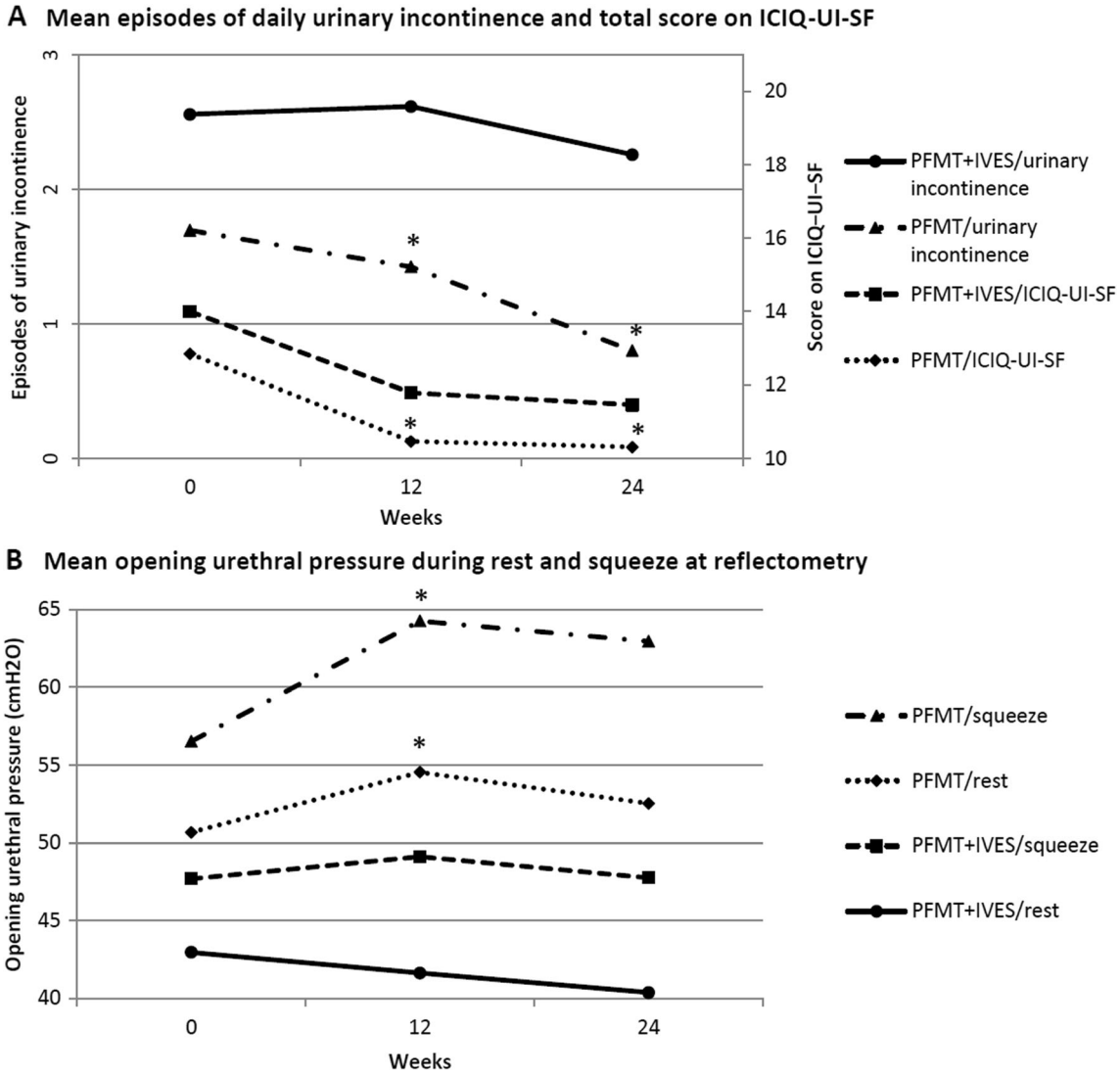

Fig. 2 Mean outcome measures at week 0, 12 and 24. Data are analyzed with paired t-test, comparing outcome measures at week 0 with week 12 and 24 according to intervention group. *$p < 0.05$. ICIQ-UI-SF, International Consultation on Incontinence Questionnaire urinary incontinence short form; PFMT, pelvic floor muscle training; IVES, intravaginal electrical stimulation

IVES is a more time-consuming treatment than PFMT, requiring 17–30 min of dedication daily compared with 7.5–10 min of PFMT. In addition, PFMT is a more accessible treatment than IVES, which requires removal of clothes to insert the vaginal probe, a private setting and good hand function to operate the devices. Further, the costs of IVES are higher than the costs of PFMT. Given these circumstances and the fact that there were no additional effects of IVES on UI compared with PFMT alone, the authors of this study cannot recommend the use of IVES in incomplete SCI women.

The statistically significant difference of 2.4 points at 12 weeks and 2.5 points at 24 weeks on the primary outcome, ICIQ-UI-SF, after PFMT was much lower than the estimated minimally important difference (MID) of 5 points used in the sample size calculation. However, the MID was suggested in a study evaluating midurethral sling operations in stress UI women [25], which would be expected to have a greater effect than a conservative treatment like PFMT. A study published after the sample size calculation was conducted suggests an MID of 2.52 (SD 2.56) after PFMT in stress UI women [26], which is comparable to the difference found in our study. When conducting a sample size calculation with an MID of 2.52 (SD 2.56), 17 women in each group should be included to detect a relevant change in ICIQ-UI-SF, which is more than we included in the study. However, as the significant difference between the groups in resting OUP and the nonsignificant differences between the groups in almost all parameters were in favor of the PFMT group, and not the IVES+PFMT group as expected, a true benefit of PFMT+IVES was not overlooked in this study because of a small sample size. Nevertheless, a significant reduction of 2.5 points on ICIQ-UI-SF and approximately 0.5 UI episodes after PFMT is a

limited effect, which should be considered when advising a woman with SCI about PFMT as treatment of UI.

The strengths of this study are its novelty and the randomized investigator-blinded design. Other strengths include the use of the validated and standardized questionnaire, ICIQ-UI-SF, and the use of the objective outcome measure, UPR.

A limitation of this study is the fact that the effect of PFMT was not compared with a placebo group. Due to a limited number of SCI women with UI living in Denmark, the authors decided not to include a placebo group in the study. Another limitation of this study is the differences in the baseline parameters between the two groups, despite the randomized design of the study. To minimize the differences, parametric data were analyzed with ANCOVA, adjusting for the baseline values. Finally, as the training interventions were conducted at home without supervision, compliance with the training program could have been lower than reported in the training diaries.

Conclusion

IVES with PFMT is not superior to PFMT alone in reducing UI, and PFMT should be recommended as the first-line conservative treatment of UI in women with incomplete SCI.

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Compliance with ethical standards

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1. Urinlækage-skema ICIQ-UI SF

Mange mennesker lækker indimellem urin. Vi prøver at finde ud af, hvor mange der lækker urin samt hvor meget det generer dem. Vi vil være taknemmelige, hvis du vil besvare nedenstående spørgsmål. Ved din besvarelse skal du tænke på hvordan du gennemsnitligt har haft det over **de sidste 4 uger.**

1. Skriv venligst din fødselsdato ☐☐ ☐☐ ☐☐☐☐
Dag måned år

2. *Hvor tit lækker du urin?*
(sæt kryds i én boks)

Aldrig	☐	0
Ca. 1 gang om ugen eller mindre	☐	1
2-3 gange om ugen	☐	2
Ca. 1 gang dagligt	☐	3
Flere gange om dagen	☐	4
Hele tiden	☐	5

3. *Vi vil gerne vide, hvor stor en mængde urin **du tror** du lækker. Du skal sætte kryds ud for den rubrik der svarer til den mængde du oftest lækker**t** (hvad enten du benytter beskyttelse eller ej)?*
(sæt kryds i én boks)

Ingen	☐	0
En lille mængde	☐	2
En moderat mængde	☐	4
En stor mængde	☐	6

4. *Hvor meget generer urinlækagen dig i din dagligdag?*
(Venligst indram et af numrene mellem 0 (overhovedet ikke) og 10 (en hel del))

0 1 2 3 4 5 6 7 8 9 10
Slet ikke **En hel del**

ICIQ score: sum score 2+3+4 ☐☐

5. *Hvornår lækker du urin? (sæt kryds i alle de bokse, som passer på dig)*

Lækker aldrig urin	☐
Lækker før jeg kan nå på toilettet	☐
Lækker når jeg hoster eller nyser	☐
Lækker når jeg sover	☐
Lækker når jeg er fysisk aktiv	☐
Lækker når jeg er færdig med at lade vandet og har fået tøj på	☐
Lækker uden nogen som helst grund	☐
Lækker hele tiden	☐

Mange tak fordi du ville besvare spørgeskemaet

2. Overaktiv blære ICIQ-OAB 08/04

Mange mennesker lækker indimellem urin. Vi prøver at finde ud af, hvor mange der lækker urin samt hvor meget det generer dem. Vi vil være taknemmelige, hvis du vil besvare nedenstående spørgsmål. Ved din besvarelse skal du tænke på hvordan du gennemsnitligt har haft det over **de sidste 4 uger.**

1. Skriv venligst din fødselsdato ☐☐ ☐☐ ☐☐☐☐
Dag måned år

2a. *Hvor ofte lader du vandet i løbet af en dag?*

En gang i timen	☐	3
Hver anden time	☐	2
Hver 3. time	☐	1
Hver 4. time eller mere	☐	0

2b. *Hvor meget generer det dig?*
Venligst indram et af numrene mellem 0 (slet ikke) og 10 (en hel del)

0 1 2 3 4 5 6 7 8 9 **10**
Slet ikke **En hel del**

3a. *Hvor mange gange skal du i gennemsnit op om natten for at lade vandet?*

Ingen	☐	0
En gang	☐	1
To gange	☐	2
Tre gange	☐	3
Mere end fire gange	☐	4

3b. *Hvor meget generer det dig?*
Venligst indram et af numrene mellem 0 (slet ikke) og 10 (en hel del)

0 1 2 3 4 5 6 7 8 9 **10**
Slet ikke **En hel del**

4a *Får du nogensinde en pludselig trang til at skulle skynde dig på toilettet for at lade vandet?*

Aldrig	☐	0
En gang imellem	☐	1
Nogen gange	☐	2
For det meste	☐	3
Hele tiden	☐	4

4b. *Hvor meget generer det dig?*
Venligst indram et af numrene mellem 0 (slet ikke) og 10 (en hel del)

0 1 2 3 4 5 6 7 8 9 **10**
Slet ikke **En hel del**

5a *Lækker/løber urinen umiddelbart efter du mærker vandladningstrang?*

Aldrig	☐	0
1 gang om ugen eller mindre	☐	1
2-3 gange om ugen	☐	2
Ca. 1 gang om dagen	☐	3
Flere gange om dagen	☐	4
Hele tiden	☐	5

5b *Hvor meget generer det dig?*
Venligst indram et af numrene mellem 0 (slet ikke) og 10 (en hel del)

0 1 2 3 4 5 6 7 8 9 **10**
Slet ikke **En hel del**

Mange tak fordi du ville besvare spørgeskemaet

Patient ID_____ Besøgs nr_____ Dato_____

Spørgeskema om livskvalitet hos patienter med en rygmarvsskade

1. Tænk tilbage over de sidste fire uger. Hvor tilfreds er du med dit liv og livssituation som helhed, i denne periode? Brug venligst en skala fra 0 (totalt utilfreds) til 10 (totalt tilfreds). Du kan bruge 0 og 10 og alle tal herimellem.

Totalt utilfreds Totalt tilfreds

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

2. Hvor tilfreds er du med dit fysiske helbred de sidste fire uger? Brug venligst en skala fra 0 (totalt utilfreds) til 10 (totalt tilfreds). Du kan bruge 0 og 10 og alle tal herimellem.

Totalt utilfreds Totalt tilfreds

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

3. Hvor tilfreds er du med dit psykiske helbred, følelser og humør de sidste fire uger? Brug venligst en skala fra 0 (totalt utilfreds) til 10 (totalt tilfreds). Du kan bruge 0 og 10 og alle tal herimellem.

Totalt utilfreds Totalt tilfreds

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

7. Patientens overordnede indtryk af forbedring (PGI-I) skala

Patient Global Impression of Improvement (PGI-I) Scale

Sæt kryds ud for det punkt der bedst beskriver hvordan din urin inkontinens er nu, sammenlignet med hvordan den var før du fik behandling

- ☐ Rigtig meget bedre
- ☐ Meget bedre
- ☐ Lidt bedre
- ☐ Ingen ændring
- ☐ Lidt værre
- ☐ Meget værre
- ☐ Betydelig værre